Renewal Assessment Report

beta-cyfluthrin

Volume 1

07 March 2017

Rapporteur Member State: Germany

Co-Rapporteur Member State: Hungary

Version history

When	What

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Level 1

beta-cyfluthrin

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 the renewal assessment report was prepared

1.1.1 Purpose for which the renewal assessment report was prepared

This renewal assessment report (RAR) has been prepared in accordance with Commission Implementing Regulation (EU) No 844/2012 and Guidance Document SANCO/2012/11251 rev. 4 in order to evaluate the application and the supplementary dossier submitted by the beta-cyfluthrin Task Force in view of a decision on the renewal of the first approval of the active substance beta-cyfuthrin according to Commission Regulation (EU) No 1107/2009.

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

According to Commission Implementing Regulation (EU) No 686/2012 Germany was assigned rapporteur Member State (RMS) and Hungary was assigned Co-rapporteur Member State (Co-RMS).

The Co-RMS was given the opportunity to comment on the draft RAR before it was sent to EFSA.

1.1.3 EU Regulatory history for use in plant protection products

Beta-cyfluthrin was first evaluated as existing active substance according to Council Directive 91/414/EEC with Germany being the designated rapporteur Member State.

Bayer AG submitted in 1995 the dossier to support first inclusion of beta-cyfluthrin in Annex I of Council Directive 91/414/EEC and Germany prepared a draft assessment report by 04 November 1996.

Following a peer review organised by the European Commission beta-cyfluthrin was included in Annex I of Council Directive 91/414/EEC with Commission Directive 2003/31/EC, entering into force on 01 January 2004. According to Commission Regulation (EU) No 540/2011 bety-cyfluthrin is deemed to have been approved under Commissio Regulation (EC) No 1107/2009.

The overall conclusions of the evaluation of beta-cyfluthrin, as finalised by the Standing Committee on the Food Chain and Animal Health at its meeting on 03 December 2002, were provided in the Review Report (beta-cyfluthrin, 6841/VI/97-final, 2 December 2002).

The draft assessment report and further information were also submitted to the Scientific Committee for Plants for separate consultation. The Committee was asked to comment on the appropriate dietary risk assessment to be used and to confirm that the available ecotoxicological data supports uses only in glasshouses and for seed treatment. In its opinion the Committee suggested that in addition to a long-term dietary intake risk assessment, as routinely carried out for plant protection products, beta-cyfluthrin should also undergo a short-term acute dietary risk assessment due to its potential neurotoxicity properties. The Committee confirmed that uses as seed dressing and in greenhouses (except where beneficial arthropods are used) can be considered safe for non-target terrestrial and aquatic organisms, due to the specific circumstances of these applications and the immobility of beta-cyfluthrin in soil. The Committee supported the conclusions reached by Member States that field spray applications have not been shown to be sufficiently safe. Following the opinion of the Committee the short term dietary risk assessment was subsequently provided and discussed with the Member States (Opinion of the scientific Committee on Plants regarding the inclusion of beta-cyfluthrin in Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market expressed by the Scientific Committee on Plants, 28 January 2000).

The peer review concluded that:
Only use as insecticide may be authorised. Uses other than ornamental in greenhouses and seed treatment are currently not adequately supported and have not shown to be acceptable under the criteria required by Annex VI. To support authorisations for such uses, data and information to prove their acceptability to human consumers and the environment will have to be generated and submitted to the Member States. This will be the case in particular for data to assess in all detail the risks of outdoor foliar uses and the dietary risks of foliar treatment in edible crops. Member States must pay particular attention to the protection of non-target arthropods.
Further, the following points were identified, which may require the submission of additional information:
- Further improved analytical methods for body fluids, surface water and air.

With Commission Regulation (EU) No 823/2012 and Commission Implementing Regulation (EU) No 950/2016 the current expitry data of the approval was set to 31 October 2017.

In accordance with Article 1 of Commission Implementing Regulation (EU) No 844/2012 the beta-cyfluthrin Task Force submitted an application to Germany as RMS and Hungary as Co-RMS notifying the intention to renew the exsisting approval of beta-cyfluthrin on 23 October 2013.

A supplementary dossier was submitted by the beta-cyfluthrin Task Force on 29 April 2014.

1.1.4 Evaluations carried out under other regulatory contexts

- FAO Specification and evaluation for Plant Protection Products – beta-cyfluthrin, 1999
- Beta-cyfluthrin was evaluated for toxicology (JMPR 2006) and residues (JMPR 2007) under the periodic review programme, and maximum residue levels for cyfluthrin, arising from the use of either cyfluthrin or beta-cyfluthrin on a number of commodities, were recommended.
- Commission Regulation (EU) No 737/2014 of 24 June 2014 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels
- Biocidal Products Committee (BPC), Opinion on the aplication for approval of the active substance Cyfluthrin, Prodct typ: 18, ECHA/BPC/090/2016, adopted 16 February 2016
- EPA Scientific Advisory Panel (SAP). 1999. US EPA Scientific Advisory Panel (SAP): Environmental Fate Assessment for the Synthetic Pyrethroids. Available online: http://www.epa.gov/scipoly/sap/1999/index.htm
- EPA Pesticide Fact Sheet: Cyfluthrin. 1987. Fact Sheet No. 164
- Environmental Fate of Cyfluthrin, Department of Pesticide Regulation, Canada

1.2 Applicant(s) information

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

The application for renewal of approval of beta-cyfluthrin is supported by the beta-cyfluthrin Task Force. The join application is submitted by:

Task Force leader
ADAMA Agricultural Solutions Limited (formerly Makhteshim Agan Holding B.V.)
Arnhemseweg 87
3832 GK Leusden
The Netherlands

Bayer CropScience AG
Alfred-Nobel-Straße 50

D-40789 Monheim am Rhein
Germany

Contact for correspondence

Contact point: [redacted]
Address: [redacted]
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Alternative contact

Contact point: [redacted]
Name: Bayer CropScience AG
Alfred-Nobel-Straße 50
D-40789 Monheim am Rhein
Germany
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

1.2.2 Producer or producers of the active substance

Confidential information, see Volume 4.

1.2.3 Information relating to the collective provision of dossiers

There was one applicant for the active substance beta-cyfluthrin. The companies Bayer CropScience and ADAMA created the beta-cyfluthrin Task Force. The beta-cyfluthrin Task force submitted a joint dossier.

1.3 Identity of the active substance

1.3.1 Common name proposed or ISO-accepted and synonyms

Beta-cyfluthrin (ISO accepted), no synonyms

1.3.2 Chemical name (IUPAC and CA nomenclature)

IUPAC: Cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
or
3-(2,2-dichloro-vinyl)-2,2-dimethyl-cyclopropane-carboxylic acid cyano-(4-fluoro-3-phenoxy-phenyl)-methyl ester

Diastereomer II
(*R*)-cyano(4-fluoro-3-phenoxyphenyl)methyl rel-(1*S*,3*S*)-3-(2,2- dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

Diastereomer IV
(*R*)-cyano(4-fluoro-3-phenoxyphenyl)methyl rel (1*S*,3R)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

CAS: Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, cyano (4-fluoro-3-phenoxyphenyl)methyl ester

Diastereomer II
cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (*R*)-cyano(4-fluoro-3-phenoxyphenyl)methyl ester, (1*S*,3*S*)-rel-

Diastereomer IV
cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (*R*)-cyano(4-fluoro-3-phenoxyphenyl)methyl ester, (1*S*,3*R*) rel-

1.3.3 Producer´s development code numbers

The technical material has the Specification No.: 102000006582 (company code), Supply Chain/UVP No.: 06075770 (company code) from Bayer CropScience AG.

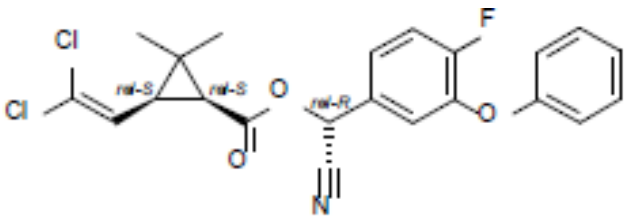
Diastereomer II: AE 1421342
Diastereomer IV: AE 1421344

1.3.4 CAS, EC and CIPAC numbers

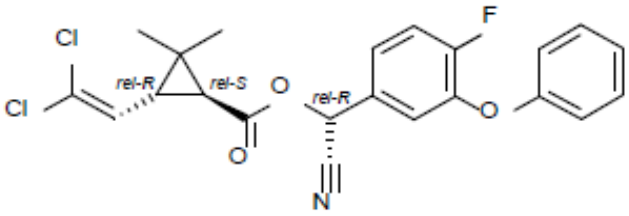
CAS: 68359-37-5 (unstated stereochemistry)
EC (EEC): 269-855-7
CIPAC: 482

1.3.5 Molecular and structural formulae, molecular mass

Molecular formular: $C_{22}H_{18}Cl_2FNO_3$
Molecular mass: 434.3 g/mol
Structural formula: Diastereomer II



Diastereomer IV



1.3.6 Method of manufacture (synthesis pathway) of the active substance

Confidential information, see Volume 4.

1.3.7 Specification of purity of the active substance in g/kg

Minimum purity 965 g/kg

Diastereomer II 300 - 400 g/kg
Diastereomer IV 570 - 670 g/kg

1.3.8 Identity and content of additives (such as stabilisers) and impurities

1.3.8.1 Additives

Confidential information, see Volume 4.

1.3.8.2 Significant impurities

Confidential information, see Volume 4.

1.3.8.3 Relevant impurities

There are no relevant impurities in the technical material.

1.3.9 Analytical profile of batches

Confidential information, see Volume 4.

1.4 Information on the plant protection product

1.4.1 Applicant

Bulldock EC 25

Name: ADAMA Agricultural Solutions Limited (formerly Makhteshim Agan Holding B.V.)
Address: Arnhemseweg 87
3832 GK Leusden
The Netherlands
Contact point: [redacted]
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Montur forte FS 230

Name: Bayer CropScience AG
Address: Alfred-Nobel-Straße 50
D-40789 Monheim am Rhein
Germany
Contact point: [redacted]
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

1.4.2 Producer of the plant protection product

Confidential information, see Volume 4.

1.4.3 Trade name or proposed trade name and producer's development code number of the plant protection product

Bulldock EC 25

Trade name: Bulldock
National trade names e.g. Ducat, Cajun, Summidog, Bulldoks, Gandalf, Keshet, Agtrin

Code number: MCW-5976

Montur forte FS 230

Trade name: Montur Forte FS 230
Beta-cyfluthrin + imidacloprid FS 230 (80 + 150 g/L)
Montur Forte

Code number: CYB+IMD FS 80+150 G (internal name)
CYB+IMD FS 230 (80+150) G (internal name)
06519113 (material No.)
0033090-001 (internal code)
0266429 (AB-number = development number)
102000010926 (specification No.)

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

Bulldock EC 25

Content of active substances:	Beta-cyfluthrin, techn.	25.6 g/L
	Beta-cyfluthrin, pure	25.0 g/L

For further information on the composition see Volume 4.

Montur forte FS 230

Content of active substances:	Beta-cyfluthrin, techn.	82.9 g/L
	Beta-cyfluthrin, pure	80.0 g/L
	Imidacloprid, techn.	154.6 g/L
	Imidacloprid, pure	150.0 g/L

For further information on the composition see Volume 4.

1.4.4.2 Information on the active substances

Bulldock EC 25

Iso common name:	Beta-cyfluthrin
CAS:	68359-37-5 (unstated stereochemistry)
EC (EEC)	269-855-7
CIPAC	482

Montur forte FS 230

Iso common name:	Beta-cyfluthrin
CAS:	68359-37-5 (unstated stereochemistry)
EC (EEC)	269-855-7
CIPAC	482

Iso common name:	Imidacloprid
CAS:	138261-41-3
EC (EEC)	428-040-8
CIPAC	582

1.4.4.3 Information on safeners, synergists and co-formulants

Confidential information, see Volume 4.

1.4.5 Type and code of the plant protection product

Bulldock EC 25

Emulsifiable concentrate (EC)

Montur forte FS 230

Flowable concentrate for seed treatment (FS)

1.4.6 Function

Bulldock EC 25

Beta-cyfluthrin is a pyrethroid insecticide (Mode of Action Group 3A).

Montur forte FS 230

Beta-cyfluthrin is a pyrethroid insecticide (Mode of Action Group 3A).
Imidacloprid is a neonicotinoid insecticide (Mode of Action Group 4A).

1.4.7 Field of use envisaged

Products containing beta-cyfluthrin are used on a large spectrum of crops in agriculture and horticulture for insect control in a variety of vegetable, orchard and arable crops in the field and greenhouse.
The representative uses for the renewal of approval of beta-cyfluthrin include foliar treatment on wheat, potato (field use) and tomato (greenhouse) and seed treatment for beet, as presented in the GAP tables for the two different products Bulldock EC 25 and Montur Forte.

1.4.8 Effects on harmful organisms

Beta-cyfluthrin is an insecticide belonging to the class of synthetic pyrethroids. It is a contact and stomach poison with neurotoxic effects. It produces a rapid knock down effect on various biting and sucking insects. The active substance is not systemic. Beta-cyfluthrin residues are not translocated in the plant. Beta-cyfluthrin predominantly remains on the plant surface (fruit, leaves) or is absorbed into the cuticle.

1.5 Detailed uses of the plant protection product

Please refer to point 1.5.1.

1.5.1 Details of representative uses

List of representative uses evaluated – Bulldock EC 25

GAP rev., date: XX

PPP (product name/code)	**Bulldock EC 25**	**Formulation type:**	**EC**
active substance 1	**beta-cyfluthrin**	**Conc. of as 1:**	**25 g/l**
safener	n.a.	**Conc. of safener:**	**n.a.**
synergist	**n.a.**	**Conc. of synergist:**	**n.a.**
Applicant:	**ADAMA**	**professional use**	☒
Zone(s):	**North, Central, South**	**non professional use**	☐
Verified by MS:	**j**		

1	2	3	4	5	6	7	8	10	11	12	13	14
Use-No.	**Member state(s)**	**Crop and/ or situation** **(crop destination / purpose of crop)**	**F G or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**			**Application rate**			**PHI** (days)	**Remarks:** e.g. safener/synergist per ha e.g. recommended or mandatory tank mixtures
					Method / Kind	Timing / Growth stage of crop & season	Max. number (min. interval between applications) a) per use b) per crop/ season	L product / ha a) max. rate per appl. b) max. total rate per crop/season	g as/ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		
1	North-Zone, Central Zone	Potato	F	Sucking and biting insects	Foliar spray	10-49	2 (14 days)	a) 0.3 l/ha b) 0.6 l/ha	a) 7.5 g as/ha b) 15 g as/ha	150 - 300	3	
2	South Zone	Potato	F	Sucking and biting insects	Foliar spray	10-49	2 (14 days)	a) 0.5 l/ha b) 1 l/ha	a) 12.5 g as/ha b) 25 g as/ha	300 - 1000	3	

1	2	3	4	5	6	7	8	10	11	12	13	14
Use-No.	**Member state(s)**	**Crop and/ or situation** **(crop destination / purpose of crop)**	**F G or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**			**Application rate**			**PHI** (days)	**Remarks:** e.g. safener/synergist per ha e.g. recommended or mandatory tank mixtures
					Method / Kind	Timing / Growth stage of crop & season	Max. number (min. interval between applications) a) per use b) per crop/ season	L product / ha a) max. rate per appl. b) max. total rate per crop/season	g as/ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		
3	North-Zone, Central Zone	Wheat	F	Sucking and biting insects	Foliar spray	Winter cereals BBCH 11-29 (autumn) BBCH 49-75 (spring) Spring cereals BBCH 10-75	2 (14 days)	a) 0.3 l/ha b) 0.6 l/ha	a) 7.5 g as/ha b) 15 g as/ha	150 - 400	21	
4	South Zone	Wheat	F	Sucking and biting insects	Foliar spray	Winter cereals BBCH 11-29 (autumn) BBCH 49-75 (spring) Spring cereals BBCH 10-75	2 (14 days)	a) 0.5 l/ha b) 1 l/ha	a) 12.5 g as/ha b) 25 g as/ha	150 - 400	21	
5	EU	Tomato	G	Sucking and biting insects	Foliar spray	all BBCH up to PHI	2 (14 days)	a) 0.7 l/ha b) 1.4 l/ha	a) 17.5 g as/ha b) 35 g as/ha	500 - 1000	3	

Remarks:

(1) Numeration of uses in accordance with the application/as verified by MS
(2) Member State(s) or zone for which use is applied for
(3) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(4) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(5) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds, developmental stages
(6) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(7) Growth stage of treatment(s) (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(8) The maximum number of applications possible under practical conditions of use for each single application and per year (permanent crops) or crop (annual crops) must be provided
(8) Min. interval between applications (days) were relevant
(10) The application rate of the product a) max. rate per appl. and b) max. total rate per crop/season must be given in metric units (e.g. kg or L product / ha)
(11) The application rate of the active substance a) max. rate per appl. and b) max. total rate per crop/season must be given in metric units (e.g. g or kg / ha)
(12) The range (min/max) of water volume under practical conditions of use must be given (L/ha)
(13) PHI - minimum pre-harvest interval
(14) Remarks may include: Extent of use/economic importance/restrictions/minor use etc.

List of representative uses evaluated – Montur Forte FS 230

GAP rev., date: XX

PPP (product name/code)	**Montur Forte FS 230**	**Formulation type:**	**FS**
active substance 1	**beta-cyfluthrin**	**Conc. of as 1:**	**80 g/kg**
active substance 2	**imidacloprid**	**Conc. of as 2:**	**150 g/kg**
safener	n.a.	**Conc. of safener:**	**n.a.**
synergist	**n.a.**	**Conc. of synergist:**	**n.a.**
Applicant:	**Bayer CropSciences**	**professional use**	☒
Zone(s):	**EU**	**non professional use**	☐
Verified by MS:	**j**		

1	2	3	4	5	6	7	8	10	11	12	13	14
Use-No.	**Member state(s)**	**Crop and/ or situation** **(crop destination / purpose of crop)**	**F G or I**	**Pests or Group of pests controlled** (additionally: developmental stages of the pest or pest group)	**Application**			**Application rate**			**PHI** (days)	**Remarks:** e.g. safener/synergist per ha e.g. recommended or mandatory tank mixtures
					Method / Kind	Timing / Growth stage of crop & season	Max. number (min. interval between applications) a) per use b) per crop/ season	kg, L product / ha a) max. rate per appl. b) max. total rate per crop/season	kg as/ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min / max		
1	EU	Beet	F	Chaetocnema spp Atomaria linearis Agriotes ssp. Pegomyia hyoscyami, Pegomyia betae Scutigerella immaculate Blaniulus guttulatus Aphids Thrips	Seed treatment	00	1	n.a.	IMD: 0.0195 CYB: 0.0104	n.a.	n.a.	Sowing rate: 1.30 u/ha 1 u = 100 000 seeds Dose rate: 0.10 L product/u 0.13 L product /ha

Remarks:

(1) Numeration of uses in accordance with the application/as verified by MS
(2) Member State(s) or zone for which use is applied for
(3) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(4) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(5) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds, developmental stages
(6) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(7) Growth stage of treatment(s) (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(8) The maximum number of applications possible under practical conditions of use for each single application and per year (permanent crops) or crop (annual crops) must be provided
(8) Min. interval between applications (days) were relevant
(10) The application rate of the product a) max. rate per appl. and b) max. total rate per crop/season must be given in metric units (e.g. kg or L product / ha)
(11) The application rate of the active substance a) max. rate per appl. and b) max. total rate per crop/season must be given in metric units (e.g. g or kg / ha)
(12) The range (min/max) of water volume under practical conditions of use must be given (L/ha)
(13) PHI - minimum pre-harvest interval
(14) Remarks may include: Extent of use/economic importance/restrictions/minor use etc.

1.5.2 Further information on representative uses

For the renewal of approval of beta-cyfluthrin, a foliar spray for field and greenhouse uses, and a seed treatment use are supported.
For the foliar sprays the maximum amount of active substance per hectare is 12.5 g/ha for field uses on potato and wheat and 17.5 g/ha for greenhouse use on tomato. For the seed treatment the rate used is 100 mL product/unit of seeds (8 g beta-cyfluthrin/unit, 15 g imidacloprid/unit, 1 unit = 100000 seed). With a maximum of 1.3 units/ha a maximum rate of 10.4 g/ha beta-cyfluthrin (8 g as/unit, max. 1.3 units/ha, 1 unit = 100000 seed) together with 19.5 g/ha imidacloprid (15 g as/unit) would be reached.

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

Bullldock 25 EC is used also in other cereals (rye, triticale, barley, oats) than wheat. It is used in several other cultures (see 1.5.4).

1.5.4 Overview on authorisations in EU Member States

Country	Product	Registered uses	Registration No.	Registration holder
Austria	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: Cereals, oilseed rape, sugar beet, head cabbage, cauliflower	2927	Makhteshim Agan Germany*
Belgium	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: Cereals, oilseed rape, sugar beet, head cabbage	9835P/B	Makhteshim Agan Holland B.V.*
Cyprus	Beta-cyfluthrin 25 g/L, SC	Foliar spray application: apples, pears, peaches, nectarines, vine, olive, peppers, cucumbers, broccoli, potatoes, cotton, sugar beet, alfalfa	2115	Spyros Stavrinides Chemicals Ltd*
Czech Republic	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: potato, sugar beet, cereals, cauliflower, cabbage, oilseed rape	4573-0	Makhteshim Agan Industries Ltd*
Denmark	Beta-cyfluthrin 25 g/L, SC	Foliar spray application: Cereals, oilseed rape, turnip rape, fresh peas (with and without pods but not sugar peas), dried peas, potatoes, sugar and fodder beets, maize for fodder, Brussels sprouts, head cabbage, Chinese cabbage, curly kale, ornamentals, apples, pears, clover for seed and grass for seed	396-42	Makhteshim Agan Holland B.V.*
Estonia	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: potato, cereals, cabbage, oilseed rape	0335	Makhteshim Agan Holland B.V.*

France	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: cereals, head cabbage, oilseed rape, kale, cauliflower, broccoli, beans, peas, flax, potato, apple, vine grapes	9000144; 9900191	Makhteshim Agan France*
Germany	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: Cereals, oilseed rape, sugar beet, head cabbage, cauliflower	3977-00	Makhteshim Agan Germany*
Greece	Beta-cyfluthrin 25 g/L, SC	Foliar spray application: apples, pears, peaches, nectarines, vine, olive, peppers, cucumbers, broccoli, potatoes, cotton, sugar beet, alfalfa	14328; 14387	ALFA AGRICULTURAL SUPPLIES S.A.*
Hungary	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: apple , pepper, potato, cereals, cabbage, tomato, plum, vine	41043	Makhteshim Agan Hungary*
Italy	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: apple, pear, peach, nectarine, apricot, sloe, wine, potatoes, flowering brassica, head cabbage, leafy brassica, cucumber, sweet pepper, aubergine green peas, green beans, onion, shallot, garlic, sugar beet, sweet corn and maize, wheat, alfalfa, tobacco, ornamentals	13820	Makhteshim Agan Italia S.R.L.*
Latvia	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: cereals, potato, cabbages, cauliflower, cruciferour vegetables, apple, oilseed rape, sugar beet	0090	Makhteshim-Agan Holland B.V.*
Lithuania	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: oilseed rape, cereals, potato, apple and pear, cabbage	010/07	Makhteshim-Agan Holland B.V.*
Poland	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: head cabbage, sugar and fodder beet, onion, potato, cereals, oilseed rape, kale, apple, leek, fresh beans and peas, field beans and peas, tomato, forestry	R-86/2010	Makhteshim Agan Poland Sp. Z o.o.*
Portugal	Beta-cyfluthrin 25 g/L, SC	Foliar spray application: potato, cabbages, apple, pear, maize, tomato, sugar beet, vine	3504 0108	Makhteshim Agan Portugal*
Slovakia	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: cereals, oilseed rape, apple	09-05-1034	Makhteshim Agan

Slovenia	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: sugar and fodder beet, cereals, potato, paprika, head cabbage, Chinese cabbage, kale, oilseed rape, tobacco	327-02-158/2003/8	Makhteshim Agan Holding B.V.
Spain	Beta-cyfluthrin 25 g/L, SC	Foliar spray application: alfalfa, cotton, endive, stone fruits, brassica, lettuce, potato, cucumber, sweet pepper, sugar beet, tomato, grapevines, olive, fig tree, ornamentals (herbaceous and bush/tree)	19191	Makhteshim Agan España, S.A.
Sweden	Beta-cyfluthrin 25 g/L, SC	Foliar spray application: potatoes, brassica, green peas, dried peas, oilseed rape, cereals, apple, pear, maize, sugar beet, grass for seed, clover, ornamentals	4365	Makhteshim-Agan Holland B.V.*
United Kingdom	Beta-cyfluthrin 25 g/L, EC	Foliar spray application: cereals, cabbage, cauliflower, oilseed rape, sugar beet	12865	Makhteshim-Agan (UK) Ltd *
Belgium	Montur Forte	Seed treatment: sugarbeet and fodder beet	9615P/B	Bayer CropScience NV/SA
Denmark	Montur Forte FS 230	Seed treatment: sugarbeet and fodder beet	18-510	Bayer CropScience DK
Poland	Montur Forte 230 FS	Seed treatment: sugarbeet and fodder beet	R33/2005	Bayer CropScience AG - GER

Level 2

beta-cyfluthrin

2 Summary of active substance hazard and of product risk assessment

2.1 Identity

2.1.1 Summary of identity

Active substance
Data concerning the identity address sufficiently the requirements of Regulation (EU) No 283/2013.

From toxicological point of view only the new proposed specification can be supported and it is proposed that this should be the new reference specification for the active substance beta-cyfluthrin.

Representative formulations
Data concerning the identity address sufficiently the requirements of Regulation (EU) No 284/2013.

2.2 Physical and chemical properties

2.2.1 Summary of physical and chemical properties of the active substance

Beta-cyfluthrin is an odourless white powder with a melting range of 82-96 °C (pure). No boiling point at atmospheric condition could be determined and its decomposition starts at 210 °C. The vapour pressure of the active substance at 20 °C is 4.5 x 10^{-7} Pa (Isomer II) and 2.2 x 10^{-6} Pa (Isomer IV). The substance as manufactured is neither flammable nor self-heating and it has no explosion or oxidising properties. Beta-cyfluthrin has low water solubility, i.e. 2.1 µg/L (Isomer II) and 1.6 µg/L (Isomer IV) at 20 °C. It does not dissociate in water. Its partition in *n*-octanol / water is 5.9 (Isomer II) / 5.8 (Isomer IV) in logarithmic units.

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

2.2.3 Bulldock 25 EC - foliar spray

Bulldock 25 EC (code MCW-5976) is an emulsifiable concentrate formulation containing 25 g/L beta-cyfluthrin. The formulation is a colourless limpid liquid. It has no explosive, oxidising or flammable properties. Its self-ignition temperature is 436 °C. In aqueous solution, it has a pH value around 7. The accelerated storage stability data indicate a shelf life of at least 2 years at ambient temperature. Its technical characteristics are acceptable for an EC formulation.

2.2.4 Montur Forte - seed treatment

Montur Forte (code 06519113) is a flowable concentrate formulation and its appearance is that of an off-white suspension with a bitter almond-like odour. It has no explosive and no oxidising properties. It has no flash point up to the boiling point and has an auto ignition temperature of 395 °C. The preparation should be regarded as being a surface active material. Its pH value is about 4.5 and in aqueous dilution about 5. Its stability allows storage under practical and commercial conditions.
However, for the storage stability tests of the formulation at elevated and ambient temperature the determination on adhesion to seeds is missing. A test for suspensibility before and after storage of the formulation at ambient temperature is also missing.

2.3 Data on application and efficacy

2.3.1 Bulldock 25 EC - foliar spray

The representative formulation MCW-5976 (Bulldock EC 25) used as a foliar spray in potato (field use), wheat (field use) and tomato (greenhouse use).

2.3.2 Montur Forte - seed treatment

The product Montur Forte FS 230 is used as an insecticide for seed treatment in beet. The active substances beta-cyfluthrin and imidacloprid contained in the product act principally as protectant insecticides. The beet seedlings are protected against soil pests during the sensitive growth stages and against foliar pests until the first insecticide foliar spray is recommended.

2.3.3 Summary of effectiveness

2.3.4 Bulldock 25 EC - foliar spray

Results of efficacy tests carried out for the registration in different European countries and several years of farmers´ use of beta-cyfluthrin gave proof of sufficient efficacy on a large number of biting and sucking pest species in several different crops like oilseed rape, potato, cereals, sugar beet and others.

2.3.5 Montur Forte - seed treatment

The beet seedlings are protected against soil pests during the sensitive growth stages and against foliar pests until the first insecticide foliar spray is recommended. Results of efficacy tests carried out for the registration in different European countries and several years of farmers use of products containing the active ingredients beta-cyfluthrin and imidacloprid gave proof of sufficient efficacy on relevant pest species in beet.

2.3.6 Summary of information on the development of resistance

2.3.7 Bulldock 25 EC - foliar spray

Grain aphids *Sitobion avenae* resistant to pyrethroids including beta-cyfluthrin have been observed in the UK and Ireland. The mechanism correlated with this resistance has been found to be a knockdown resistance (KDR). Reduced efficacy of pyrethroids against this species has also been found in parts of Germany.
Pyrethroid resistance (KDR and super-KDR) has also been reported in the polyphagous aphid *Myzus persicae* in Europe, which occurs on a large number of different crops including potato, oilseed rape and beet.
The Colorado potato beetle *Leptinotarsa decemlineata* is also known to show resistance to pyrethroids in several European countries (metabolic resistance as well as KDR).

2.3.8 Montur Forte - seed treatment

Montur Forte FS 230 contains two chemically different insecticides (a pyrethroid and a neonicotinoid) which act on different molecular target-sites. Between these insecticide groups no cross-resistance is known globally.

No resistance against beta-cyfluthrin is known from non plant-specific soil pests like wireworms. Additionally no resistance against pyrethroids including beta-cyfluthrin is not known from most beet pest insects such as C*haetocnema concina* and *C. tibialis, Atomaria linearis, Pegomyia betae/hyoscyami,* or *Aphis fabae*.
Only the peach-potato aphid or green peach aphid *Myzus persicae* which does also occur on beet, has developed resistance against pyrethroids (KDR and super-KDR). So far no pyrethroid resistance of *Myzus persicae* has been reported in connection with occurrence on sugar beet. However both *Myzus persicae* and *Aphis fabae fabae* (and any other aphid species, which can be considered to show a high-

er risk) are not targeted by the beta-cyfluthrin in Montur Forte FS 230, since no pyrethroid is systemic. Therefore the pyrethroid beta-cyfluthrin remains locally in the soil around the seed and on the seed. It does not come in contact with the aphids.

Imidacloprid, the second active ingredient of Montur Forte FS230 is from the neonicotinoid class, acting agonistically on insect nicotinic acetylcholine receptors located in the central nervous system. Imidacloprid and all other neonicotinoids (IRAC mode of action class 4A) are all supposed to act at the same binding site.
Some insect pests such as whiteflies *Bemisia tabaci* and *Trialeurodes vaporariorum*, the brown planthopper *Nilaparvata lugens*, the green peach aphid *Myzus persicae*, the colorado potato beetle *Leptinotarsa decemlineata* and a few others have developed resistance to neonicotinoids in parts of the world.
There are no reports on neonicotinoid resistance mechanisms in other sucking, chewing and soil pests controlled by imidacloprid in Montur Forte FS 230 used as seed treatment in beet, including thrips and major aphid species occurring in sugar beet such as *Aphis fabae*. The only exception is the recently observed and so far locally developed resistance to neonicotinoid sprays in *M. persicae* in peaches in southern France, northern Spain and northern Italy. This resistance is based on a target-site mutation in the nicotinic acetylcholine receptor ß-subunit. Up to now no reports of resistance are known from any secondary host yet, including sugar beet and vegetables.

2.3.9 Summary of adverse effects on treated crops

2.3.10 Bulldock 25 EC - foliar spray

No phytotoxic effects on treated crops have been observed in the long period of commercial use of beta-cyfluthrin in several countries with a wide range of different crops. No adverse effects on quality or yield of treated crops have been observed.

2.3.11 Montur Forte - seed treatment

No important phytotoxic effects on treated crops have been observed in the long period of commercial use of beta-cyfluthrin and imidacloprid containing product in several countries with a wide range of different crops. No adverse effects on quality or yield of treated crops have been observed.

2.3.12 Summary of observations on other undesirable or unintended side-effects

2.3.13 Bulldock 25 EC - foliar spray

No undesirable or unintended side-effects of the product Bulldock EC 25 have been observed. Experience from the long commercial use of beta-cyfluthrin in a large number of countries with a wide range of crops showed no adverse effects on quality or yield of adjacent crops or succeeding crops, or plants or plant products used for propagation.

2.3.14 Montur Forte - seed treatment

No undesirable or unintended side-effects of the product Montur Forte FS 230 have been described. Experience from the long commercial use in several countries with a wide range of crops showed no adverse effects on quality or yield of adjacent crops or succeeding crops, or plants or plant products used for propagation.

2.4 Further information

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

Handling
Advice on safe handling:
Use only in area provided with appropriate exhaust ventilation.

Advice on protection against fire and explosion:
Dust may form explosive mixture in air. Keep away from heat and sources of ignition.

Hygiene measures:
Avoid contact with skin, eyes and clothing. Keep working clothes separately. Wash hands immediately after work, if necessary take a shower. Remove soiled clothing immediately and clean thoroughly before using again. Garments that cannot be cleaned must be destroyed (burnt).

Storage
Requirements for storage areas and containers:
Store the active substance in the original container. Keep containers tightly closed in a dry, cool and well-ventilated place. Store in a place accessible by authorised persons only.

Advice on common storage:
Keep away from food, drink and animal feeding stuffs.

Suitable materials:
Combination of sheet metal and HDPE (high density polyethylene)

Firefighting measures
Suitable extinguishing media:
Water spray, carbon dioxide, foam, sand

Special hazards arising from the substance or mixture:
In the event of fire the following may be released: Hydrogen chloride (HCl), hydrogen cyanide (hydrocyanic acid), hydrogen fluoride, carbon monoxide (CO), nitrogen oxides (NO_x)

Special protective equipment for fire-fighters:
In the event of fire and/ or explosion do not breathe fumes. In the event of fire, wear self-contained breathing apparatus.

Further information:
Contain the spread of the fire-fighting media. Do not allow run-off from firefighting to enter drains or water courses.

2.4.2 Summary of procedures for destruction or decontamination

Waste disposal according to 91/689/EEC in the corresponding versions (hazardous waste).
Consider classifications (European waste catalogue) 02 01 or 07 04.
Consult the appropriate local authorities regarding special requirements.
Dispose of contents/container in accordance with local/national/international regulations.

2.4.3 Summary of emergency measures in case of an accident

First Aid measures
- Remove patient from exposure/terminate exposure under self-protection (e.g. long gloves).
- Thorough skin decontamination with copious amounts water and soap/detergent, as pyrethroids are not very soluble in plain water. Please note that warm water may increase the subjective severity of the irritation/paresthesia, which is not a sign of systemic posioning.
- Flushing of the eyes with lukewarm water for 15 minutes, apply soothing eye drops, if needed anesthetising eye drops.
- Induction of vomiting should only be considered if a significant amount has been swallowed (more than a mouthful), if the ingestion was less than one hour ago, and if the patient is fully conscious. Induced vomiting can remove maximum 50 % of the ingested substance.

Note: Induction of vomiting is forbidden, if a formulation containing organic solvents has been ingested!

Treatment
- Gastric lavage should be considered in cases of significant ingestions within the first 2 hours; however, the application of activated charcoal and sodium sulphate is always advisable in significant ingestions.
- There is no specific antidote for pyrethroids, any treatment thus can only be symptomatic. Reports from the USA seem to indicate a positive effect of vitamin-E-containing oils on the irritation/paresthesia, however, there is no real proof of this. The skin application of oils or lotions containing vitamin E may be considered. The skin irritation may be painful and require the application of analgesics.
- Anaesthetic eye drops may be required in case of eye contamination after flushing.
- In cases of severe ingestions cardiac and respiratory function should be monitored.
- In case of convulsions diazepam is the anticonvulsant of choice. Thus seizure management should follow standard practice using benzodiazepines (with oxygen and airway protection), if insufficiently effective followed by phenobarbital infusion as required for status epilepticus. A suggested regimen would be: start with 10 to 30 mg diazepam by intravenous injection according to body weight, for children pro rata. This dose is to be repeated every 10 to 30 minutes according to the patient's response.

Contraindications
- Adrenergic compounds (except for CRP) and high dose atropine.
- Pyrethroid poisoning should not be confused with carbamate or organophosphate poisoning.
- If salivation is very strong a single dose of atropine may be of help: 0.6-1.2 mg for adults, 0.02 mg/kg body weight for children. Recovery is spontaneous and without sequelae.

2.5 Methods of analysis

2.5.1 Methods used for the generation of pre-authorisation data

Beta-cyfluthrin content in beta-cyfluthrin technical
The method AM038113FP1 is used for the determination of the diastereomeric purity of beta-cyfluthrin (AE 1430672 / FCR4545). With this method the content of the cyfluthrin diastereomers II and IV (AE 1421342, AE 1421344) can be determined in pure and technical grade beta-cyfluthrin. Alternatively, this method can be used to deliver the diastereomer distribution in area-%. In this case the total content of beta-cyfluthrin has to be determined by another analytical method for content calculation in % w/w.
Principle of the method: All above mentioned diastereomers are separated by high performance liquid chromatography (HPLC) and detected by UV. The content of the diastereoisomers in the test item is calculated by comparison of the individual UV spectra via HPLC-UV/VIS-Diode-Array-Detection with the UV spectra of the corresponding reference item.
The method is considered acceptably validated.

Content of impurities in beta-cyfluthrin
Methods for the determination of diastereomers I and III and impurities in the technical material are available.

Beta-cyfluthrin content in Bulldock 25 EC
Beta-cyfluthrin was determined by HPLC according to CIPAC method 482/EC/M/3 (normal phase HPLC method, CIPAC Handbook H, pg. 48). The active substance content was determined after dispersing the formulated product in 1,4-dioxane and dilution in n-heptane. The separation was achieved by using normal phase liquid chromatography with ultraviolet detection (wavelength: 235 nm), mobile phase n-heptane / methyl tert. butyl ether (97.5/2.5 v/v). Quantitative determination was carried out by

external standardisation.
The analytical method for the determination of beta-cyfluthrin has been fully validated for MCW-5976 (Bulldock 25 EC) in terms of specificity, linearity, precision and accuracy and is therefore considered acceptable.

Beta-cyfluthrin and imidacloprid content in Montur Forte
Beta-cyfluthrin and imidacloprid were determined by HPLC (method AM008706MF1). The components are separated by reversed phase chromatography (XBridge-Phenyl) using gradient elution (1 L water + 5 mL 1N sulfuric acid / acetonitrile). After ultraviolet detection (wavelength: 245 nm), the quantitative evaluation is carried out by comparing the peak areas with those of reference substances using an external standard. The HPLC method AM008706MF1 has been completely validated by checking the parameters linearity, precision, accuracy, specificity and interference from excipients.
The HPLC method for the determination of the content of beta-cyfluthrin and imidacloprid in formulations is considered to be acceptably validated.
The analytical method CIPAC 482 is applicable to the formulation and allows the quantification of the single diastereomers of beta-cyfluthrin.

Beta-cyfluthrin residue analytical methods used for the generation of data for risk assessment
Analytical methods used for pre-authorisation data are evaluated based on Guidance document SANCO/3029/99 rev 4. The methods used in residue studies (field trials, animal feeding and storage stability studies) are completely evaluated and mostly considered as valid.

The best (i.e. most sensitive) analytical method used in field soil dissipation studies of beta-cyfluthrin was considered as barely acceptable. All other methods provided for this purpose are not acceptable, because of insufficient sensitivity.

A particular method for the determination of beta-cyfluthrin in feeding stuffs for birds (see Ecotoxicological studies – Terrestrial vertebrates) was not provided in the dossier. However, the typical high residue amounts in feeding stuffs of such tests do not provoke any analytical difficulties.

Analytical methods used in ecotoxicological studies with aquatic organisms are completely evaluated and considered to be valid for concentrations of 0.005 µg/L beta-cyfluthrin in test water.

A particular method for the determination of beta-cyfluthrin in honey bees was not provided. But analytical methods for the determination of beta-cyfluthrin in matrices of animal origin are completely evaluated and considered as valid also for honey bees.

Most toxicological studies which contain analytical parts are conducted before adoption of SANCO/3029/99 rev.4 from 11/07/00. Such studies are considered acceptable when specific safety factors between typical LOQs (obtained at about 1985) and lowest reported concentrations are maintained. Experimental tests of operator or worker exposure were not conducted.

Studies on analytical methods required for other environmental fate studies are neither provided nor identified by the RMS. Also particular methods for the determination of beta-cyfluthrin in efficacy studies are neither provided nor identified by the RMS.

2.5.2 Methods for post control and monitoring purposes

2.5.2.1 Formulation analysis

see 2.5.1

2.5.2.2 Residue analysis

Evaluation and Assessment

The submitted methods enable the enforcement of beta-cyfluthrin based on the relevant residue definitions and limits listed below:

Matrix	Limit		Comment
Plants and plant products			
Commodities with high water content	0.02	mg/kg	Residue definition: cyfluthrin, including other mixtures of constituent isomers (sum of isomers)
Commodities with high fat content	0.02	mg/kg	
Acidic commodities	0.02	mg/kg	
Dry commodities	0.02	mg/kg	
Animal products			
Meat, fat, liver/kidney	0.05	mg/kg	Residue definition: cyfluthrin, including other mixtures of constituent isomers (sum of isomers)
Milk, egg	0.02	mg/kg	
Soil	0.05	mg/kg	Common limit for non-herbicidal pesticides Residue definition: beta-cyfluthrin
Drinking water	0.1	µg/L	EU drinking water limit; Residue definition: beta-cyfluthrin
Surface water	0.0002	µg/L	based on the EC_{50} for *Hyaella azteca*; Residue definition: beta-cyfluthrin
Air	0.07	µg/m³	based on a proposed AOEL inhalative: 0.000243 mg/kg bw/d, residue definition: beta-cyfluthrin
Tissues	0.1	mg/kg	classified as T+, residue definition: beta-cyfluthrin
Body fluids	0.05	mg/L	classified as T+, residue definition: beta-cyfluthrin

For the assessment of the analytical methods for the determination of beta-cyfluthrin residues the following criteria were used:

- Mean recovery rates and standard deviation at each fortification level according to table 1 of SANCO/825/00 rev. 8.1.
- No interfering blanks (<30 % of the LOQ).
- Methods must employ the simplest approach, involve the minimum cost, and require commonly available equipment.
- The enforcement method for food must be suitable for the determination of all compounds included in the residue definition and must be checked in an independent laboratory.
- The enforcement methods for environmental matrices must be able to analyse for all compounds of toxicological and/or ecotoxicological significance in soil, water and air.
- An additional confirmatory method for all matrices is supplied.
- According to these criteria adequate analytical methods are listed in the Table 2.5-1.

Table 2.5-1: Methods for the determination of residues

Matrix type	Matrix	Method	Limit of quantification		Reference	Owner
Crop	Orange fruit Lettuce head Oil seed rape (seeds) Dry beans (seeds) Wheat grain	00086/M088 (DFG S19) GC-MS, EI VF-5 ms m/z 226, 206, 199, 165	0.01	mg/kg	Weber (2009) (ASB2014-2283) ILV: Merdian (2009) (ASB2014-2281	Bayer CropScience
Crop	Wheat grain Oil seed rape Tomato Grapes	DFG S19 GC-MS, EI DB-5 column m/z 207, 209, 171	0.01	mg/kg	Airs (2013) ASB2014-6696	Bayer CropScience
Crop	Oil seed rape (seeds) Cereal straw Cereal green material Cereal grain Sugar beet leafs Sugar beet body	LC-MS/MS C18 column, ESI+ m/z 451→191	0.01	mg/kg	Schöning (2005), MET2006-93	Bayer CropScience
Animal matrices	Milk Egg Meat Fat	method 00086/M045 (DFG S19) GC-ECD, DB-1 capillary column	0.01	mg/kg	Steinhauer (2002) MET2005-856 ILV: Reichert (2002) MET2005-640	Bayer CropScience
Animal matrices	Liver Kidney	DFG S19 GC-ECD, ZB-Multi Residue-1 capillary column and VF-1701 MS capillary column	0.01	mg/kg	Merdian (2009) ASB2014-2284	Bayer CropScience
Animal matrices	Egg Fat Liver Kidney	method 00086/M045 (DFG S19) GC-ECD, DB-1 capillary column	0.01	mg/kg	Meyer and Zietz (2010) ASB2014-2282	Bayer CropScience
Soil	Standard soil Lufa 2.2	DFG S19 GC-ECD, XTI-5 capillary column	0.05	mg/kg	Weeren and Pelz (1999) MET1999-1227	Bayer CropScience
Soil	Silty clay loam from Filis /France	NCI-GC-MS, HP-5ms capillary column, m/z 207, 209, 171	0.01	mg/kg	Robinson (2014) ASB2014-7708	Bayer CropScience

Matrix type	Matrix	Method	Limit of quantification		Reference	Owner
Water	Accepted for drinking water	Method 01342 LC-MS/MS, C18 column, ESI, m/z 451→191, 451→127	0.01	µg/L	Braune (2012) ASB2014-7713 ILV: Bomke (2013) ASB2014-7714	Bayer CropScience
Air	Air, 35 °C, 81 % rel. humidity, 6 h sampling	Method P 2474G GC-MS/MS, VF-5ms column, EI, m/z 163→127, 226→206	0.069	µg/m³ for each isomer	Bacher (2013) ASB2014-7709	Bayer CropScience
Body fluids	Blood	Method 01127 LC-MS/MS, C18 column, ESI, m/z 451→191, 451→127	0.05	mg/L	Krebber and Braune, (2009) ASB2014-2286	Bayer CropScience
Body tissues	Liver, kidney	DFG S19 GC-ECD, ZB-Multi Residue-1 capillary column and VF-1701 MS capillary column	0.01	mg/kg	Merdian (2009) ASB2014-2284	Bayer CropScience

An overview of the accepted enforcement methods (incl. confirmatory methods and independent lab validation) submitted by the applicant is given in the following table.

Table 2.5-2: Studies submitted by the applicant, which describe appropriate analytical procedures for beta-cyfluthrin (completeness check of analytical methods for monitoring purposes and post-registration control in accordance to guidance document SANCO/825/00 rev. 8.1)

Matrix type/ crop group	Primary Method	Confirmatory method	Independent Lab Validation
Cereals and other dry crops	DFG S19 Weber (2009) ASB2014-2283	DFG S19 Weber (2009) ASB2014-2283 LC-MS/MS Schöning (2005) MET2006-93	DFG S19 Merdian (2009) ASB2014-2281 Airs (2013) ASB2014-6696
Commodities with high water content	DFG S19 Weber (2009) ASB2014-2283	DFG S19 Weber (2009) ASB2014-2283 LC-MS/MS Schöning (2005) MET2006-93	DFG S19 Merdian (2009) ASB2014-2281 Airs (2013) ASB2014-6696
Fruits with high acid content	DFG S19 Weber (2009) ASB2014-2283	DFG S19 Weber (2009) ASB2014-2283	DFG S19 Merdian (2009) ASB2014-2281 Airs (2013) ASB2014-6696

Matrix type/ crop group	Primary Method	Confirmatory method	Independent Lab Validation
Commodities with high fat content	DFG S19 Weber (2009) ASB2014-2283	DFG S19 Weber (2009) ASB2014-2283 LC-MS/MS Schöning (2005) MET2006-93	DFG S19 Merdian (2009) ASB2014-2281 Airs (2013) ASB2014-6696
Commodities which are difficult to analyse	Not required (no intended use in difficult matrices)	Not required (no intended use in difficult matrices)	Not required (no intended use in difficult matrices)
Milk	DFG S19 Steinhauer (2002) MET2005-856	DFG S19 Reichert (2002) MET2005-640	DFG S19 Reichert (2002) MET2005-640
Egg	DFG S19 Steinhauer (2002) MET2005-856	DFG S19 Meyer and Zietz (2010) ASB2014-2282	DFG S19 Meyer and Zietz (2010) ASB2014-2282
Meat	DFG S19 Steinhauer (2002) MET2005-856	DFG S19 Reichert (2002) MET2005-640	DFG S19 Reichert (2002) MET2005-640
Fat	DFG S19 Steinhauer (2002) MET2005-856	DFG S19 Meyer and Zietz (2010) ASB2014-2282	DFG S19 Meyer and Zietz (2010) ASB2014-2282
Kidney/liver	DFG S19 Merdian (2009) ASB2014-2284	DFG S19 Merdian (2009) ASB2014-2284	DFG S19 Meyer and Zietz (2010) ASB2014-2282
Soil	DFG S19 Weeren and Pelz (1999) MET1999-1227	NCI-GC-MS Robinson (2014) ASB2014-7708	Generally not required
Drinking water	Braune (2012) ASB2014-7713	Braune (2012) ASB2014-7713	Bomke (2013) ASB2014-7714
Surface water	missing	missing	Generally not required
Air	Bacher (2013) ASB2014-7709	Bacher (2013) ASB2014-7709	Generally not required
Body fluids	Krebber and Braune (2009) ASB2014-2286	Krebber and Braune (2009) ASB2014-2286	Generally not required
Body tissues	Merdian (2009) ASB2014-2284	Merdian (2009) ASB2014-2284	Generally not required

This overview shows that for residues in all types of plant and animal products and for residues in soil, drinking water, air as well as for residues in body fluid and tissues sufficiently validated analytical methods and confirmatory methods are available. For surface water sufficiently validated primary and confirmatory methods are missing, which allow the determination of 0.0002 µg/L beta-cyfluthrin.

2.6 Effects on human and animal health

2.6.1 Justification for Read-across between toxicological studies on cyfluthrin and beta-cyfluthrin

Cyfluthrin (FCR 1272) and beta-cyfluthrin (FCR 4545) have the same chemical structure (see figure below). The common molecular structure shows three asymmetric carbon atoms. These lead to four diastereomers, each consisting of an enantiomer pair. While cyfluthrin consists of all four diastereomers (referred to as diastereomer I, II, III and IV), beta-cyfluthrin consists of the two most active diastereomers II and IV. Bridging of the properties of cyfluthrin and beta-cyfluthrin is considered scientifically appropriate and was generally accepted due to the very similar toxicological profile. Therefore, it is concluded that studies with cyfluthrin might be applied for beta-cyfluthrin risk assessment. Additional studies on absorption, distribution, metabolism and excretion generated for this submission give further support to this concept.

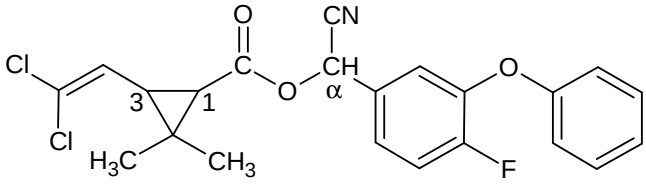


Figure 2.6-1: Diastereoisomeric pairs of beta-cyfluthrin

Table 2.6-1: Stereoisomers in cyfluthrin and beta-cyfluthrin

Diastereomer	Cyfluthrin			Beta-cyfluthrin
I.	1R - 3R - αR			
	1S - 3S - αS			
II.	1R - 3R - αS			
	1S - 3S - αR			
III.	1R - 3S - αR			Beta-cyfluthrin
	1S - 3R - αS			(FCR 4545)
IV.	1R - 3S - αS			
	1S - 3R - αR			

2.6.2 Summary of absorption, distribution, metabolism and excretion in mammals

The EU dossier submitted for Annex I inclusion of beta-cyfluthrin contained ADME studies conducted with radiolabeled cyfluthrin (see Table 2.6-2). Three new ADME studies (absorption, distribution, metabolism and excretion; [redacted] 2013a (ASB2014-7716), 2013b (ASB2014-7718), 2014 (ASB2014-7717)) conducted with radiolabeled beta-cyfluthrin are additionally provided here and summarised under Table 2.6-3. No significant differences in toxicokinetic behaviour compared to cyfluthrin were observed. Thus the toxicokinetic data on cyfluthrin are considered representative for beta-cyfluthrin, further supporting a bridging of toxicological data.

[redacted] (2013b, ASB2014-7718) investigated the metabolic fate of the cyclopropyl-moiety of the molecule ([cyclopropane-1-^{14}C] beta-cyfluthrin), also using PEG 300 as a vehicle. This moiety was not investigated in the older dataset on cyfluthrin and is thus considered to complete the assessment of the metabolic fate of beta-cyfluthrin.
To address an additional point in the new data requirements of Regulation 283/2013, a comparative *in vitro* metabolism study in rat/human liver microsomes has been included ([redacted] 2014, ASB2014-7719). All metabolites observed with human material have also been observed in rat cells. It is thus concluded that the available safety dataset in the rat is relevant and that there is no unique human metabolite that would deserve further attention in risk assessment.
A literature research for the Renewal Assessment Report (RAR) including publications from the last 10 years was performed by the RMS. The publications were considered as supplemental information (see Table 2.6-4).

Absorption:
The previously evaluated studies with cyfluthrin on rats showed a high degree of absorption (approximately 90 %: 50 % urinary, 12 % faecal, 33 % biliary, a fraction of the total amount via the bile was subject to an enterohepatic circulation) of the radioactivity. The biliary value is based on the experiments with bile cannulated animals. Unfortunately, from the three new toxicokinetic studies information about radioactivity present in bile was not provided since the animals were not bile cannulated. Therefore, it cannot be assumed that this proportion represents material which had undergone systemic absorption. For beta-cyfluthrin a minimum absorption of 60 % can be derived from these studies (single oral low and high dose: 0.5 and 10 mg/kg bw).
The extent of absorption depends largely on the polarity of the formulation vehicle. Cyfluthrin in Cremophor EL/distilled water is absorbed faster (maximum 1 hour) and more intensively than cyfluthrin in polyethylene glycol 400 (maximum 6 hours). Accordingly, rats receiving cyfluthrin in Cremophor EL/distilled water showed signs of toxicity (i.e. hypersalivation, piloerection, diarrhea) whereas rats receiving cyfluthrin in polyethylene glycol 400 had no symptoms ([redacted] 1982, RIP9400865).
Approximately one third of the retrieved radioactivity was excreted via bile fluid during the first 2 hours and more than 90 % within the first 6 hours post application. Relating these results to the faecal excretion of intact rats following both routes of administration, it can be stated that at least one half of the faecally excreted radioactivity is due to an absorbed and biliary eliminated amount. A part of the biliary radioactivity is subject to entero-hepatic circulation ([redacted] 1983, RIP9400867).

Distribution:
The radioactivity is slowly distributed into the tissues and the distribution of radioactivity from the intravascular space into the tissues is low ([redacted] 1983, RIP9400867; [redacted] 1983, RIP9400866). The highest values were found in fatty tissue, adrenals, kidney and liver in each case. At the end of the studies (up to 10 days after administration) very low levels were found in the brain, spleen, testes, erythrocytes and plasma. Maximum relative plasma concentrations were reached 2 hours after oral administration of the low dose or the high dose. The plasma concentrations were around 1.2 times higher in the females than those measured in the males ([redacted] 1983, RIP9400867, [redacted], 2013a (ASB2014-7716), 2013b (ASB2014-7718), 2014 (ASB2014-7717)).
After oral administration of 10 mg/kg bw cyfluthrin, at the time of maximum plasma level (1.5 hours after administration) values in the liver and in the kidneys were markedly higher in comparison to other organs/tissues. Parallel to the onset of excretion in urine and bile, a slow redistribution of radio-activity into the fatty tissue occurs ([redacted] 1983, RIP9400866).

Metabolism:
The new studies submitted for renewal were conducted with beta-cyfluthrin. The test substance was either radiolabelled in the fluorophenyl- ([redacted], 2014, ASB2014-7717) or in the cyclopropyl-moiety ([redacted], 2013b, ASB2014-7718), of the molecule.
The investigation of the metabolite pattern in urine and faeces revealed that beta-cyfluthrin was extensively metabolised independent of dose and sex.
When radiolabelled in the cyclopropyl-moiety urinary metabolite pattern consisted of at least 6 metabolite fractions.

The main metabolites in urine are a glucuronide conjugate of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DCVA acyl glucuronide, 26.3 - 39.1 % of recovered radioactivity) and cis/trans DCVA (25.7 - 48.8 %). All other fractions were ≤3 % of dose. No unchanged parent was detected in urine whereas it was the major test-related material found in faeces.
The faecal metabolite pattern revealed at least 9 metabolite fractions. The metabolite pattern was dominated by three major fractions: cis/trans DCVA accounted for 7.9 and 8.4 % in males for the high and low dose respectively, and for 4.6 and 4.7 % in females for the high and low dose, respectively. Unchanged beta-cyfluthrin was found from 14.9 - 7.7 % in males for the high and low dose, respectively, and from 26.5 - 7.6 % in females for the high and low dose, respectively. The proposed metabolic pathway is the following: beta-cyfluthrin → DCVA → DCVA glucuronide conjugate ([redacted], 2013b, ASB2014-7718).
When radiolabelled in the fluorophenyl-moiety the main metabolites in urine after 48 h are a sulphate conjugate of OH-FPB (46.7 % of recovered radioactivity), its free form (2 %) and FPB-acid (14.6 %). Only 0.5 % unchanged parent compound was detected in the urine while the parent compound was the major test substance related material detected in faeces (20.03 %) ([redacted], 2014, ASB2014-7717).
In metabolism studies with cyfluthrin, 65 – 72 % of the recovered radioactivity in the dose groups A and B (both single low dose) and approximately 82 % in the dose groups C (multiple low dose groups) and D (single high dose) which were eliminated via the urine and faeces could be identified. The main metabolites were a conjugate of 4'-hydroxy-4-fluoro-3-phenoxybenzoic acid (OH-FPB acid; 51 – 52 % of recovered radioactivity), its free form ("FCR 3145", 3.0 - 5.0 % of recovered radioactivity) and 4-fluoro-3-phenoxybenzoic acid (FPB-acid, approx. 10 % of recovered radioactivity). The unchanged parent compound FCR1272 accounted for approximately half of the faecally eliminated portion ([redacted] 1983, RIP9400868).
The first step in the process of biotransformation is the cleavage of the ester bond and oxidation to FPB-acid, which then undergoes further hydroxylation and conjugation or is bound to glycine with formation of the appropriate hippuric acids. Depending upon the dose groups, unchanged parent compound and metabolites account for 65 – 82 % of the recovered radioactivity and 4 – 8 % of the radio-activity was unextractable. The metabolism is slightly dose-dependent, with the proportion of the OH-FPB acid conjugate decreasing with dose and the proportion of FPB-acid increasing with dose.
A common metabolic scheme for cyfluthrin in rats, hens and cows has been established and is depicted in Figure 2.6-2.
As demonstrated in the bile cannulation study with cyfluthrin, the parent found in faeces was absorbed and subject to enterohepatic circulation. Like with cyfluthrin, the first step in the process of biotransformation is the cleavage of the ester bond and oxidation to FPB-acid, which then undergoes further hydroxylation and conjugation. Unchanged parent compound and metabolites account for 25.46 % after 48 hours of the recovered radioactivity and 1.13 % of the radioactivity was unextractable. A metabolic scheme for beta-cyfluthrin in rats has been established and is depicted in Figure 2.6-3.
Moreover, a comparative *in vitro* metabolism study of [fluorophenyl-UL-^{14}C] beta-cyfluthrin ([redacted] 2014, ASB2014-7719) revealed that after adding to liver microsomes [^{14}C] beta-cyfluthrin was rapidly and more extensively metabolised in rat than in human liver microsomes. All metabolites observed with human material have also been observed in rat material. It is thus concluded that the available safety dataset in the rat is relevant and there is no unique human metabolite that would deserve further attention in risk assessment.

Elimination:
Cyfluthrin and beta-cyfluthrin are eliminated fast from the body. Thus, > 97 % of the orally and intravenously administered dose had been eliminated from the body after two days.
Beta-cyfluthrin and cyfluthrin were predominantly excreted via urine and faeces (renal/faecal: approx. 2:1). Excretion via expired gases is small, 48 hours after the oral administration of 10 mg/kg bw cyfluthrin, less than 0.001 % of the administered dose is expired ([redacted] 1983, RIP9400866). The amount of radioactivity excreted is proportional to the dose levels tested and independent of the sex of the animals.

Accumulation:
The kinetics of excretion of cyfluthrin and beta-cyfluthrin, as well as the concentration curves in the

individual tissues and organs, indicate that these substances do not accumulate, but are continuously eliminated.

Table 2.6-2: ADME studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study Type	Test substance Dosing regime	Scope of study	Reference
Comparative study of rats on absorption of FCR 1272 after single oral administration in polyethylene glycol 400 or Cremophor EL/water as formulation vehicle. (GLP: no; guideline: no, not acceptable)	Cyfluthrin, isomer ratio: I 26.6 %; II 19.1 %; III 33.7 %; IV 20.6 %; purity not reported. 10 mg/kg bw (one single oral dose, ♂ only) Different vehicles: Polyethylene glycol 400 and Cremophor EL/distilled water	Provides comparative data on oral uptake from different vehicles (PEG400 and Cremophor/water): The higher toxicity of cyfluthrin in Cremophor EL/distilled water is caused by faster and higher absorption.	[redacted] (1982) RIP9400865
Fluorophenyl-UL-14C cyfluthrin (FCR 1272) biokinetic study in rats. GLP: no; guideline, partly OECD TG 417	Cyfluthrin, cis/trans ratio of 42/58, purity: 97.5 % a) 0.5 mg/kg bw (single i.v. or intraduodenal, ♂), b) 0.5 mg/kg bw (single oral, ♂), c) 10 mg/kg bw (single oral, ♂) d) 0.5 mg/kg bw (single oral, ♀)	Information on accumulation, absorption, excretion, and distribution over 10 days	[redacted] (1983) RIP9400866
Biokinetic part of the general metabolism studies in the rat. GLP: no; guideline according to EPA specifications compatible to Directive 87/302/EEC, Part B.	Cyfluthrin, cis/trans ratio of 42/58, purity: 97.5 % Vehicle: Cremophor/saline Administration (♂ only): a) 0.5 mg/kg bw (single i.v. or intraduodenal) b) 0.5 mg/kg bw (single oral) c) 0.5 mg/kg bw/day (oral: 14 nonradioactive doses + single radioactive dose) d) 10 mg/kg bw (single oral)	Provides mass balance and distribution of radiolabel in excreta and carcass following different routes of administration.	[redacted] (1983) RIP9400867
[Fluorobenzene-UL-^{14}C]cyfluthrin: Metabolism part of the general metabolism studies in the rat. GLP: no; guideline according to EPA specifications	Cyfluthrin, cis/trans ratio of 42/58, radiochemical purity: 98 % Vehicle: Cremophor/saline Administration (♂ only): a) 0.5 mg/kg bw (single i.v.) b) 0.5 mg/kg bw (single	Identification of metabolites in excreta	[redacted] (1983) RIP9400868

Study Type	Test substance Dosing regime	Scope of study	Reference
compatible to Directive 87/302/EEC, Part B.	oral) c) 0.5 mg/kg bw/day (oral: 14 nonradioactive doses + single radioactive dose) d) 10 mg/kg bw (single oral)		
Thiocyanate excretion in rats' urine after intraperitoneal administration of FCR 1272 and decamethrin in comparable doses and after exposure to defined FCR 1272 concentrations in the inhalation air. (GLP: no, Guideline: no, supplemental)	Cyfluthrin, isomer ratio: I 24.9 %; II 17.9 %; III 30.0 %; IV 22.2 %; purity: 95 %; Decamethrin purity: 99.2 % 0, 1, 5, 10, 15 mg/kg bw i.p. (♂ only); 0, 59, 93, 180 mg/m³ inhalative (♂+♀)	Focus on thiocyanate excretion in urine following i.p. and inhalation exposure of cyfluthrin and decamethrin	[redacted] (1981) RIP9400855
Biotransformation of [F-phenyl-UL-14C]cyfluthrin; characterisation and preliminary identification of the metabolites. (GLP: no, Guideline: no)	Cyfluthrin, cis/trans ratio of 42/58, radiochemical purity: 98 % 10 mg/kg bw oral (only ♂); vehicle not reported	Preliminary study for identification of urinary metabolites	[redacted] (1982) RIP9400862

Table 2.6-3: ADME studies submitted for Renewal Assessment Report (RAR)

Study Type	Test substance Dosing regime	Scope of study	Reference
Absorption, Distribution and Excretion of [fluorophenyl-UL-^{14}C] beta-cyfluthrin in Male Rats After Single Oral Administration at One Dose Level GLP: yes; OECD TG 417	Beta-cyfluthrin, fluorophenyl-UL-^{14}C, radiochemical purity 99.3 % 10 mg/kg bw (single oral) Vehicle: Cremophor EL	Absorption, tissue distribution, excretion pattern und kinetics. No metabolism.	[redacted] (2013a) ASB2014-7716
Absorption, Distribution, Excretion and Metabolism of [fluorophenyl-UL-^{14}C] Beta-cyfluthrin in Male Rats After Single Oral Administration at One	Beta-cyfluthrin, fluorophenyl-UL-^{14}C, radiochemical purity 99.3 % 10 mg/kg bw (single oral) Vehicle: PEG400	Absorption, tissue distribution, metabolism, excretion pattern und kinetics	[redacted] (2014) ASB2014-7717

Study Type	Test substance Dosing regime	Scope of study	Reference
Dose Level. GLP: yes; OECD TG 417			
Absorption, Distribution, Excretion and Metabolism of [cyclopropane-1-^{14}C] Beta-cyfluthrin in Male and Female Rats After Single Oral Administration at Two Dose Levels. GLP: yes; OECD TG 417	Beta-cyfluthrin, cyclopropane-1-^{14}C, radiochemical purity 99.3 % 0.5, 10 mg/kg bw (single oral) Vehicle: PEG400	Absorption, tissue distribution, metabolism, excretion pattern und kinetics	[redacted] (2013b) ASB2014-7718
Comparative *in vitro* Metabolism of [fluoro-phenyl-UL-^{14}C] beta-cyfluthrin in Rat and Human Liver Microsomes. GLP: yes, Guideline: no	Beta-cyfluthrin, fluorophenyl-UL-^{14}C, radiochemical purity 99.3 % 10 µM	*In vitro* comparison of metabolism in rat and human liver microsomes	[redacted] (2014) ASB2014-7719

Table 2.6-4: Literature research for the Renewal Assessment Report (RAR):

Study Type	Test substance Dosing regime	Scope of study	Reference
In vitro metabolism of pyrethroid pesticides by rat and human hepatic microsomes and cytochrome P450 isoforms	Beta-cyfluthrin and other pyrethroid purity >98 %, different vehicles	*In vitro* metabolism in rat and human microsomes	Scollon et al. (2009) ASB2015-931
Differential induction of cytochrome P450 isoforms and peroxisomal proliferation by cyfluthrin in male Wistar rats	Cyfluthrin, purity 94 % 10 or 20 mg/kg bw (single oral), vehicle: corn oil	Peroxisome proliferator, effects on hepatic CYP1A, CYP4A subfamilies	Anadón et al. (2013) ASB2015-926

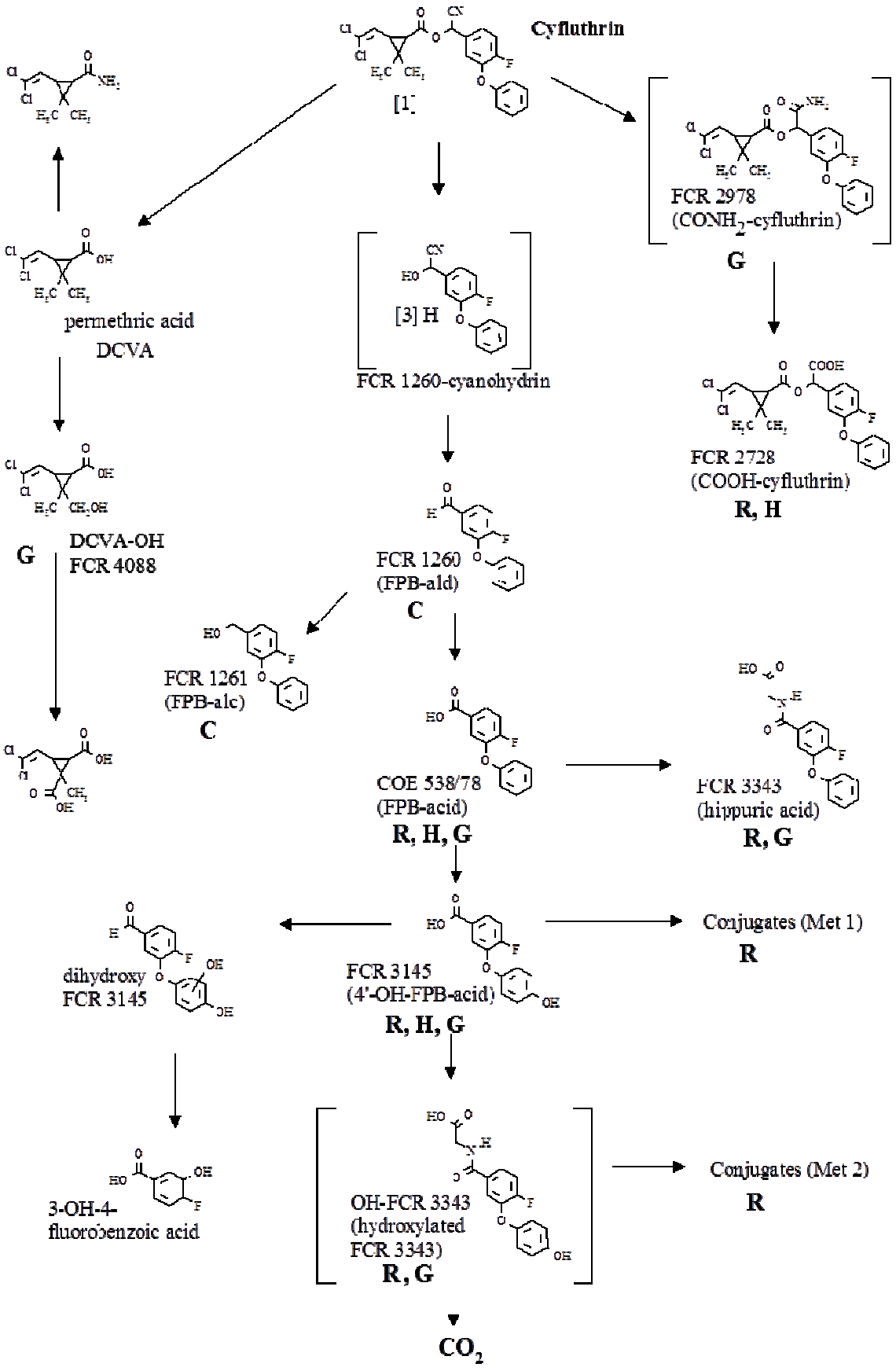


Figure 2.6-2: **Proposed metabolic pathway for cyfluthrin in rats (R), laying hens (H), cows (C) and goats (G)**

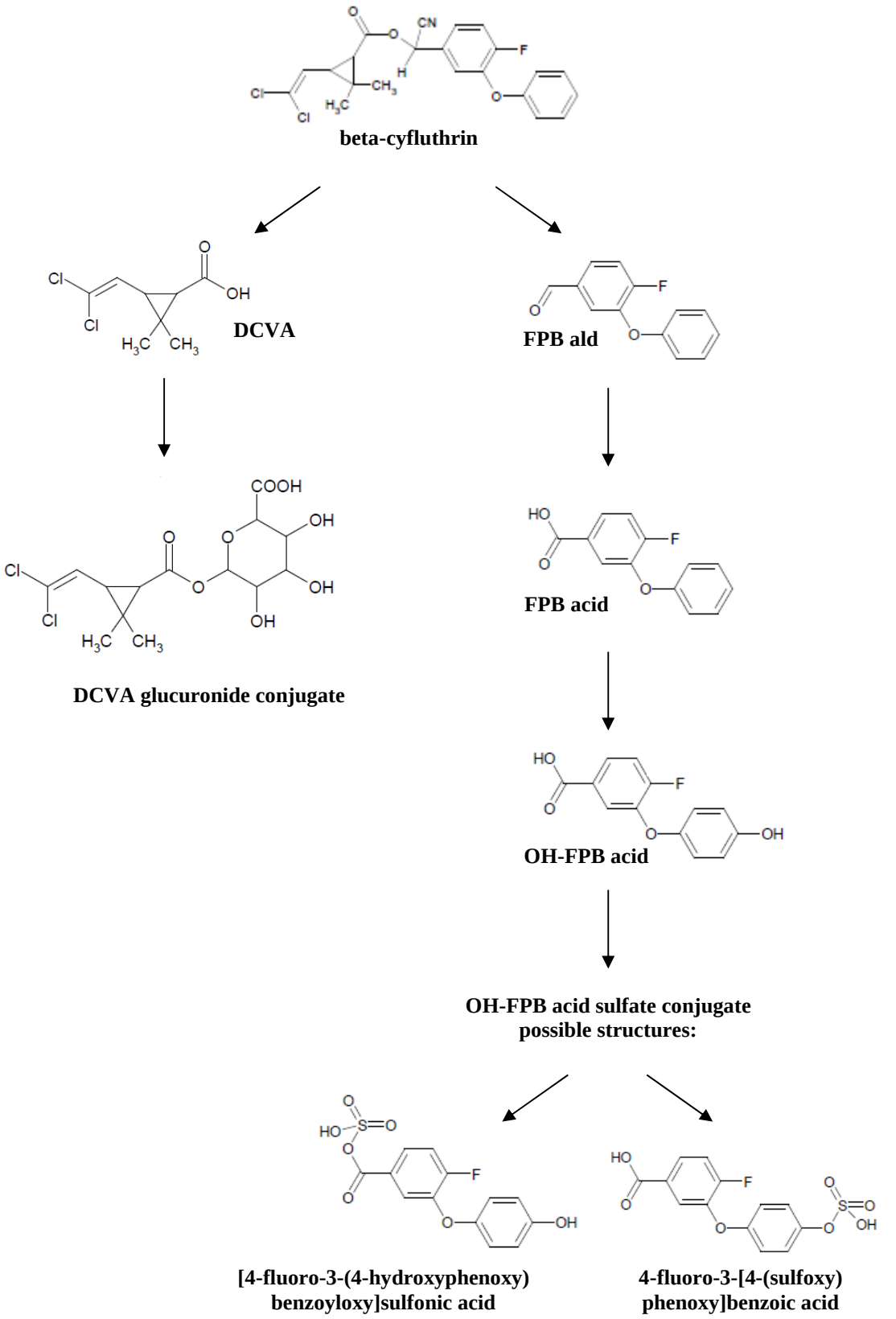


Figure 2.6-3: Proposed metabolic pathway for beta-cyfluthrin in rats

Table 2.6-5: Toxicokinetics and metabolism in rats - Excretion of total radioactivity and radioactive residues in the rat 48 hours after application of [fluorophenyl-UL-14C] cyfluthrin (values are given in % of recovered radioactivity) (Vol.3, Table B.5.1.1.1-1)

Report	Administration	Dose [mg/kg bw]	Sex	CO_2	Bile	Urine	Faeces	Total excreted	Ratio Urine/ Faeces	Body without GIT	GIT	Recovery (% of applied)
[redacted] 1983 RIP9400867	intraduodenal	0.5	m	-	33	54	12	99	4.5	0.5	0.15	103
	oral[1)]	10	m	<0.001	-	67	31	98	2.2	1.3	0.27	106
	Intravenous	0.5	m	-	-	69	24	93	2.9	5.6	0.74	94
	Oral	0.5	m	-	-	74	25	99	3.0	1.1	0.22	93
	pretreat. Oral	0.5	m	-	-	73	26	99	2.8	1.2	0.24	91
	Oral	10	m	-	-	66	33	99	2.0	1.4	0.23	99
	Oral	10	f	<0.001	-	67	31	98	2.2	2.1	0.42	98
	Intravenous	0.5	f	-	-	65	28	93	2.3	6.5	0.78	93
	Oral	0.5	f	-	-	61	37	98	1.6	1.6	0.59	101
	pretreat. Oral	0.5	f	-	-	63	36	99	1.8	1.2	0.32	96
	Oral	10	f	-	-	52	45	97	1.2	1.6	0.45	101
[redacted] 1983, RIP9400866	intraduodenal	0.5	m	-	33.5	54.2	11.6	99.3	4.7	0.5	0.15	103.1
	oral[1)]	10	m	<0.001	-	59.1	39.3	98.4	1.5	1.4	0.30	95.0
	Intravenous	0.5	m	-	-	69.5	24.1	93.6	2.9	5.7	0.75	93.5
	Oral	0.5	m	-	-	74.2	24.5	98.7	3.0	1.1	0.21	93.8
	Oral	0.5	f	-	-	61.7	36.7	97.4	1.7	1.6	0.60	99.3
	Oral	10	m	-	-	65.9	32.4	98.3	2.0	1.4	0.25	99.4
[redacted] 1983,	Intravenous	0.5	m	-	-	67.0	26.6	93.6	2.5	6.4		90.0
	Intravenous	0.5	f	-	-	65.2	25.3	90.5	2.6	9.5		87.6

Report	Administration	Dose [mg/kg bw]	Sex	CO_2	Bile	Urine	Faeces	Total excreted	Ratio Urine/ Faeces	Body without GIT	GIT	Recovery (% of applied)
RIP9400868	Oral	0.5	m	-	-	73.0	25.7	98.7	2.8	1.3		97.1
	Oral	0.5	f	-	-	61.4	36.5	97.9	1.7	2.1		94.0
	pretreat. oral	0.5	m	-	-	71.8	26.7	98.5	2.7	1.5		87.4
	pretreat. oral	0.5	f	-	-	62.2	35.4	97.6	1.8	2.4		93.6
	Oral	10	m	-	-	65.0	33.4	98.4	1.9	1.6		94.8
	Oral	10	f	-	-	59.6	37.8	97.4	1.6	2.6		96.9

GIT: gastrointestinal tract;
[1)] Preliminary study to assess the volatility of cyfluthrin.

Table 2.6-6: Toxicokinetics and metabolism in rats - Relative concentration of radioactivity (P) in individual parts of the body of rats after application of [fluorophenyl-UL-14C] cyfluthrin (all values are multiplied with the factor 100)

Report	Administration	Dose (mg/kg bw)	Sex	Time (h)	Body without GIT	Plasma	Erythrocytes	Testes or Ovaries	Femur	Brain	Skin	Heart	Spleen	Liver	Kidney	Renal fat	Adrenal
[redacted] 1983 RIP9400867	intravenous	0.5	m	48	6	17	4,5	1,2	2.0	0.6	6.2	3.4	13	14	5.4	53	16
	Oral	0,5	m	48	1.1	0.94	0.2	0.16	0.38	0.065	1.3	0.26	0.54	2.0	1.1	16	1.4
	pretreat.oral	0.5	m	48	1.3	1.1	0.31	0.18	0.23	0.057	1.8	0.27	0.36	2.1	1.3	9	2.3
	Oral	10	m	48	1.6	0.86	0.44	0.21	0.42	0.07	1.8	0.29	0.27	2.5	1.3	18	1.6
	intravenous	0.5	f	48	6.6	18	4.7	2.7	2.8	0.57	9.7	3.9	16	15	7.4	33	24
	Oral	0.5	f	48	1.8	3.2	0.56	3.2	0.54	0.13	2.2	0.67	0.48	3.4	3.2	12	3.9
	pretreat.oral	0.5	f	48	1.3	2.4	0.47	1.6	0.39	0.077	1.8	0.51	0.24	2.3	2.0	5.3	1.5
	Oral	10	f	48	1.8	2.6	0.52	3.0	0.43	0.12	2.5	0.8	0.36	3.0	2.7	11	2.4
[redacted] 1983, RIP9400866	Oral	10	m	1.5	44	220	48	16	15	-	35	-	22	170	130	36	73
	Oral	10	m	4	33	130	30	16	10	-	29	-	14	100	85	60	32
	Oral	10	m	8	21	65	12	11	5.5	-	18	-	5.8	51	46	42	10
	Oral	10	m	24	4.7	12	2.6	2.2	1.6	-	5.0	-	1.6	8.3	7.0	24	5.3
	Oral	10	m	48	2.0	1.6	0.51	0.35	0.72	-	1.9	-	0.61	2.8	1.5	22	10
	Oral	10	m	72	1.1	0.49	0.18	0.1	0.52	-	1.1	-	0.14	1.8	0.7	17	0.89
	Oral	10	m	144	0.5	0.24	0.064	0.061	0.39	-	0.29	-	0.059	0.9	~0.35	8.4	0.79
	Oral	10	m	240	0.26	0.061	0.037	0.017	0.14	-	~0.13	-	0.016	~0.43	0.13	6.1	~0.19

P= measured activity / g tissue or plasma administered activity / g bw

Table 2.6-7: Toxicokinetics and metabolism in rats - Distribution of metabolites in the excreta of rats 48 hours after administration of [fluoro-phenyl-UL-14C]cyfluthrin. (values are given in % of the recovered radioactivity = > 87 % of applied)

Report	Administra-tion	Dose (mg/kg)	Excretion	Sex	Met.1 ❶	FCR 3145	Met. 2 ❷	FCR 3343	COE 538/78	FCR 1272	un-known	unex-tractable	Total
[redacted] 1983, RIP94008 68	intravenous	0.5	Urine	m	47.0	2.9	1.5	2.4	12.1	-	1.1	-	67.0
	intravenous	0.5	Faeces	m	0.1	1.9	0.1	-	-	0.4	24.1	8.0	26.6
			∑		47.1	4.8	1.6	2.4	12.1	0.4	25.2	8.0	93.6
	intravenous	0.5	Urine	w	44.4	4.4	1.5	2.3	10.8	-	1.8	-	65.2
	intravenous	0.5	Faeces	w	0.2	4.9	-	-	0.3	0.5	12.1	7.3	25.3
			∑		44.6	9.3	1.5	2.3	11.1	0.5	13.9	7.3	90.5
	oral	0.5	Urine	m	52.0	3.8	2.1	3.6	10.1	-	1.4	-	73.0
	oral	0.5	Faeces	m	-	1.1	0.1	-	-	0.1	19.5	4.9	25.7
			∑		52.0	4.9	2.2	3.6	10.1	0.1	20.9	4.9	98.7
	oral	0.5	Urine	w	41.1	3.9	2.6	2.4	9.9	-	1.5	-	61.4
	oral	0.5	Faeces	w	-	4.6	0.4	0.2	0.3	0.1	23.9	7.0	36.5
			∑		41.1	8.5	3.0	2.6	10.2	0.1	25.4	7.0	97.9
	pretr.oral	0.5	Urine	m	47.4	3.2	3.0	6.7	10.5	-	1.0	-	71.8
	pretr.oral	0.5	Faeces	m	-	0.8	0.1	-	0.1	11.6	8.9	5.2	26.7
			∑		47.4	4.0	3.1	6.7	10.6	11.6	9.9	5.2	98.5
	pretr.oral	0.5	Urine	w	41.8	4.4	2.9	2.7	8.3	-	2.1	-	62.2
	pretr.oral	0.5	Faeces	w	-	6.4	-	0.3	-	16.2	8.9	3.6	35.4
			∑		41.8	11.0	2.9	3.0	8.3	16.2	11.0	3.6	97.6
	oral	10	Urine	m	35.9	1.8	0.8	0.5	24.1	-	1.9	-	65.0

Report	Administra-tion	Dose (mg/kg)	Excretion	Sex	Met.1 ❶	FCR 3145	Met. 2 ❷	FCR 3343	COE 538/78	FCR 1272	un-known	unex-tractable	Total
	oral	10	Faeces	m	-	1.2	-	0.4	-	16.6	10.2	5.0	33.4
			∑		35.9	3.0	0.8	0.9	24.1	16.6	12.1	5.0	98.4
	oral	10	Urine	w	35.2	4.5	2.1	17.3		-	0.5	-	59.6
	oral	10	Faeces	w	-	4.3	-	-		19.0	9.5	5.0	37.8
			∑		35.2	8.8	2.1	17.3		19.0	10.0	5.0	97.4

❶: Conjugate of FCR 3145
❷: Probably conjugate of hydroxylated FCR 3343.

2.6.3 Summary of acute toxicity

The experimental oral LD_{50} values are covering a broad range. This finding could be evoked by different factors:
First, the acute oral toxicity seems to be dependent on the vehicle used. This may be due to different polarity leading to modified absorption in the gastrointestinal tract. Furthermore, beta-cyfluthrin generally possesses vehicle-dependent a higher acute oral toxicity than cyfluthrin. This observation could be inferred from its particular isomer composition (beta-cyfluthrin: more toxic isomer 2 and only little amount of less toxic isomer 3, Vol. 3, B.6.8). The results are compiled in Table 2.6-8 and Table 2.6-10.
The lowest LD_{50} values determined in acceptable studies with beta-cyfluthrin were 77 mg/kg bw (acetone/peanut oil) in rats and 91 mg/kg bw (PEG 400) in mice. The lowest LD_{50} values determined in acceptable studies with cyfluthrin were 14.3 mg/kg bw (Cremophor/water) in rats and 291 mg/kg bw (PEG 400) in mice ([redacted] 1982, TOX9401946). The classification for acute oral toxicity was based on cyfluthrin (solvent: Cremophor/water). Furthermore, there are indications that beta-cyfluthrin tested in Cremophor/water leads to the same classification (Vol. 3, B.6.2). The applicant disagrees with the decision to use this value for classification and labelling due to the fact that Cremophor enhances the absorption of drugs. Further the applicant stated that for pyrethroids, data generated using an oil based vehicle are best suited for references purposes. Therefore, the LD_{50} value of 77 mg/kg bw, the lowest value generated using acetone/peanut oil as vehicle is the most appropriate scientifically for classification and labelling purposes.
However, the RMS is still of the opinion that the classification for acute oral toxicity should be based on an LD_{50} value of 14.3 mg/kg bw cyfluthrin in solvent cremophor/water. This is consistent with the actual CLP regulation, which states “If there are different LD_{50} values from tests using different vehicles, generally the lowest valid value would be the basis for classification”.

The dermal toxicity of beta-cyfluthrin and cyfluthrin is very low (Table 2.6-8 and Table 2.6-10). The lowest dermal LD_{50} value in rats determined in an acceptable study with beta-cyfluthrin was used for classification decision (>2000 mg/kg bw, solvent: PEG 400).
The LC_{50} values of beta-cyfluthrin and cyfluthrin were determined in rodents after exposure to either dust or aerosol (Table 2.6-8 and Table 2.6-10). Based on the worst-case LC_{50} value determined in an acceptable inhalation study, the LC_{50} value in rats used for classification was 0.081 mg/L air (beta-cyfluthrin in ethanol/PEG 400, 4h-exposure, head-nose only). The lowest rat LC_{50} value after dust exposure was 0.532 mg/L air (beta-cyfluthrin, 4h-exposure, head-nose only).
Beta-cyfluthrin like cyfluthrin is not irritating to the skin but exhibits mild eye irritant activity (not sufficient for classification, Table 2.6-9, Table 2.6-11). No evidence of a skin-sensitising potential was found (Table 2.6-9, Table 2.6-11).
According to Commission Regulation (EU) No. 283/2013 phototoxicity testing is required if the test compound absorbs electromagnetic radiation in the range 290-700 nm (molar extinction coefficient ≥ 10 L mol^{-1} cm^{-1}). Beta-cyfluthrin consists mainly of isomer II and IV. The corresponding molar extinction coefficients are 80 L mol^{-1} cm^{-1} and 85 L mol^{-1} cm^{-1} at 291 nm (neutral conditions), respectively (Vol 3, B.2). Therefore, phototoxicity testing is needed. A study addressing this endpoint was submitted by the applicant (Volume 3, B.6.2). However, the study is considered not acceptable as the phototoxic potential was tested at wavelengths where no relevant absorption takes place (criteria according to OECD-TG 431). Hence, the phototoxic potency of beta-cyfluthrin cannot be evaluated.
The applicant submitted an expert statement on phototoxicity testing of beta-cyfluthrin. However, on the basis of the information given in this statement together with the criteria for a valid phototoxicity study (OECD TG 432), the availbale phototoxicity study is considered not sufficient to thoroughly assess the phototoxic potential of beta-cyfluthrin (further information is given in Vol. 3).

Table 2.6-8: Overview on acute toxicity of beta-cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Reference
acute oral LD_{50}	rat	male female male female	PEG 400	655 mg/kg bw[1,2] 1369 mg/kg bw[1,2] 380 mg/kg bw 651 mg/kg bw	[redacted] 1987, TOX9550258
acute oral LD_{50}	rat	male female male female	acetone/ peanut oil	141 mg/kg bw[1,2] 108 mg/kg bw[1,2] 84 mg/kg bw 77 mg/kg bw	[redacted] 1987, TOX9550257
acute oral LD_{50}	rat	male female male female	xylene	307 mg/kg bw[1,2] 343 mg/kg bw[1,2] 211 mg/kg bw 336 mg/kg bw	[redacted] 1987, TOX9550255
acute oral LD_{50}	rat	male	acetone/corn oil	200 mg/kg bw	[redacted] 2005, ASB2014-7720
acute oral LD_{50}	mice	male female	PEG 400	91 mg/kg bw 165 mg/kg bw	[redacted] 1987, TOX9550256
acute oral LD_{50}	chicken	female	cremophor/water	>5000 mg/kg bw[1,2,3]	[redacted] 1985, TOX9550253
acute dermal LD_{50}	rat	male female	PEG 400	>5000 mg/kg bw >5000 mg/kg bw	[redacted] 1987, TOX9550259
acute dermal LD_{50}	rat	male female	xylene	>5000 mg/kg bw >5000 mg/kg bw	[redacted] 1987, TOX9550260
acute dermal LD_{50}	rat	male female	PEG 400	>2000 mg/kg bw >2000 mg/kg bw	[redacted] 2005, ASB2014-7721
acute inhal. LC_{50} (4 h, head-nose)	rat	male female male female	ethanol/PEG 400 ethanol/PEG 400 dust dust	~90 mg/m³ air ~100 mg/m³ air ~967 mg/m³ air ~695 mg/m³ air	[redacted] 1985, TOX9550261
acute inhal. LC_{50} (4 h, head-nose)	rat	male female male female	ethanol/PEG 400 ethanol/PEG 400 dust	~82 mg/m³ air 81 mg/m³ air 532 mg/m³ air	[redacted] 1988, TOX9550264

* Not-acceptable studies were not included.
[1] Animals not fasted.
[2] These studies are considered supplementary.
[3] These studies were not submitted by the applicant (but available to RMS e.g. from literature search in database or other applications).

Table 2.6-9: Overview on skin/eye irritation and skin sensitisation studies with beta-cyfluthrin*

Parameter	Species	Vehicle	Result	Reference
skin irritation	rabbit	water	non-irritant	[redacted] 2005, ASB2014-7723
eye irritation	rabbit	unclear	non-irritant[1]	[redacted] 1985, TOX9550265

Parameter	Species	Vehicle	Result	Reference
eye irritation	rabbit	undiluted	non-irritant[1]	[redacted] 2005, ASB2014-7724
skin sensitisation	guinea pigs	cremophor/saline	no sensitiser[2]	[redacted] 2005, ASB2014-7725

[*] Not-acceptable studies were not included.
[1] Slight effect, does not reach the criteria for classification.
[2] The study is considered supplementary.

Table 2.6-10: Overview on acute toxicity of cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Reference
acute oral LD_{50}	rat	male male male male	cremophor/water acetone/oil dimethylsuphoxide *N*-methylpyrrolidone	16.2 mg/kg bw 254 mg/kg bw 396 mg/kg bw 500-1000 mg/kg bw	[redacted] 1982, TOX9401854
acute oral LD_{50}	rat	male	cremophor/water	20 mg/kg bw	[redacted] 1984, TOX9401948
acute oral LD_{50}	rat	male	cremophor/water	20 mg/kg bw	[redacted] 1984, TOX9401949
acute oral LD_{50}	rat	male	cremophor/water	20 mg/kg bw[3]	[redacted] 1984, Z17076
acute oral LD_{50}	rat	male	cremophor/water	14.3 mg/kg bw	[redacted] 1982, TOX9401946
acute oral LD_{50}	rat	male	cremophor/water	18 mg/kg bw	[redacted] 1983, TOX9401947
acute oral LD_{50}	rat	male	cremophor/water	15 mg/kg bw[2]	[redacted] 1994, TOX2001-1764
acute oral LD_{50}	rat	male	cremophor/water	19.6 mg/kg bw	[redacted] 1983, TOX9401941
acute oral LD_{50}	rat	male	PEG 400	500 mg/kg bw	[redacted] 1988, TOX9401950
acute oral LD_{50}	rat	male female	PEG 400	869 mg/kg bw[1,2,3] 1271 mg/kg bw[1,2,3]	[redacted] 1980, TOX9401853
acute oral LD_{50}	rat	male female	PEG 400	590 mg/kg bw[3] 1189 mg/kg bw[3]	[redacted] 1980, TOX9401853
acute oral LD_{50}	rat	male female	acetone/peanut oil	155 mg/kg bw[3] 160 mg/kg bw[3]	[redacted] 1987, TOX9401862
acute oral LD_{50}	mouse	female	cremophor/water	<100 mg/kg bw[2,3]	[redacted] 1982, TOX9401854
acute oral LD_{50}	mouse	male female	PEG 400	291 mg/kg bw[3] 609 mg/kg bw[3]	[redacted] 1980, TOX9401853

Parameter	Species	Sex	Vehicle	Result	Reference
acute oral LD_{50}	rabbit	male	PEG 400	>1000 mg/kg bw[2,3]	[redacted] 1980, TOX9401853
acute oral LD_{50}	dog	male	PEG 400	>100 mg/kg bw[2,3]	[redacted] 1980, TOX9401853
acute oral LD_{50}	dog	male female	cremophor/water	>100 mg/kg bw[1,2,3]	[redacted] 1981, TOX9401856
acute oral LD_{50}	chicken	female	cremophor/water	>5000 mg/kg bw[1,2,3]	[redacted] 1985, TOX9401860
acute oral LD_{50}	chicken	female	PEG 400	~5000 mg/kg bw[1,2]	[redacted] 1981, TOX9401916
acute oral LD_{50}	chicken	female	PEG 400	~4500 mg/kg bw[1,2,3]	[redacted] 1985, TOX9401861
acute dermal LD_{50}	rat	male female	cremophor/water	>5000 mg/kg bw[2,3]	[redacted] 1982, TOX9401854
acute dermal LD_{50}	rat	male female	PEG 400	>5000 mg/kg bw[2,3]	[redacted] 1982, TOX9401854
acute dermal LD_{50}	rat	male female	NaCl solution	>5000 mg/kg bw[2,3]	[redacted] 1982, TOX9401854
acute inhal. LC_{50} (1 h, nose only)	rat	male female	ethanol/PEG 400	>1089 mg/m³ air³	[redacted] 1980, TOX9401853
acute inhal. LC_{50} (4 h, nose only)	rat	male female	ethanoPEG 400	469-592 mg/m³ air³	[redacted] 1980, TOX9401853
acute inhal. LC_{50} (4 h, head/nose only assumed)	rat	male female	ethanol/PEG 400 ethanol/PEG 400	1010 mg/m³ air³ 1020 mg/m³ air³	[redacted] 1984, TOX9401866
acute inhal. LC_{50} (4 h, head/nose only)	rat	male female	ethanol/PEG 400	405 mg/m³ air³	[redacted] 1987, TOX9401867
acute inhal. LC_{50} (4 h, head/nose only)	rat	male female male female	water water DMSO DMSO	>735 mg/m³ air³ 200-735 mg/m³ air³ 575 mg/m³ air³ 490 mg/m³ air³	[redacted] 1982, TOX9401864
acute inhal. LC_{50} (5 x 6 h, nose only)	rat	male female	ethanol/PEG 400	47-196 mg/m³ air[2,3]	[redacted] 1980, TOX9401853

Parameter	Species	Sex	Vehicle	Result	Reference
acute inhal. LC_{50} (4 h, head/nose only)	mouse	male female	ethanol/PEG 400	~141 mg/m³ air[3]	[redacted] 1989, TOX9401871
acute inhal. LC_{50} (4 h, whole body)	chicken	female	ethanol/PEG 400 or water/cremophor	>596 mg/m³ air[2]	[redacted] 1983, TOX9401865

* Not-acceptable studies were not included.
[1] Animals not fasted.
[2] These studies are considered supplementary.
[3] These studies were not submitted by the applicant (but available to the RMS e.g. from other applications).

Table 2.6-11: Overview on skin/eye irritation and skin sensitisation studies with cyfluthrin*

Parameter	Species	Vehicle	Result	Reference
skin irritation	rabbit	undiluted	non-irritant[2,3]	[redacted] 1982, TOX9401872
skin irritation	rabbit	unclear	non-irritant[2,3]	[redacted] 1980, TOX9401853
eye irritation	rabbit	undiluted	irritant[1,2,3]	[redacted] 982, TOX9401872
eye irritation	rabbit	unclear	irritant[2,3,4]	[redacted] 1980, TOX9401853
skin sensitisation	Guinea pig	PEG 400	no sensitiser[3]	[redacted] 1994, ASB2007-2854

* Not-acceptable studies were not included.
[1] From the data given it remains unclear whether from the today's perspective the outcome would be positive, too.
[2] The study is considered supplementary.
[3] These studies were not submitted by the applicant (but available to RMS e.g. from other applications).
[4] If gradings are comparable with today, the substance would be considered as not irritating to eyes (based on mean scores after 24, 48, 72 h).

The following tables (Table 2.6-12 - Table 2.6-15) present the critical results for the different toxicological endpoints used for classification and labelling and further list the criteria required from CLP regulation.

Table 2.6-12: Results of acute toxicity studies in comparison with CLP criteria*

Toxicological result	CLP criteria
Oral LD_{50}, rat: 14.3 mg/kg	Cat 4 (H302): $300 < LD_{50} \leq 2000$ mg/kg (oral) Cat. 3 (H301): $50 < LD_{50} \leq 300$ mg/kg (oral) Cat. 2 (H300): $5 < LD_{50} \leq 50$ mg/kg (oral) Cat. 1 (H300): $LD_{50} \leq 5$ mg/kg (oral)
Dermal LD_{50}, rat: >2000 mg/kg bw	Cat. 4 (H312): $1000 < LD_{50} \leq 2000$ mg/kg (dermal) Cat. 3 (H311): $200 < LD_{50} \leq 1000$ mg/kg (dermal) Cat. 2 (H310): $50 < LD_{50} \leq 200$ mg/kg (dermal) Cat. 1 (H310): $LD_{50} \leq 50$ mg/kg (dermal)
Inhalation LC_{50}, rat: 0.081 mg/L (highest attainable conc. 0.097 mg/L, aerosol ethanol/PEG 400, 4 h, head-nose only)	Cat. 4 (H332): $10.0 < LC_{50} \leq 20.0$ mg/L (vapours) $1.0 < LC_{50} \leq 5.0$ (dusts and mists) Cat. 3 (H331): $2.0 < LC_{50} \leq 10.0$ mg/L (vapours) $0.5 < LC_{50} \leq 1.0$ (dusts and mists) Cat. 2 (H330): $0.5 < LC_{50} \leq 2.0$ mg/L (vapours) $0.05 < LC_{50} \leq 0.5$ (dusts and mists) Cat. 1 (H330): $LC_{50} \leq 0.5$ mg/L (vapours) $LC_{50} \leq 0.05$ (dusts and mists)

* Only acceptable studies were used for classification.

Table 2.6-13: Results of eye irritation studies in comparison with CLP criteria*

Toxicological result	CLP criteria
Mean score (24 - 72 h): corneal opacity: 0.0 (no animal ≥1) iris leson: 0.0 (no animal ≥1) conjuntival redness: not above 1.3 (no animal ≥2) oedema of the conjunctivae (chemosis): not above 1 (no animal ≥2) ([redacted] 1985, TOX9550265) Mean score (24 - 72 h): corneal opacity: 0.0 (no animal ≥1) iris leson: 0.0 (no animal ≥1) conjuntival redness: not above 1.0 (no animal ≥2) oedema of the conjunctivae (chemosis): not above 0.3 (no animal ≥2) ([redacted] 2005, ASB2014-7724)	Irritating to eyes (Category 2, H319): at least in 2/3 tested animal a positive response of: corneal opacity: ≥1 and/or iritis: ≥1 and/or conjunctival redness: ≥2 and/or conjunctival oedema (chemosis): ≥2

* Only acceptable studies were used for classification.

Table 2.6-14: Results of skin irritation studies in comparison with CLP criteria*

Toxicological result	CLP criteria
Mean erythema and oedema scores (24 - 72 h): 0.0 and 0.0, respectively (no animal ≥2.3). ([redacted] 2005, ASB2014-7723)	Irritating to skin (Category 2, H315): at least in 2/3 tested animal a positive response of: Mean value of ≥2.3 - ≤4.0 for erythema/eschar or for oedema

* Only acceptable studies were used for classification.

Table 2.6-15: Results of skin sensitisation tests in comparison with CLP criteria*

Toxicological result	CLP criteria
0 % animals positive 5 % intra dermal induction concentration 50 % topical administration 25 % topical administration 5 % animals positive 5 % intra dermal induction concentration 50 % topical administration 50 % topical administration ([redacted] 1994, ASB2007-2854)	Guinea pig maximisation test Category 1A (H317): ≥30 % responding at ≤0.1 % intradermal induction dose or ≥60 % responding at >0.1 % to ≤1 % intradermal induction dose Category 1B (H317): ≥30 % to <60 % responding at >0.1 % to ≤1 % intradermal induction dose or ≥30 % responding at >1 % intradermal induction dose
No acceptable non-adjuvant type study submitted	Buehler assay Category 1A (H317): ≥15 % responding at ≤0.2 % topical induction dose or ≥60 % responding at >0.2 % to ≤20 % topical induction dose Category 1B (H317): ≥15 % to <60 % responding at >0.2 % to ≤20 % topical induction dose or ≥15 % responding at >20 % topical induction dose

* Only acceptable studies were used for classification.

Based on the results listed above, the proposed classification and labelling for the rat oral LD_{50} and LC_{50} endpoint is **Acute Tox Oral 2, H300 – Fatal if swallowed** and **Acute Tox Inhal 2, H330 - Fatal if inhaled**, respectively. In contrast to this, beta-cyfluthrin does not meet the criteria for dermal toxicity classification. No classification regarding skin and eye irriation/corrosion or skin sensitisation is triggered.

2.6.4 Summary of short-term toxicity

No new data on short-term toxicity have been generated since Annex-I inclusion and the publication of Addendum 1 (2002). All studies here have been previously submitted. For the renewal process they were again evaluated (see Table 2.6-16 - Table 2.6-19).
Two studies from the original monograph of cyfluthrin were additionally evaluated. The studies were considered acceptable (see Table 2.6-19).

A literature search for the Renewal Assessment Report (RAR) including publications from the last 10 years was performed by the RMS. The publications were considered as supplemental information or where considered not acceptable (see Table 2.6-21).
In oral short-term toxicity experiments in rats and dogs oral administration of high doses of cyfluthrin led to general behavioural disturbances, lower body weight development and choreoathetotic signs. No relevant effects on haematological, clinicochemical and urin analytical parameters were detected, nor did gross or histopathological investigations afford any evidence of specific organ or tissue damage. This concerned also the tissues (nerve, muscle, eye) which were investigated in detail in a 28-day study on rats ([redacted] 1988, TOX9550271). In a 3-month feeding study in rats with cyfluthrin ([redacted] 1983, TOX9401881) a reversible slight axonal degeneration was noted in some rats dosed with 1000 ppm (60.9 mg/kg bw/d) (see Table 2.6-19).
A slight increase in liver weight, noticed in the 4-week study ([redacted] 1988, TOX9550271) was not observed in a 13-week study on rats at a higher dose ([redacted] 1988, TOX9550272). Alterations (clinical signs, reduced body weight development, increased liver weight) during the course of 4-week test substance exposure were reversible in a recovery period without test substance intake.
The resulting NOAEL of 125 ppm in the 13-week study on rats, corresponding to 9.5 mg/kg bw/d in male and 10.9 mg/kg bw/d in female rats was based on mortalities, clinical signs and a reduction of body weight gain at the next higher dose (500 ppm).
In a 90-day study on dogs ([redacted] 1987, TOX9550274) the NOAEL of 60 ppm, equal to 1.5 mg/kg bw/d, was based on motor disturbances, vomiting, diarrhea in males and females and a reduced body weight gain in females at the next higher dose of 360 ppm. A 12-month feeding study in dogs ([redacted] 1997, TOX9800225, see Table 2.6-20) revealed slight to severe motor disturbances, vomiting, diarrhea and a reduction in body weight gain at ≥360 ppm (10.6-18 mg/kg bw/d). The study revealed a NOAEL of 100 ppm (2.4/3.6 mg/kg bw/d). This study supersedes the 12-month feeding study in dogs ([redacted] 1983, TOX9401903) which was considered not acceptable (see Table 2.6-16).

Table 2.6-16: Summary of short-term oral toxicity studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
4 week, gavage; Wistar rat (4-week recovery)	0-0.25-1-4-16 mg/kg bw/d	Beta-cyfluthrin purity: 98.5 % Vehicle: Cremophor/water	1	Mortality, clinical signs, reduced bw development, increased liver weight	[redacted] (1988) TOX9550271
90-day, feeding; Wistar rat	Males: 2.3, 9.5, 38.9/37* mg/kg bw/d Females: 2.5, 10.9, 42.4/43* mg/kg bw/d * Recovery (correspond to: 0, 30, 125 and 500 ppm)	Beta-cyfluthrin purity: 99.7 %	9.5/10.9 mg/kg bw/d (125 ppm)	Mortality, clinical signs, reduced bw and water intake, skin lesions, reduced red blood cell parameters, increased calcium levels in urine	[redacted] 1988 TOX9550272

90-day, feeding; Beagle dog	0-0.4-2.4-14 mg/kg bw/d (correspond to 0-10-60-360 ppm)	Beta-cyfluthrin purity: 99.7 %	2.4 mg/kg bw/d /22.1 mg/animal/d (60 ppm)	Motor disturbances (hind limb), vomiting, diarrhea, reduced bw	[redacted] 1987 TOX9550274
12-month, feeding, Beagle dog (not acceptable, not included in the assessment)	0-1.5-6.2-25 mg/kg bw/d (correspond to 0-40-160-640 ppm)	Cyfluthrin, purity not known	6.2 mg/kg bw/d (160 ppm)	Slight motor disturbances on a single occasion (hind limb), vomiting, diarrhea, reduced bw	[redacted] 1983 TOX9401903

Behavioural disturbances and an effect on body weight gain were also noted in inhalation studies on rats which failed to afford evidence of significant pathological lung changes but resulted in a slight, compensatory acidosis. In the 4-week study, no test substance related findings were apparent in the pathological and histopathological investigations. The slightly changed clinical parameters were interpreted as a result of compensatory reactions due to a slight respiratory acidosis. Additional lung function tests produced no evidence of pathophysiological lung changes. The NOAEC in this study was 0.2 mg beta-cyfluthrin/m³ air (corresponding to approx. 0.07 mg/kg bw/d), based on clinical signs and a reduced body weight gain at the next higher doses.

Table 2.6-17: Summary of short-term inhalation toxicity studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Analyt. conc. [mg/m³ air]	Test substance	NO(A)EC [mg/m³ air]	Targets / Main effects	Reference
5 d, Wistar rat range finding	0*-0.25-3.8-28 Aerosol	Beta-cyfluthrin (purity: 98 %) Vehicle: ethanol/PEG 400 (1:1)	0.25	Clinical signs, transient reduction of bw, lung findings	[redacted] 1988 TOX9550275
4-week, Wistar rat	0-0.2-2.7-23.5 Aerosol	Beta-cyfluthrin (purity:97.9 %) Vehicle: ethanol/PEG 400 (1:1)	0.2 (0.07 mg/kg bw/d)	Clinical signs, reduction of bw	[redacted] 1989 TOX9550276
13-week, Wistar rat	0-0-0.09-0.71-4.52 mg/m³ air Aerosol	Cyfluthrin purity: 94.9 % Vehicle: polyethylene glycol E 400: ethanol (1 : 1)	0.09 (approx. 0.02 mg/kg bw/d)	Behavioural disturbances (agitation, (erected tail), reduction of bw	[redacted] 1984 TOX9401887

* = air and vehicle control.

Studies on dermal toxicity on rat and rabbit are available for cyfluthrin, only. In a 3-week study on rabbits with cyfluthrin no specific effects were observed ([redacted] 1980, TOX9401883). In a 22/23-dermal toxicity study in rats ([redacted] 1996, TOX2001-1769, see Table 2.6-20) systemic effects in the form of dark red discharge from the nose and urine staining in males and fe-

males, respectively, and a reduced food intake occurred at the highest dose of 1000 mg/kg bw/d. At a dose up to 340 mg/kg bw/d severe skin lesions were noted (ulceration, hyperkeratosis, acanthosis, inflammation, and dermal fibrosis). These changes persisted throughout the recovery period. The systemic NOAEL was established at 340 mg/kg bw/d, the local NOAEL at 100 mg/kg bw/d.

Table 2.6-18: Summary of short-term dermal toxicity studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
3-week dermal toxicity in rabbits	0, 50, and 250 mg/kg bw/d	Cyfluthrin, purity: 83.5 % Vehicle: polyethylene glycol 400	250 mg/kg bw/d	No effects	[redacted] 1980 TOX9401883
7-day dermal toxicity in rats (not acceptable)	approx. 0-80-160-240-320 mg/kg bw	Cyfluthrin, purity not known Vehicle: ethyl alcohol	LOAEL 80 mg/kg bw	Mortalities and clinical signs, impairment of liver function	[redacted] 1986 TOX9401884

Table 2.6-19: Summary of short-term toxicity studies evaluated in the original monograph of cyfluthrin by the RMS in September, 1996 (ASB2010-10393)

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
3-month oral (feeding) toxicity in rats	0-100-300-1000 ppm (corr. to 6.21-18.98-60.90 mg/kg bw/d males, 7.29-21.22-68.47 mg/kg bw/d females)	Cyfluthrin, purity: 95 %	100 ppm (6.21 mg/kg bw/d)	Gait abnormalities, salivation, slight axonal degeneration of sciatic nerve (reversible)	[redacted] 1983 TOX9401881
4-week inhalation toxicity in rats	03-30-300 mg/m³ air (analyt. conc 0.44-6.04-46.6 mg/m³ air)	Cyfluthrin, purity: 93.8 %	0.44 mg/m³ air (0.16 mg/kg bw/d)	Clinical signs (ruffled coat, hyperactivity, bradypnoea), growth retardation	[redacted] 1989 TOX9401886

Table 2.6-20: Summary of studies evaluated in Addendum 1 to the monograph of beta-cyfluthrin (2002):

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
12-month, feeding, Beagle dog	0-1.36-2.43-10.64-15.47 mg/kg bw/d in males 0-1.46-3.61-	Cyfluthrin, purity: 94.8 - 95.1 %,	2.43 / 3.61 mg/kg bw/d (100 ppm)	640/500 ppm: Premature sacrifice for welfare reasons ≥360 ppm:	[redacted] 1997 TOX9800225

	10.74-17.99 mg/kg bw/d in females (corr. to 0-50-100-360-640/500 ppm			reduced bw, neurological disorders (gait abnormalities)	
22/23-day dermal toxicity in rats	0-100-340-1000 mg/kg bw/d (including recovery at 0 and 1000 mg/kg bw/d)	Cyfluthrin, purity: 95.5 - 95.9 %	Systemic: 340 mg/kg bw/d Local: 100 mg/kg bw/d	Systemic effects at 1000 mg/kg bw/d: Dark red discharge from the nose in males (including recovery group), urine stains in females, reduced food consumption Local effects: skin lesions	[redacted] 1996 TOX2001-1769

Table 2.6-21: Literature research for the Renewal Assessment Report (RAR):

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
Biochemical and histological changes in rat liver caused by cypermethrin and beta-cyfluthrin (supplemental)	Beta-cyfluthrin: 1.27-1.69-2.53-5.07 mg/kg bw/d (7, 14, 21, 28 days)	Cypermethrin + beta-cyfluthrin, purity: 95 %, vehicle: physiological saline	Not applicable	Liver: increased AST, ALT, LDH activity, decreased ALP	Bhushan et al. (2013) ASB2015-644
Beta-cyfluthrin induced histochemical alterations in the liver of the albino rat (not acceptable)	Beta-cyfluthrin: 1.68-2.53-5.06 mg/kg bw/d (7, 14, 21 days)	Beta-cyfluthrin, purity not known Vehicle: ethyl alcohol	Not applicable	Liver: decrease in hepatic proteins, and increase of hepatic DNA	Bhushan et al. (2010) ASB2015-1098
Selenium modulates beta-cyfluthrin-induced liver oxidative toxicity in rats (supplemental)	0, 200 (selenium), 15 (beta-cyfluthrin), 15 and 200 (beta-cyfluthrin and selenium) mg/kg bw/d, 30 days	Beta-cyfluthrin, purity: > 99 %, Vehicle: not known	Not applicable	Liver: oxidative stress, increase in lipid peroxidation	Jebur et al. (2013) ASB2015-921

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
Cyfluthrin-induced hepatotoxicity in rats (not acceptable)	0, 100, 200 ppm, gavage, 15 weeks	Beta-cyfluthrin, purity not known Vehicle: lecithin in water	Not applicable	Liver	Omotuyi et al. (2006) ASB2015-924

Table 2.6-22: Toxicological results (at dose levels below the guidance values) in comparison with criteria of specific target organ toxicity – repeated exposure

CLP criteria
Category 1 (H372): Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of: reliable and good quality evidence from human cases or epidemiological studies; or observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Equivalent guidance values for 28-day and 90-day studies: Oral, rat: 28-day: ≤30 mg/kg bw/d 90-day: ≤10 mg/kg bw/d
Category 2 (H373): Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2. Equivalent guidance values for 28-day and 90-day studies: Oral, rat: 28-day: ≤300 mg/kg bw/d 90-day: ≤100 mg/kg bw/d

Comparison with criteria in CLP regulation:

Some findings were observed in rats and dogs at dose levels below the respective guidance values. Even though some of the observed findings were severe findings (such as clinical signs, motor disturbances and/or gait abnormalities), they were considered to represent acute toxic/neurotoxic effects of beta-cyfluthrin/cyfluthrin. Due to intensive metabolism and rapid excretion of beta-cyfluthrin/cyfluthrin, daily administrations of beta-cyfluthrin/cyfluthrin are considered to represent a sequence of acute intoxications. A proposal for classification for acute effects is already made. Hence, it is proposed not to classify beta-cyfluthrin/cyfluthrin for STOT-RE/“Danger of serious damage to health by prolonged exposure”.

2.6.5 Summary of genotoxicity

The genotoxic potential of beta-cyfluthrin and cyfluthrin was studied using various *in vitro* test systems on bacteria and mammalian cells and *in vivo* by means of the micronucleus test (Table 2.6-23, Table 2.6-24). None of the test systems used revealed any evidence of a genotoxic or mutagenic potential of beta-cyfluthrin and cyfluthrin. However, experiments with the positive controls led to the expected results. Therefore, an *in vivo* study in germ cells was not triggered.

According to Commission regulation (EU) No. 283/2013 photomutagenicity testing is not required if the UV/visible molar extinction/absorption coefficient of the active substance is less than 1000 L mol^{-1} cm^{-1}). The absorption coefficient for 290-700 nm was below this value. Therefore, photomutagenicity testing is not triggered.

Table 2.6-23: Mutagenicity and genotoxicity studies (beta-cyfluthrin)*

Test system	Test object	Concentration or dose tested	Results	Reference
Gene mutations in bacteria	TA98, TA100, TA1535, TA1537	between 20 and 12500 µg/plate	negative with/without S9 mix[1]	Herbold, 1986, TOX9550277
Gene mutations in bacteria	TA1535, TA100, TA1537, TA98, and TA102	between 16 and 5000 µg/plate	negative with/without S9 mix[1]	Herbold, 2008, ASB2014-7875
HGPRT	Chinese hamster ovary cells (CHO)	between 20 and 100 µg/mL	negative with/without S9 mix	Lehn, 1988, TOX9550280
Unscheduled DNA synthesis[2]	rat primary hepatocytes	between 1.01 and 1010 µg/mL	negative	Cifone, 1987, TOX9550278
Micronucleus test	Male and female mice (Bor:NMRI [SPF Han])	80 mg/kg bw	negative[1]	Herbold, 1988, TOX9550279

* Not-acceptable studies are not included.
[1] The study is considered supplementary.
[2] The study is not included in the data requirement according to Commission regulation (EU) No. 283/2013.

Table 2.6-24: Mutagenicity and genotoxicity studies (cyfluthrin)*

Test system	Test object	Concentration or dose tested	Results	Reference
Gene mutations in bacteria	TA1513, TA100, TA1537, TA98	between 20 and 12500 µg/plate (including negative control)	negative with/without S9 mix[1,2]	Herbold, 1980, TOX9401890
Gene mutations in bacteria	*E. coli* B/r WP2 try-hcr-, TA1535, TA1537, TA1538, TA98, TA100	between 5 and 5000 µg/plate (including negative control)	negative with/without S9 mix[1,2]	Nagane, Hatanaka, Iyatomi, 1982, TOX9401894
Gene mutations in bacteria	*E. coli* B/r WP2 hcr, TA1535, TA1537, TA1538, TA98, TA100	between 50 and 25000 µg/plate (including negative control)	negative with/without S9 mix[1,2]	Ohta and Moriya, 1982, TOX9401895

Test system	Test object	Concentration or dose tested	Results	Reference
HGPRT	Chinese hamster ovary cells (CHO)	between 3 and 10 µl/ml (including negative control)	negative with/without S9 mix[1,2]	Yang, 1985, TOX9401899
Cytogenetic study (clastogenic effects)	Chinese hamster lung cells	between $3 \cdot 10^{-5}$ and $3.3 \cdot 10^{-3}$ M (including negative control)	negative with/without S9 mix[1,2]	Sasaki, Imanishi, Watanabe, Ohta, 1986, TOX9401901
Micronucleus test	Male and female mice (NMRI/ORIG Kisslegg)	2·7.5 mg/kg bw or 2·15 mg/kg bw (including negative control)	negative[1,2]	[redacted] 1980, TOX9401891

* Not-acceptable studies are not included.
[1] The study is considered supplementary.
[2] These studies were not submitted by the applicant (but available to RMS e.g from other applications).

For cyfluthrin other at least supplementary genotoxicity studies (not submitted by the applicant, but available to the RMS [e.g. from other applications]) are listed in Vol. 3, B.6.4 in the monograph. As these studies are focussing on endpoints not included in the today's data requirement according to Commission Regulation (EU) No. 283/2013 (e.g. rec-assay), no details are given here. Taken together, all these studies do not point to mutagenic or genotoxic effects of cyfluthrin.
A publication by Ila et al. (2008, ASB2014-7878) presenting different mutagenicity and genotoxicity studies with cyfluthrin was submitted by the applicant. The authors report on some positive results *in vitro* and *in vivo*. However, a questionable study design, cytotoxic effects and poor presentation of data question the robustness, reliability and informative value of the studies. Therefore, the study is less reliable for the evaluation.
The following table lists the criteria required for germ cell mutagenicity classification from CLP regulation.

Table 2.6-25: Results of germ cell mutagenicity studies in comparison with CLP criteria

CLP regulation
The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans. The classification in Category 1B is based on: - positive result(s) from *in-vivo* heritable germ cell mutagenicity tests in mammals; or - positive result(s) from in-vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or - positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people. The classification in Category 2 is based on: - positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from: - somatic cell mutagenicity tests *in vivo*, in mammals; or - other *in vivo* somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays. Note: Substances which are positive in *in vitro* mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

Many of the submitted *in vitro* and all *in vivo* studies are merely considered supplementary. However, if taken together no data gap is indicated. The publication by Ila et al. (2008, ASB2014-7878) is considered less reliable and for this reason excluded from the evaluation. The overall conclusion is based on a weight of evidence approach using all studies that are considered as acceptable or supplementary. First, many relevant endpoints of the current data requirement regarding mutagenicity and genotoxicity *in vitro* were addressed in the studies (gene mutations in bacteria and mammalian cells, clastogenic effects in mammalian cells). The available *in vitro* studies with cyfluthrin and beta-cyfluthrin did not indicate a mutagenic or genotoxic potential. However, the positive controls led to the desired effects. The studies conducted *in vivo* also led to negative results even though positive controls showed positive responses. Furthermore, no indication for carcinogenicity was found in long-term studies.

Comparison with criteria in CLP regulation:

As no human data were available for beta-cyfluthrin, no tests regarding germ cell mutagenicity were performed and no reliable positive results in *in vivo* genotoxicity/mutagenicity tests were obtained, classification into category 1A or 1B is not applicable. As further all the *in vitro* studies were negative, category 2 is also not considered necessary.
For this reason, the classification of beta-cyfluthrin for genotoxicity/mutagenicity is considered not required.

2.6.6 Summary of long-term toxicity and carcinogenicity

No new data on chronic toxicity and carcinogenicity have been generated since Annex-I inclusion of cyfluthrin/beta-cyfluthrin and the publication of Addendum 1 (2002). All studies here have been previously submitted. For the renewal process they were again evaluated.
A literature search for the Renewal Assessment Report (RAR) including publications from the last 10 years was performed by the RMS. For the chapter long-term toxicity and carcinogenicity no new publications were found.
Chronic toxicity and carcinogenicity studies are available only for cyfluthrin but can be read across to beta-cyfluthrin. No evidence of a carcinogenic potential of cyfluthrin was found in chronic feeding studies with rats and mice. Cyfluthrin does not possess a tumour-promoting potential. The studies also produced no evidence of specific organotoxicity, especially neurotoxicity, of cyfluthrin.
When compared to the short-term studies in rats and mice, no additional effects were revealed in the long-term studies.
Due to a variety of deviations from the guideline, the 2-year toxicity study in rats and the 23-month study in mice ([redacted] 1983a (TOX9401904), 1983b (TOX9401905)) are not considered acceptable anymore. The 2-year study in rats originally served as the basis for ADI derivation.
A more recent study ([redacted] 1997, TOX9850068) confirmed the dietary NOAEL of 50 ppm in rats from the older study of [redacted] (1983a (TOX9401904), 1983b (TOX9401905)), but the resulting NOAEL was somewhat higher (2.6/3.3 mg/kg bw/d), based on higher food consumption per kg bw. Reduction in body weight gain was the only systemic effect.
No NOAEL could be derived for females in an 18-month feeding study in mice ([redacted] 1998, TOX2001-1770) since their body weight development was impaired from the lowest dose onwards (200 ppm). Body weight gain was impaired in male mice at the highest dose of 1400 ppm (233 mg/kg bw/d). From 750 ppm onwards (115/141 mg/kg bw/d) skin lesions were observed at the tip of the ear. Chronic inflammation and acanthosis were considered to be the result of scratching due to paresthesia.
The NOAEL in males was 32 mg/kg/day (200 ppm).

Table 2.6-26: Summary of long-term toxicity and carcinogenicity studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
2 year, feeding; Wistar rat (1-year interim sacrifice) (not acceptable)	0-2.02/2.71-6.19/8.15-19.20/25.47 mg/kg bw/d in males and females resp. (corresponding to 0-50-150-450 ppm)	Cyfluthrin (purity not reported)	2.02 (50 ppm)	bw decreased; no increase in tumour incidences	[redacted] (1983a) TOX9401904
Chronic toxicological study on mice (feeding study over 23 months) (not acceptable)	11.6-45.8-194.5 mg/kg bw/d in males; 15.3-63.0-259.9 mg/kg bw/d in females (corresp. to 0-50-200-800 ppm)	Cyfluthrin (purity not reported)	No NOAEL was derived	Increased alkaline phosphatase activities in males at all dose levels, lower bw of males and females at 200 and 800 ppm. No increase in tumour incidences.	[redacted] (1983b) TOX9401905

Table 2.6-27: Summary of long-term toxicity and carcinogenicity studies evaluated in the addendum 1 to the monograph of beta-cyfluthrin (2002):

Study	Dose levels	Test substance	NO(A)EL [mg/kg bw/d]	Targets / Main effects	Reference
24-month combined chronic toxicity and oncogenicity (1-year interim sacrifice); Fischer rats	0-2.6/3.3-11.6/14.4-22.8/28.3 mg/kg bw/d in males and females resp. (corresponding to 0-50-225-450 ppm)	Cyfluthrin (purity 93.9-95.1 %)	2.6/3.3 mg/kg bw/d (50 ppm)	bw decreased; no increase in tumour incidences	[redacted] (1997) TOX9850068
18-month oncogenicity study in the mouse	0–31.9–115–233 mg/kg bw/d males; 0–38.4–141–310 mg/kg bw/d females (corresponding to 0–200–750–1400/1600 ppm)	Cyfluthrin (purity 93.9–95.1 %,	Males: 32 mg/kg bw/d Females: <38 mg/kg bw/day (200 ppm)	Decreased bw gains in females at all dose levels, in males of the highest dose level; from 750 ppm onwards: in addition skin	[redacted] (1998) TOX2001-1770

				lesions (acanthosis, chronic inflammation) at the tip of ear due to paresthesia. No increase in tumour incidences.	

Table 2.6-28: Criteria for classification

CLP regulation
A substance is classified in Category 1 (known or presumed human carcinogens) for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as: Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from: - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or - animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
The placing of a substance in Category 2 (suspected human carcinogens) is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.
3.6.2.2.3: Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms ‘sufficient’ and ‘limited’ have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows: (a) Carcinogenicity in humans The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories: - sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence; - limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites;
- limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

3.6.2.2.4:

Additional considerations (as part of the weight of evidence approach (see 1.1.1)). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here.

3.6.2.2.5:

The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

3.6.2.2.6:

Some important factors which may be taken into consideration, when assessing the overall level of concern are:

(a) tumour type and background incidence;
(b) multi-site responses;
(c) progression of lesions to malignancy;
(d) reduced tumour latency;
(e) whether responses are in single or both sexes;
(f) whether responses are in a single species or several species;
(g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity;
(h) routes of exposure;
(i) comparison of absorption, distribution, metabolism and excretion between test animals and humans;
(j) the possibility of a confounding effect of excessive toxicity at test doses;
(k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

Mutagenicity: it is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a substance has a potential for carcinogenic effects.

Comparison with criteria in CLP regulation:
There are no relevant data from epidemiological studies submitted by the applicant indicating a carcinogenic potential to humans. Hence, classification with Category 1A according CLP regulation is not possible.
Long-term dietary toxicity studies were conducted in rats and mice. There was no increase in tumour incidences in either study. Hence no classification according to carcinogenicity is proposed.

2.6.7 Summary of reproductive toxicity

After Annex I inclusion, a developmental neurotoxicity screening study with beta-cyfluthrin in rats was conducted (for registration in the USA) that was previously not evaluated on EU level ([redacted] 2003, ASB2007-2856, reported in Vol. 3, B.6.7).
No further new data on reproductive toxicity have been generated since Annex-I inclusion of cyfluthrin/beta-cyfluthrin and the publication of Addendum 1 (2002). All studies here have been previously submitted. For the renewal process they were again evaluated.
A literature research for the Renewal Assessment Report (RAR) including publications from the last 10 years was performed by the RMS. The publications were considered as supplemental information or not acceptable. The results had no influence on the derivation of threshold values or on classification and labelling of beta-cyfluthrin.

2.6.7.1 Fertility studies with cyfluthrin

In a 2-generation study in Sprague-Dawley rats ([redacted] 1996, TOX2001-1771), cyfluthrin at dietary levels of 125 ppm caused reduced parental and pup body weight. Food consumption in parental animals was decreased. Moreover, increased incidences of coarse tremors were found in pups. In addition at 400 ppm, clinical signs of neurotoxicity (splayed hind limbs) were observed in F0 and F1 females during lactation.
The parental and offspring NOAEL is 50 ppm, equivalent to 3.3 mg/kg bw/day (default calculation for males and females). Fertility parameters were not affected by cyfluthrin at doses up to and including 400 ppm (equivalent to 26.7 mg/kg bw/day).
The NOAEL of 50 ppm (3.3 mg/kg bw/d) was confirmed in a supplemental 2-generation study ([redacted] 1997, TOX2001-1772) showing that transient reductions in pup weight noted in the previous study at 50 ppm were not test-substance related.

Table 2.6-29: Summary of fertility studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
3-gen. study OECD 416 Oral, diet, Wistar rat (not acceptable)	0-50-150-450 ppm (3.7-4.0, 11-14, 35-40 and 5.1-5.5, 14-16, 47-50 mg/kg bw/d in males and females)	Cyfluthrin, purity not reported	NOAEL parental: 50 ppm (3.74 mg/kg bw/d) NOAEL reproductive: 50 ppm (3.74 mg/kg bw/d)	Parental: lower fertility index, lower bw gain Offspring: decreased bw gain reductions in viability and lactation index; decreased total number of pups; increased number of dead pups	[redacted] 1983 TOX9401906

Table 2.6-30: Summary of fertility studies evaluated in Addendum 1 to the monograph of beta-cyfluthrin (2002):

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
2-gen. study OECD 416 Oral, diet, SD rat	0-50-125-400 ppm (3-7, 9-19, 29-59 mg/kg bw/day) Default calculation for males and females: 0-3.3-8.3-26.7 mg/kg bw/d	Cyfluthrin, 94.6 - 96.2 %	NOAEL parental: 50 ppm (3.3 mg/kg bw/d) NOAEL offspring: 50 ppm (3.3 mg/kg bw/d) NOAEL reproductive: 400 ppm (26.7 mg/kg bw/d)	Parental: Splaying of the hind limbs in females; decreased bw Offspring: Coarse tremors, decreased bw	[redacted] 1996 TOX2001-1771
Supplemental 2-gen study OECD 416 Oral, diet; SD rat (supplemental)	0-25-50 ppm (1.9-4.1, 3.8-8.0 mg/kg bw/d) Default calculation for males and females: 0-1.7-3.3 mg/kg bw/d	Cyfluthrin, 94.6 - 96.2 %	NOAEL reproductive, offspring, parental: 50 ppm (3.3 mg/kg bw/d)	No effects	[redacted] 1997 TOX2001-1772

Table 2.6-31: Literature research for the Renewal Assessment Report (RAR):

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
The antiandrogenic activity of pyrethroid pesticides cyfluthrin and beta-cyfluthrin. (supplemental)	cyfluthrin (6-18-54 mg/kg bw/d) beta-cyfluthrin (4-12-36 mg/kg bw/d)	Cyfluthrin, purity 92.6 % Beta-cyfluthrin, purity 97 %	Not applicable	Cyfluthrin (18 and 54 mg/kg) and beta-cyfluthrin (36 mg/kg): decrease in the weight of seminal vesicle, ventral prostate, dorsolateral prostate, LABC, Cowper's glands	Zhang et al., 2008 ASB2015-918

Table 2.6-32: Adverse effects on sexual function and fertility:

CLP criteria
Category 1A: Known human reproductive toxicant Category 1B: Presumed human reproductive toxicant largely based on data from animal studies - clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects, or - the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects Category 2: Suspected human reproductive toxicant - some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility and - and where the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study) - the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects

Comparison with criteria in CLP regulation:
There are no epidemiological data to evaluate effects on fertility. Hence, classification with Category 1A according to CLP regulation is not possible.

It should be noted that sperm parameter (number, mobility, morphology) and data on spermatogenesis are not reported in the generational studies in rats. Anyhow, the rat (multigeneration study) is a limited model to assess certain adverse effects on fertility, because an impact on fertility rate in rats is observed only after severe reductions of sperm numbers (e.g., Working, 1998[1]), whereas in humans fertility rate is reduced already by lower sperm number reductions. The value and relevance of histological evaluation of testes is also emphasised in the OCED test guideline 443 and some RAC opinions on harmonised classification of chemicals. Overall, the RMS sees no evidence for adverse effects on reproduction and therefore, proposes no classification.

No effects on fertility were noted in a 2-generation study in rats. Hence no classification for fertility according to CLP regulation is proposed.

2.6.7.2 Teratogenicity studies

In rats, a maternal NOAEL of 3 mg/kg bw/d was derived in the teratogenicity study of [redacted] (1982, TOX9401908) with cyfluthrin. A high-stepping gait, occasionally ataxia and reduced motility were observed in a few dams after administration of the mid- and high-dose (10 and 30 mg/kg bw/d). Doses up to 30 mg/kg bw had no lethal effect and did not affect average weight gain.
No general, embryotoxic and/or teratogenic effects were observed in the offspring, resulting in a developmental NOAEL of 30 mg/kg bw/d.
The maternal NOAEL of 3 mg/kg bw/d was confirmed in an oral teratogenicity of [redacted] (1996, TOX2001-1773, see Table 2.6-35) with beta-cyfluthrin. An increased incidence of mortality and clinical findings (hypoactivity, locomotor incoordination, salivation) were confined to the high-dose group (40 mg/kg bw/d). From 10 mg/kg bw/d onwards a reduction in body weight gain was noted in the dams. A decrease in foetal weight gain and a retarded ossification was noted at 40 mg/kg bw/d and a developmental NOAEL of 10 mg/kg bw/d was derived.
Likewise, no effects were noted in the offspring of HM rabbits up to oral doses of 45 mg/kg bw/d. The maternal NOAEL was 15 mg/kg bw/d, based on abortion ([redacted] 1983, TOX9401914).
In CH rabbits ([redacted] 1992, TOX9401915) the maternal and developmental NOAEL

[1] Working (1988): Male reproductive toxicology: comparison of the human to animal models, Environmental health perspectives 77, 37-44.

was 20 mg/kg bw/d based on decreased food consumption and body weights loss in the dams and on an increased incidence of post-implantative resorptions in the offspring (see Table 2.6-33).
Inhalative exposure to cyfluthrin caused a physiological maternal compensation mechanism (hypothermia with respiratory alkalosis) followed by reflex bradypnoea after sensory irritation.
Summarised, a NOAEL of <0.46 mg/m³ air resulted for maternal toxicity, based on decreased food intake and body weight development, hypothermia and bradypnoea (hypoventilation) in dams at this dose. At higher doses clinical signs in dams and retarded development of the foetuses occurred in addition. At doses of 11.9 and 12.8 (+O_2) mg/m³ air clear signs of maternal toxicity occurred in the form of respiratory disturbances and hypoactivity in dams. In the offspring higher incidences (compared to historical control data) of microphthalmia and anophthalmia occurred ([redacted] 1993, TOX9401829).
In another teratogenicity study with inhalative exposure ([redacted] 1988, TOX9401910) a maternal and developmental NOAEL of 0.59 mg/m³ air was based on reduced body weight development in the dams, reduced foetal weight and retarded ossification at the next higher dose of ≥1.1 mg/m³ air. In addition at ≥4.16 mg/m³ air (+O_2) clinical signs occurred in the dams and an increased incidence of resorptions and of microphthalmia was noted in the offspring (see Table 2.6-34).
After Annex I inclusion a developmental neurotoxicity screening study with beta-cyfluthrin in rats has been conducted ([redacted] 2003, ASB2007-2856, see Vol.3, B.6.7).
A literature search for the Renewal Assessment Report (RAR) including publications from the last 10 years was performed by the RMS. The studies are considered not acceptable.

Table 2.6-33: Summary of oral teratogenicity studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Teratogenicity; FB 30 rats Gavage 6th -15th day	0-3-10-30 mg/kg bw/d	cyfluthrin (purity: approx. 85 %) vehicle: polyethylene glycol E 400	NOAEL maternal: 3 mg/kg bw/d NOAEL developmental: 30 mg/kg bw/d	Maternal: High-stepping gait, ataxia, reduced motility Offspring: No effects	[redacted] 1982 TOX9401908
Teratogenicity; Wistar rats Gavage 6th -15th day of gestation	0-1-3-10 mg/kg bw/d	cyfluthrin (purity 93.4 %) vehicle: cremophor EL/distilled water (1 % v/v)	NOAEL maternal and developmental: ≥10 mg/kg bw/d	No effects	[redacted] 1983 TOX9401909
Teratogenicity; HM rabbits, gavage, 6th -18th day of gestation	0-5-15-45 mg/kg bw/d	cyfluthrin (purity: 95.0 %) vehicle: Cremophor EL/water (0.5 %)	Maternal: 15 mg/kg bw/d Developmental: 45 mg/kg bw/d	Maternal: Abortion Offspring: No effects	[redacted] 1983 TOX9401914
Teratogenicity; CH rabbits, gavage, 6th -18th day of gestation	0-20-60-180 mg/kg bw/d	cyfluthrin (purity 96.0 %) formulated in corn oil	Maternal: 20 mg/kg bw/d Developmental: 20 mg/kg bw/d	Maternal: decreased food consumption, bw loss Offspring: Increased post-implantative resorptions	[redacted] 1992 TOX9401915

Table 2.6-34: Summary of inhalative teratogenicity studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Teratogenicity; Wistar rats, aerosol, head-nose exposure 6th -15th day of gestation, 6 h per day	1st exp.: 0-1.1-4.7-23.7 mg/m³ air 2nd exp.: 0-0.09-0.25-0.59-4.16 + O_2 mg/m³ air	cyfluthrin (1st exp. purity: 92.9 – 93 %; 2nd exp. purity 96.2 %) formulated in ethanol/ polyethylene glycol E 400 as aerosol	Maternal and developmental: 0.59 mg/m³ air	≥1.1 mg/m³ air: reduced bw development, reduced fetal weight, retarded ossification In addition ≥ 4.16 mg/m³ air+O_2: Clinical signs of the dams In addition at 23.7 mg/m³ air: Increased incidence of resorptions increased frequency of microphthalmia	[redacted] 1988 TOX9401910
Teratogenicity; Wistar rats, aerosol, head-nose exposure 6th -15th day of gestation, 6 h per day	0-0.46-2.55-11.9-12.8+O_2 mg/m³ air	cyfluthrin (purity 94.7 - 96.2 % formulated in ethanol/ polyethylene glycol E 400	Maternal: <0.46 mg/m³ air Developmental: 0.46 mg/m³ air	≥0.46 mg/m³ air: Decreased food intake and bw development in dams, hypothermia and bradypnoea (hypoventilation) in dams In addition ≥2.55 mg/m³ air: Clinical signs in dams, retarded development of fetuses In addition ≥11.9 mg/m³ air: Respiratory disturbances and hypoactivity in dams, higher incidence of microphthalmia and anophthalmia	[redacted] 1993 TOX9401829

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Determination of the FCR 1272 concentration in the plasma of rats following inhalative exposure	0.5, 2.5, 12.5 and 12.5 + O_2 mg/m³ air	cyfluthrin (purity 92 %) first dissolved in 5 mL 1,4-dioxane, this solution made up to 50 mL with n-hexane	Not applicable	Very low concentrations of cyfluthrin were only found in the high-dose groups 12.5 mg/m³ air and 12.5 mg/m³ air (+39 % oxygen).	[redacted] 1993 TOX9401913

Table 2.6-35: Summary of teratogenicity studies evaluated in Addendum 1 to the monograph of beta-cyfluthrin (2002):

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Teratogenicity; Wistar rats Gavage 6th -15th day of gestation	0–3–10–40 mg/kg bw/d	beta-cyfluthrin technical (purity: 96.5 - 97.3 %) vehicle: 1 % aqueous Cremophor	NOAEL maternal: 3 mg/kg bw/d NOAEL developmental: 10 mg/kg bw/d	Maternal: 40 mg/kg bw/d: Mortality, clinical findings (hypoactivity, locomotor incoordination, salivation); ≥10 mg/kg bw/d: decreased body weight gain and food consumption Offspring: 40 mg/kg bw/d: decreased weight; retarded ossification	[redacted] 1996 TOX2001-1773

Table 2.6-36: Literature research for the Renewal Assessment Report (RAR):

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Evaluation of teratogenic potential of cyfluthrin, a synthetic pyrethroid in Swiss albino mice (not acceptable)	0-16-32 mg/kg bw (2 doses daily from day 5-14 and 14-18 of gestation)	SOLFAC 050 EW (5 % cyfluthrin, purity unknown) Vehicle: tap water	Not applicable	32 mg/kg bw SOLFAC 050 EW: Maternal: Burrowing behaviour, reduction in bw gain Offspring: Reduced litter size and number of live foetuses, lower foetal bw, increased	Syed et al., 2010 ASB2015-933
Perinatal toxicity of cyfluthrin in mice:	0-16-32 mg/kg bw (2 doses daily from day 5-14	SOLFAC 050 EW (5 % cyfluthrin, purity	Not applicable		Soni et al., 2010 ASB2015-925

Study	Dose levels	Test substance	NO(A)E(C)L	Targets / Main effects	Reference
Developmental and behavioral effects (not acceptable)	and 14-18 of gestation)	unknown) Vehicle: tap water		number of resorbed foetuses 16 and 32 mg/kg bw SOLFAC 050 EW: Offspring: Hydrocephaly, anophthalmia, microphthalmia, pulmonary edema, subcutaneous edema	
Comments on: 'Perinatal toxicity of cyfluthrin in mice: Developmental and behavioral effects' by Soni and colleagues (not acceptable)	0-16-32 mg/kg bw (2 doses daily from day 5-14 and 14-18 of gestation)	SOLFAC 050 EW (5 % cyfluthrin, purity unknown) Vehicle: tap water	Not applicable	Not applicable	Shafer and Crofton, 2011 ASB2013-932
Teratogenicity; mice Orally at day 6th of gestation, single dose (not acceptable)	1.25, 2.50 and 5.00 µg/g	Beta-cyfluthrin (purity not reported; vehicle: distilled water)	Not applicable	From 1.25 µg/g onwards: Lower bw, crown rump length, brain size, length and width of eye, length of fore/hind limbs length of tail; malformations (microcephaly, anophthalmia, micromelia, dysmorfogenesis, dysplasia)	Ahmad et al., 2012 ASB2015-922

Table 2.6-37: Adverse effects on development:

CLP criteria
Category 1A: Known human reproductive toxicant Category 1B: Presumed human reproductive toxicant largely based on data from animal studies - clear evidence of an adverse effect on development in the absence of other toxic effects, or - the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects Category 2:

Suspected human reproductive toxicant
- some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on development and
- the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study).
- the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects

Comparison with criteria in CLP regulation:
There are no appropriate epidemiological studies available on developmental effects in humans. Hence, classification with Category 1A according CLP regulation is not possible.

The prenatal developmental toxicity of beta-cyfluthrin and cyfluthrin was investigated in rats and rabbits and the studies were considered acceptable.
In inhalational teratogenicity studies in rats with cyfluthrin, the increased frequency of malformations (microphthalmia, anophthalmia, bone malformations) in the offspring at 11.9, 12.8 (with oxygen supplement), and 23.7 mg cyfluthrin /m³ air was considered to represent a secondary effect due to hypoxic conditions in the dams ([redacted] 1988, TOX9401910; [redacted] 1993, TOX9401829). Due to the irritating properties of the test substance at these dose levels a reflex bradypnoea occurred in the dams which was compensated by hypothermia and a reduction in metabolic activity. In addition, an increased incidence of resorptions occurred at a dose level of 23.7 mg/m^3 ([redacted] 1988, TOX9401910). It can be assumed that the occurrence of the mentioned malformations, especially microphthalmia, in the offspring does not represent a direct toxic effect of the test substance. This assumption is supported by reproductive toxicity studies with orally administered beta-cyfluthrin/cyfluthrin where no treatment-related malformations were observed. It is therefore proposed not to classify cyfluthrin for embryotoxic effects in the presence of maternal toxicity (cat. 2). Anyhow, it is proposed to classify and label beta-cyfluthrin/cyfluthrin according to the respiratory irritating effects (STOT-SE 3 H335 May cause respiratory irritation).
Even though some of the observed findings in the dams were severe findings (such as clinical signs, motor disturbances and/or gait abnormalities), they were considered to represent acute toxic/neurotoxic effects of beta-cyfluthrin/cyfluthrin. Due to intensive metabolism and rapid excretion of beta-cyfluthrin/cyfluthrin, daily administrations of beta-cyfluthrin/cyfluthrin are considered to represent a sequence of acute intoxications. A proposal for classification for acute effects is already made.
Manifestations of developmental toxicity seen in rats and rabbits were accompanied by maternal toxicity. Abortion was observed in two (top dose) rabbits, and one dam resorbed its implants completely ([redacted] 1983, TOX9401914). From 60 mg/kg bw/d an increase in the number of post-implantative resorptions was the only observed change in rabbits interpretable as a sign of reproduction toxicity ([redacted] 1992, TOX9401915). Taken together, based on the small number of animals affected, these findings are considered not severe enough to justify a classification in Category 2 (H361d).
An increased incidence of coarse tremors and the decreased pup body weight observed during the lactation phase (as early as lactation day 5 and ceased by lactation day 18 after weaning) in F_1 and F_2 pups at and above 125 ppm (19 and 59 mg/kg bw/d) occurred in the presence of maternal toxicity ([redacted] 1996, TOX2001-1771). The excretion of cyfluthrin in rat milk has not been determined but it can be concluded that the presence of adverse effects in the offspring at 125 ppm was due to transfer of cyfluthrin or of its metabolite(s) in the milk during the lactation period. This conclusion is supported by the absence of adverse treatment effects on prenatal or peri-natal litter parameters. Cyfluthrin exposure through the milk is considered to be the main determinant of offspring neurotoxicity and it is proposed to classify beta-cyfluthrin as reproductive toxicant in category for effects via lactation.

In a position paper submitted by the applicant an argumentation for the rebutting of this classification proposal is provided. In this statement it is agreed that the tremors seen in the early phase of lactation is attributed to exposure of the pups to cyfluthrin via the milk of the lactating parent females. It is further stated that these coarse tremors are transient and characteristic of acute neurotoxicity associated with Type II pyrethroids. Finally it is concluded that the age-dependent sensitivity in young

rats is consistent with a mode of action that is not relevant to infants and children, because it is a high-dose phenomenon associated with a limited metabolic capacity of neonatal rats (in rats pyrethroids are primarily metabolised by cytochrom P450 enzymes and in humans by carboxylesterase enzymes) ([redacted] 2014, ASB2014-7900).
However, the argumentation provided by the applicant in the position paper is not convincing and the relevance for humans cannot be excluded. Thus, the proposal for classification and labelling with Lact. H362 *'May cause harm to breast-fed children'* is sustained by the RMS.

Classification and labelling for reproductive toxicity according to Regulation (EC) No 1272/2008 (GHS):

Lact. H362: May cause harm to breast-fed children.

2.6.8 Summary of neurotoxicity

No further new data on neurotoxicity have been generated since Annex-I inclusion of cyfluthrin/beta-cyfluthrin and the publication of Addendum 1 (2002). For the renewal process they were evaluated again. Older studies evaluated in the original monograph of beta-cyfluthrin (October 1996) were performed with cyfluthrin, recently submitted studies and studies evaluated in Addendum 1 to the monograph (2002) were mainly performed with beta-cyfluthrin.
The safety pharmacological studies are reported in this chapter because they were focused on neurological disorders. These studies were performed in rats and mice with cyfluthrin. In rats, higher doses of beta-cyfluthrin may cause clinical and histological signs of neurotoxicity. These acute neurotoxic effects of beta-cyfluthrin were behavioural disturbances typical of α-cyanopyrethroids (choreoathetosis and salivation). However, the effects were found reversible following withdrawal of the test substance (see Table 2.6-38).
The submitted studies for determination of delayed neurotoxicity were performed in hens with cyfluthrin. With the exception of the study for effect on the neurotoxic target enzyme (NTE) in chicken ([redacted] 1985, TOX9401919) all experimental studies were considered as supplemental information since the studies were not conducted under GLP conditions and the study design did not or only partially followed an accepted guideline. No evidence of delayed neurotoxicity of cyfluthrin, in the form of a neuropathy of delayed onset, was observed in hens, based on clinical, biochemical and histological evidence (see Table 2.6-39).
In the study of [redacted] (1999, TOX2001-1264) a pharmacological NOAEL for acute neurotoxic effects was set at 3 mg/kg bw based on the occurrence of clinical signs and reduced slip angle at ≥7.5 mg/kg bw.
An acute neurotoxicity study with beta-cyfluthrin in rats used Cremophor/water as vehicle ([redacted] 1997, TOX2001-1265), which is a vehicle leading to worst-case exposure as not achievable under realistic conditions and has been shown to elicit higher acute toxicity. For FOB parameters, motor activity and locomotor activity, treatment-related effects were noted at 10 mg/kg bw. Compound-related microscopic lesions were not evident in males or females. The acute NOAEL for both sexes was 2 mg/kg bw.
The subchronic neurotoxicity feeding study with beta-cyfluthrin ([redacted] 1997, TOX2001-1266), showed reversible FOB-related findings at 400 ppm (26.8/30.8 mg/kg bw/day for males and females, respectively). Paraesthesia and a decrease of body weights occurred from 125 ppm (8/9.4 mg/kg bw/d for males and females, respectively) onwards. The overall NOAEL for both sexes was 2.02 mg/kg bw/day (see Table 2.6-40).
After Annex I inclusion, a developmental neurotoxicity study with beta-cyfluthrin in rats was conducted (for registration in the USA) and was not previously evaluated on EU level (see Table 2.6-41). Lower body weight development during gestation and lactation was noted in dams. In the offspring, reduced pup weight gain, and minimal resistance during handling as well as a reduced startle response was observed in FOB. The maternal and offspring NOAEL was 125 ppm (11 mg/kg bw/d).
A literature search (see Table 2.6-42) for the Renewal Assessment Report (RAR) including publications from the last 10 years was performed by the RMS. The publications were considered as supplemental information.

Table 2.6-38: Summary of safety pharmacological studies evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Safety pharmacology study on oral administration; male mice, gavage (no guideline, supplemental)	0-0.1-0.3-1 mg/kg bw	cyfluthrin (purity 94.9 %) vehicle: Cremophor EL/water	0.3 mg/kg bw	1.0 mg/kg bw: prolongation and deepening of hexobarbital narcosis in the sleep test	[redacted] 1982 TOX9401943
Study of FCR 1272 on neuromuscular dysfunction in the tilting plane test on rats male rats, gavage (no guideline, not acceptable)	1st exp.: 0-0.1-0.3-1.0 mg/kg bw 2nd exp.: 0-0.01-0.03-0.1 mg/kg bw	cyfluthrin (purity not specified) vehicle: Cremophor EL/water	0.01 mg/kg bw	≥0.03 mg/kg bw: neuromuscular dysfunction	[redacted] 1984 TOX9401944
CNS safety pharmacology study on oral administration, male mice and rats, gavage (no guideline, not acceptable)	0-3-10-30 mg/kg bw	cyfluthrin (purity not specified) vehicle: polyethylene glycol 400	10 mg/kg bw	30 mg/kg bw: Mortalities, seizures, disappearance of the righting reflex	[redacted] 1985 TOX9401945
Study for nerve damage effect; rats, gavage, 5-months application (no guideline, supplemental)	30-80 mg/kg bw/d	cyfluthrin (purity 83.3 %) vehicle: polyethylene glycol 400	None	≥30 mg/kg bw/d: Mortality, behaviour disturbances	[redacted] 1982 TOX9401922
Special toxicological study (morphological effects on the nervous system of rats), gavage, 14 days (no guideline, supplemental)	0-80(40) mg/kg bw/d	cyfluthrin (purity 95 %) vehicle: polyethylene glycol 400	None	80(40) mg/kg bw/d: Acute toxic symptoms, decreased bw, reversible nerve fibre degeneration	[redacted] 1983 TOX9401923

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Study for neurotoxic effect on rats after subacute oral administration, gavage, 14 days (no guideline, supplemental)	0, 50 (males only) and 60 mg/kg bw/d	cyfluthrin (purity: 96.5 %) vehicle: polyethylene glycol 400	None	60 mg/kg bw/d: Mortality ≥50 mg/kg bw/d: acute toxic symptoms, decreased bw	[redacted] 1983 TOX9401924
The effects of type I and type II pyrethroids on motor activity and the acoustic startle response in the rat, gavage (no guideline, supplemental)	10-50 mg/kg bw/d	cyfluthrin (purity not specified) vehicle: corn oil	None	≥10 mg/kg bw/d: reduction in locomotor activity, decreased amplitude and an increased latency to onset of the acoustic startle response.	[redacted] 1988 TOX9401952

Table 2.6-39: Summary of studies for delayed neurotoxicity testing in hens evaluated in the original monograph of beta-cyfluthrin by the RMS in October, 1996 (ASB2010-10436)

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Investigative neurotoxicity studies in hens, single (gavage) and repeated administration (partly OECD TG 418 and 419, supplemental)	1st exp.: 5000 mg/kg bw 2nd exp.:2 x 5000 mg/kg bw	1st exp.: cyfluthrin (purity: 84.8 %) 2nd exp.: cyfluthrin (purity: 89.3 %) vehicle: carbowax batch no.: A7A	None	1st exp.: bw loss 2nd exp.: clinical signs No evidence of delayed neurotoxic activity of cyfluthrin in doses up to 2 x 5000 mg/kg bw	[redacted] 1981 TOX9401952

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Neurotoxicity studies on hens, diet, (non-guideline, supplemental)	1st exp.: 1000-2500-5000 mg/kg bw, single doses 2nd exp.:2 x 5000 mg/kg bw 3rd exp.:5 x 5000 mg/kg bw	1st exp.: cyfluthrin (batch no.: 16001/79 purity: 85.3 %) 2nd exp.: cyfluthrin (batch no.: 16003/79 purity: 84.4 %) 3rd exp.: cyfluthrin (batch no.: 16003/80 purity: 94.3 %) vehicle: polyethylene glycol E 400	None	1st exp.: Mortality and slight degenerative changes in sciatic nerves at 5000 mg/kg bw ≥2500 mg/kg bw: clinical signs, decreased bw	[redacted] 1981 TOX9401916
Acute delayed neurotoxicity study with FCR 1272 in the hen, single (gavage) and repeated administration (partly OECD TG 418 and 419, supplemental)	1st exp.: 4300 mg/kg bw 2nd exp.:2 x 4300 mg/kg bw 3rd group: 5 x 1500 mg/kg bw	cyfluthrin (batch no. 233 590 478 purity 93.5 %) vehicle: polyethylene glycol E 400	None	Mortality and clinical signs in all groups No evidence of delayed neurotoxic activity of cyfluthrin	[redacted] 1986 TOX9401920
Study for effect on the neurotoxic target enzyme (NTE) in chicken, gavage, no guideline, acceptable	3 x 5000 mg/kg bw	cyfluthrin (batch no.: 233490583 purity 92.9 %) vehicle: polyethylene glycol E 400	None	Mortality after 3rd administration, clinical signs No evidence of delayed neurotoxic esterase activity	[redacted] 1985 TOX9401919
Cyfluthrin neurotoxicity study on chickens after cutaneous administration. (no guideline, supplemental)	1st exp.: 5 x 5000 mg/kg bw (23 h/d; 5 days) 2nd exp.: 15 x 5000 mg/kg bw (6 h/d; 5 days)	cyfluthrin (batch no. 816170019 and 816170019 purity 91.4 - 95.0 %) vehicle: Cellulose MN 300	None	Mortality, clinical signs (systemic and dermal), decreased bw No evidence of delayed neurotoxic activity of cyfluthrin	[redacted] 1982 TOX9401921
Study for acute and subacute inhalation toxicity on chicken and rats Partly OECD	Rat: 0.596 mg/L air (single, 4 h, whole body) Hen: 596 mg/m³ (single, 4 h, whole body)	cyfluthrin (batch number: 816 170 019 purity 95.0 %) vehicle: ethanol/polyethylene glycol E 400, 1:1	None	Rat: Mortality, clinical symptoms Hen: itrritating effects on eye mucosa, clinical symptoms	[redacted] 1983 TOX9401865

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
TG 403 and 412, supplemental	Hen: 15 x 614 mg/m³, (6 h/d, 5 days)			No evidence of delayed neurotoxic activity of cyfluthrin	

Table 2.6-40: Summary of neurotoxicity studies with beta-cyfluthrin evaluated in Addendum 1 to the monograph of beta-cyfluthrin (2002)

Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Special Study for Acute Oral Toxicity in Rats (Slip Angle Test), gavage, no guideline	0.015-9 mg/kg bw	cyfluthrin (purity: 96.1 %) vehicle: aqueous Cremophor ® EL	3 mg/kg bw (slip angle)	7.5 and 9 mg/kg bw: Clinical signs, reduced slip angle	[redacted] 1999 TOX2001-1264
Acute oral neurotoxicity screening study in rats, gavage, US-EPA-FIFRA Pesticide Assessment Guideline No. 540/09-91-123	0–0.5–2 and 10 mg/kg bw	beta-cyfluthrin, (batch-no: 3030125/0250074; purity: 96.9 - 97.3 %) vehicle: 1 % Cremophor ® EL	2 mg/kg bw	10 mg/kg bw: clinical signs in FOB (reduced motor and locomotor activity) reversible (on day 7 post treatment)	[redacted] 1997 TOX2001-1265
Subchronic neurotoxicity study in rats US-EPA-FIFRA Pesticide Assessment Guideline No. 540/09-91-123, diet	0-30-125-400 ppm (equal to 0-2.02-7.99-26.81 mg/kg bw/d for males and 0-2.34-9.40-30.83 mg/kg bw/d for females).	beta-cyfluthrin (Batch-No. 3030125/0250074 purity: 96.5 - 97.3 %)	30 ppm (2.02 mg/kg bw/d)	400 ppm: clinical signs in FOB ≥125 ppm: clinical signs (paresthesia), decreased bw	[redacted] 1997 TOX2001-1266

Table 2.6-41: Developmental neurotoxicity study submitted for the renewal assessment report (RAR):

Table Study	Dose levels	Test substance	NO(A)EL	Targets / Main effects	Reference
Developmental Neurotoxicity Screening Study in Rats; diet	0-30-125-200 ppm (equal to 0-2.4-11.0-17.8 mg/kg bw/d during	beta-cyfluthrin (Batch-No. 8030130/380566042, purity:	125 ppm (11 mg/kg bw/d during gestation)	Maternal: 200 ppm: Lower bw development during gestation	[redacted] 2003 ASB2007-2856

OECD TG 426	gestation and 0-5.9-25.4-40.9 mg/kg bw/d during lactation).	95.1 - 97.6 %)		and lactation Offspring: 200 ppm: Reduced pup weight gain, FOB: minimal resistance during handling, reduced startle response	

Table 2.6-42: Literature research for the Renewal Assessment Report (RAR):

Table Study	Dose levels	Test substance	NO(A)EL	Targets/ Main effects	Reference
Relative potencies for acute effects of pyrethroids on motor function in rats (supplemental)	0.05-15 mg/kg bw/d 8 doses	Cyfluthrin (purity: 99.2 %); vehicle: corn oil	Not applicable	All pyrethroids produced dose-dependent decreases in motor activity.	Wolansky et al., 2006 ASB2013-7265
Comparative FOB study of twelve commercial pyrethroid insecticides in male rats following acute oral exposure (supplemental)	12.5, 25, and 45 mg/kg bw	Beta-cyfluthrin (purity not reported); vehicle: corn oil	Not applicable	Identification of a common mode of action of pyrethroids	Weiner et al., 2009 ASB2015-934
Evidence for a separate mechanism of toxicity for the Type I and the Type II pyrethroid insecticides (supplemental)	No information provided	Beta-cyfluthrin (purity not reported); vehicle: corn oil	Not applicable	Identification of a mode of action of pyrethroids	Breckenridge et al., 2009 ASB2015-830
Neurotoxic implications of the agonistic action of CS-syndrome pyrethroids on the N-type Cav2.2 calcium channel (supplemental)	No information provided	Cyfluthrin (purity and vehicle not reported)	Not applicable	Identification of a mode of action of pyrethroids	Clark and Symington, 2008 ASB2015-918

Evaluation of changes in monoamine levels and apoptosis induced by cyfluthrin in rats (supplemental)	0-14 mg/kg bw/d intraperitoneally	Cyfluthrin (purity: 97.2 %); vehicle: corn oil	Not applicable	Cyfluthrin toxicity in CNS and effect on neurotransmitter	Guvenc et al., 2014 ASB2015-923

2.6.9 Summary of further toxicological studies on the active substance

A number of supplementary studies on beta-cyfluthrin and cyfluthrin were already evaluated previously. A re-evaluation was performed for the renewal process. To the submitted studies belonged biochemical studies, antidote studies, acute oral combination toxicity studies, studies on tumour promotion, mechanistic studies, a study concerning the risk of indoor use, acute toxicity studies using other routes than oral, dermal or inhalative as well as studies addressing the sensory irritant potential. All studies – unless an antidote test with atropine and methocarbamol ([redacted] 1984, TOX9401942, Vol. 3, B.6.8) as well as two acute toxicity studies [redacted] 1985, TOX9550254, [redacted] 1980, TOX9550282, Vol. 3, B.6.8) – were evaluated as acceptable or supplementary. The studies considered as not acceptable are not summed up hereafter.

2.6.9.1 Biochemical studies (cyfluthrin)

Cyfluthrin as well as some cyfluthrin metabolites were less efficient inhibitors of Na^+-, K^+ or Mg^{2+}-activated transport ATPases than other substances like ouabain or DDT ([redacted] 1982, TOX9401939).
Exposure of rats to concentrations of cyfluthrin above the sensory irritant threshold resulted in refectory respiratory changes that are associated with transient effects on thermoregulation as well as the physiological acid-base status ([redacted] 1992, TOX9401940).
In further studies available to RMS (e.g. from other applications) cyfluthrin aerosol (up to 101 mg/m³ air) had no toxicologically relevant impact on the arterial blood gases of rats but led to hypothermia ([redacted] 1988, TOX9401870, [redacted] 1988, Z14816). However, after oral administration (up to 500 mg/kg bw in PEG 400) no impact on body temperature was observed in rats ([redacted] 1991, TOX9401863).

2.6.9.2 Antidote studies (cyfluthrin)

A reduced acute toxicity was observed after administration of Musaril ([redacted] 1983, TOX9401941).

2.6.9.3 Acute oral combination toxicity studies (cyfluthrin)

Following combined administration of cyfluthrin with other insecticides no super-additive acute toxic effects were observed, but sub-additive acute toxic effects were recorded ([redacted] 1982, TOX9401946, [redacted] 1983, TOX9401947, [redacted] 1984, TOX9401948, [redacted], 1984, TOX9401949, [redacted] 1994, TOX2001-1764). A slight super-additive effect was observed after simultaneous administration of cyfluthrin and omethoate ([redacted] 1988, TOX9401950).

2.6.9.4 Study on tumour promotion (cyfluthrin)

Cyfluthrin did not exhibit a tumour-promoting potential *in vitro* (Wärngard and Flodström, 1989, TOX9401951).

2.6.9.5 Mechanistic studies (cyfluthrin)

Cyfuthrin was detected in serum, fat and brain of rats after inhalation or oral exposure as well as after dietary administration to rats ([redacted] 1996, TOX2001-1767, [redacted] 1996, TOX2001-1768).
It has been shown that beta-cyfluthrin and cyfluthrin are associated with oxidative stress (beta-cyfluthrin *in vitro*, cyfluthrin *in vivo*) (Sadowska-Woda et al., 2009, ASB2015-790, Yilmaz et al., 2014, ASB2015-888). Furthermore, these substances disturb the antioxidant defence system (publications from literature search in the database Scopus).

2.6.9.6 Indoor use (cyfluthrin)

The RD_{50} values after 1h-exposure to cyfluthrin (aerosol, PEG; nose only) in rats and mice were 47 and 51 mg/m³ air, respectively. A subacute exposure did not affect the responsiveness or magnitudes of changes in breathing patterns. Therefore, the effects were rather non-cumulative. Furthermore, pyrethroid burden in the indoor environment from carpets seems to be low (Pauluhn, 1996, TOX2001-880).

2.6.9.7 Other routes for LD_{50} determination

After intraperitoneal injection beta-cyfluthrin led to lower LD_{50} values than cyfluthrin. The higher toxicity of beta-cyfluthrin could be due to the different composition of the less and more toxic isomers (beta-cyfluthrin more toxic isomer 2 and only little amount of less toxic isomer 3, Vol. 3, B.6.8).

Table 2.6-43: Other routes for LD_{50} determination: beta-cyfluthrin*

Route	Species	Sex	Vehicle	Result	Reference
i.p.	rat	male female	PEG 400	8.5 mg/kg bw 17 mg/kg bw	[redacted] 1987, TOX9550269
i.p.	mice	male	PEG 400	18 mg/kg bw	[redacted] 1988, TOX9550270

* All studies are considered acceptable.

Table 2.6-44: Other routes for LD_{50} determination: cyfluthrin*

Route	Species	Sex	Vehicle	Result	Reference
i.p.	mice	male	PEG 400	63 mg/kg bw	[redacted] 1988, TOX9550270
i.p.	rat	male female	PEG 400	66 mg/kg bw[1] 104 mg/kg bw[1]	[redacted] 1980, TOX9401853
i.p.	rat	male female	PEG 400	34 mg/kg bw[1] 94 mg/kg bw[1]	[redacted] 1982, TOX9401854
i.p.	rat	male female	chremophor/water	20 mg/kg bw[1] 24 mg/kg bw[1]	[redacted] 1982, TOX9401854
s.c.	mice	male female	PEG 400	>2500 mg/kg bw[1]	[redacted] 1980, TOX9401853

* All studies are considered acceptable.
[1] These studies were not submitted by the applicant (but available to RMS e.g. from literature in database or other applications).

2.6.9.8 Sensory irritant potential

Inhalation of beta-cyfluthrin led to bradypnoea due to its sensory potential (RD_{50}, respiratory decrease). The RD_{50} values were 38 mg/m³ air or 37 mg/m³ air for rats and mice, respectively. The RD_{50}

values after exposure to cyfluthrin amounted to 47-50 mg/m³ air in rats and 51-67 mg/m³ air in mice.

Table 2.6-45: RD_{50} values: beta-cyfluthrin*

Parameter	Species	Sex	Vehicle	Result	Reference
Inhalative RD_{50} (45 min, head-nose)	rat	male	Ethanol/PEG 400	38 mg/m³ air	[redacted] 1988, TOX9550263
Inhalative RD_{50} (45 min, head-nose)	mice	male	Ethanol/PEG 400	37 mg/m³ air	[redacted] 1988, TOX9550262

* All studies are considered acceptable.

Table 2.6-46: RD_{50} values: cyfluthrin

Parameter	Species	Sex	Vehicle	Result	Reference
Inhalative RD_{50} (45 min, head-nose)	mouse	male	Ethanol/PEG 400	RD50 ~ 67 mg/m³ air[1,2]	[redacted] 1988, TOX9401869
Inhalative RD_{50} (60 min, head-nose)	rat	male	Ethanol/PEG 400	RD50 ~ 50 mg/m³ air[1]	[redacted] 1995, TOX9552072
Inhalative RD_{50} (60 min, nose)	rat and mice	male female	PEG 400	Rat: RD_{50} = 47 mg/m³ air[1,2,3] Mouse: RD_{50} = 51 mg/m³ air[1,2,3]	[redacted] 1996, TOX2001-880

[1] These studies were not originally submitted by the applicant (but available to RMS e.g. from literature in database or other applications).
[2] These studies are considered supplementary.
[3] The study is part of the submitted dossier (and reference list). A detailed description of the study is given in the appropriate chapter of the RAR.

2.6.10 Summary of studies regarding endocrine disrupting properties

Designated studies on endocrine disrupting properties of beta-cyfluthrin have not been conducted by the applicant. The examined endpoints in reproduction toxicity studies did not indicate specific disrupting properties of beta-cyfluthrin. The available fertility studies showed no effects on male or female fertility. The developmental neurotoxicity study ([redacted] 2003, ASB2007-2856) did not reveal effects on developmental landmarks or sexual maturation.
Anyhow it should be noted that male animals were examined less extensively than female animals. Male animals were treated with beta-cyfluthrin only in generational/fertility studies. They were not treated in the teratogenicity studies and data on sperm parameters (number, motility, morphology) and spermatogenesis were not provided in either study on rats and dogs. In addition, based on the information provided, effects on hormone-sensitive tissues like reproductive organs, thyroids and pituitary were not reported in the available repeat-dose toxicity studies.

2.6.11 Summary of toxicological data on impurities and metabolites

The available tests with cyfluthrin metabolites were submitted previously. The results of the re-evaluation – if studies were evaluated as acceptable or supplementary – are presented in Table 2.6-47.

Table 2.6-47: Summary of studies with metabolites

Metabolite (abbreviation)	Endpoint	Test organism	Result	Reference
3-Phenoxy-4-fluorobenzyl alcohol (FPB_{alc})	acute oral toxicity	rat (male and female)	male: LD_{50} = 1599 mg/kg bw female: LD_{50} = 1600-1800 mg/kg bw	[redacted] 1987 (15419) TOX9401933[2]
	mutagenicity (Ames test)	bacterial strains (TA1535, TA100, TA1537, TA98)	negative +/- S9 mix	Herbold, 1987 (15909) TOX9401936[2]
3-Phenoxy-4-fluoro-benzaldehyde (FPB_{ald})	acute oral toxicity	rat (male and female)	male: LD_{50} = 1248 mg/kg bw female: LD_{50} = 1040 mg/kg bw	[redacted] 1981 (9942) TOX9401927
	acute dermal toxicity	rat (male and female)	24 h contact: LD_{50} > 5000 µl/kg bw	[redacted] 1981 (9942) TOX9401927
	acute inhalative	rat (male and female)	whole body exposure for 7 h: after dynamic vaporisation of 50 g test compound: no animal died	[redacted] 1981 (9942) TOX9401927[2]
	skin irritation	rabbit (sex unclear)	negative	[redacted] 1981 (9942) TOX9401927
	eye irritation	rabbit (sex unclear)	not primary irritant to mucous membranes	[redacted] 1981 (9942) TOX9401927
	mutagenicity (Ames test)	bacterial strains (TA1535, TA100, TA1537, TA98)	negative +/- S9 mix	Herbold, 1985 (13429) TOX9401928[2]
3-Phenoxy-4-fluoro-benzoic acid (FPB_{acid})	acute oral toxicity	rat (male and female)	male: LD_{50} > 5000 mg/kg bw female: LD_{50} > 5000 mg/kg bw	[redacted] 1986 (14800) TOX9401930[2]

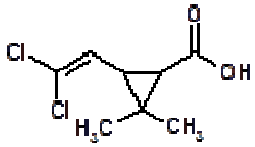
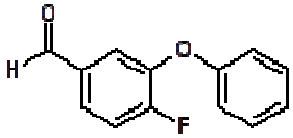
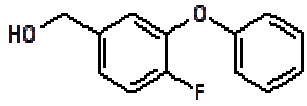
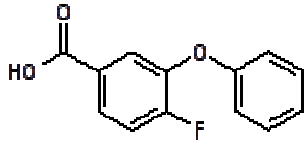
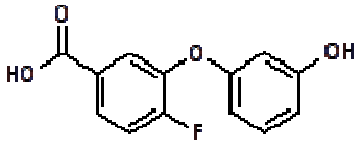
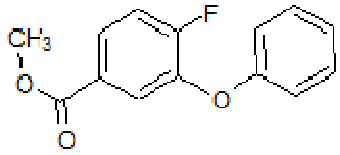
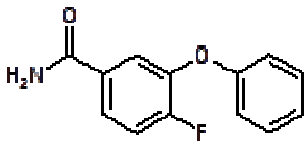
Metabolite (abbreviation)	Endpoint	Test organism	Result	Reference
3(4'-Hydroxyphenoxy)-4-fluorobenzoic acid (4-OH-FPB$_{acid}$)	acute oral toxicity	rat (male and female)	male: LD_{50} > 1000 mg/kg bw female: LD_{50} > 1000 mg/kg bw	[redacted] 1987 (15532) TOX9401934[2]
	mutagenicity (Ames test)	bacterial strains (TA1535, TA100, TA1537, TA98)	negative +/- S9 mix	Herbold, 1987 (15724) TOX9401935[2]
3-Phenoxy-4-fluoro-benzoic acid amide (FPB$_{amide}$)	acute oral toxicity	rat (male and female)	male: LD_{50} > 5000 mg/kg bw female: LD_{50} > 5000 mg/kg bw	[redacted] 1986 (14799) TOX9401929[2]
	mutagenicity (Ames test)	bacterial strains (TA1535, TA100, TA1537, TA98)	negative +/- S9 mix	Herbold, 1988 (16703) TOX9401938[2]
+,-(R,S)-α-Carboxy-[3-phenoxy-4-fluoro]benzyl-1-(R,S)-trans-3-(2',2'-dichloroethen-1'-yl)-2,2-dimethylcyclo-propanecarboxylic acid ester (Cyfluthrin$_{acid}$)	acute oral toxicity	rat (male and female)	male: LD_{50} > 2500 mg/kg bw female: LD_{50} > 2500 mg/kg bw	[redacted] 1986 (15239) TOX9401931[2]
+,-(R,S)-α-Carboxamido-[3-phenoxy-4-fluoro]benzyl-1-(R,S)-trans-3-(2,2-dichloroethen-1-yl)-2,2-dimethyl-cyclopropanecarboxylic acid ester	acute oral toxicity	rat (male and female)	male: LD_{50} > 2500 mg/kg bw female: LD_{50} > 2500 mg/kg bw	[redacted] 1986 (15241) TOX9401932[2]
FCR 1272-Phenoxyethylester[1]	acute oral toxicity	rat (male and female)	LD_{50} > 2500 mg/kg bw	[redacted] 2002 (PH-32041) TOX2002-1390
	mutagenicity (Ames test)	bacterial strains (TA1513, TA100, TA1537, TA98, TA102)	negative +/- S9 mix	Herbold, 2002 (PH-32175) TOX2002-1391[2]

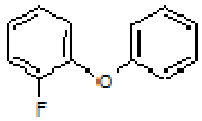
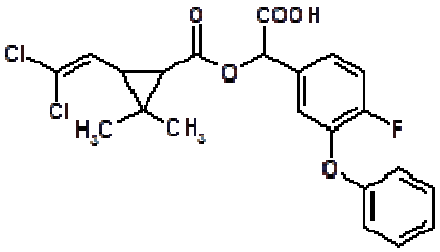
[1] These studies were not submitted by the applicant (but available to RMS e.g. from other applications).
[2] These studies are considered supplementary.

2.6.11.1 Metabolites in residue metabolism studies

The following metabolites were identified in residue metabolism studies (see Table 2.6-48).

Table 2.6-48: Chemical structures of metabolites occurring in residue metabolism studies

Metabolite	Abbreviation (Code number)	Chemical structure
Permethric acid	DCVA	
3-Phenoxy-4-fluorobenzaldehyde	FPB_{ald} (FCR 1260)	
3-Phenoxy-4-fluorobenzyl alcohol	FPB_{alc} (FCR 1261)	
3-Phenoxy-4-fluoride benzoic acid 3-Phenoxy-4-fluorobenzoic acid	FPB_{acid} (FCR 2899, FCR 3191, COE 538/78)	
3(4'-Hydroxyphenoxy)-4-fluorobenzoic acid 4-Fluoro-3-(4-hydroxy-phenyoxy)-benzoic acid 4'-Hydroxy-3-phenoxy-4-fluorobenzoic acid	4-OH-FPB_{acid} (FCR 3145)	
4-Fluoro-3-phenoxybenzoic acid methyl ester	Me-FPB_{acid} (COE 263/78)	
3-Phenoxy-4-fluoride benzoic acid amide	FPB_{amide} (FCR 2947)	

Metabolite	Abbreviation (Code number)	Chemical structure
1-Fluoro-2-phenoxybenzene	FPB (FCR 3030)	
+,-(R,S)-α–Carboxy-[3-phenoxy-4-fluoro]benzyl-1-(R,S)-trans-3-(2',2'-dichloroethen-1'-yl)-2,2-dimethylcyclo-propanecarboxylic acid ester +,- (R,S)-α-Carboxy-4-fluoro-3-phenoxybenzyl] -1-(R,S)-trans-3-(2,2-dichloroethene-l-yl)-2,2-dimethylcyclopropane carboxylate	$Cyfluthrin_{acid}$ (FCR 2728)	

Some of the listed metabolites were reported in the ADME studies with rats (Vol. 3, B.6.1). The urinary metabolite pattern after oral administration of radioactive labelled beta-cyfluthrin or cyfluthrin is summed up in Table 2.6-49. Studies evaluated as not acceptable are not included. Furthermore, toxicological studies for acute toxicity and/or mutagenicity (Ames test) with some of the listed metabolites (Table 2.6-47) were submitted.

Table 2.6-49: Renal metabolites of beta-cyfluthrin or cyfluthrin detected in oral ADME studies with rats

Test compound	Dose [mg/kg bw]	Metabolite	Percentage of dose	Reference
[Fluorobenzene-UL-^{14}C] cyfluthrin	0.5[2]	FPB_{acid}	10 %	[redacted] 1983 RIP9400868
		4-OH-FPB_{acid}	4 %	
		4-OH-FPB_{acid} conjugate	41 - 52 %	
	10[2]	FPB_{acid}	17 – 24 %[1]	
		4-OH-FPB_{acid}	2 – 5 %	
		4-OH-FPB_{acid} conjugate	35 – 36 %	
[Fluorophenyl-UL-^{14}C] beta-cyfluthrin	10	FPB_{acid}	15 %	[redacted], 2014, ASB2014-7717
		4-OH-FPB_{acid}	2 %	
		4-OH-FPB_{acid} sulfate	47 %	

[Cyclopropane-1-^{14}C] beta-cyfluthrin	0.5	cis/trans DCVA	27 – 49 %	[redacted] 2013, ASB2014-7718
		DCVA acyl glucuronide	26 – 39 %	
	10	cis/trans DCVA	26 – 31 %	
		DCVA acyl glucuronide	28 – 35 %	

[1] Another metabolite is included in the lower limit.
[2] The values are related to total recovered in urine, faeces, body (almost 100 %).

Studies conducted with FPB_{acid} (acute oral toxicity) and 4-OH-FPB_{acid} (acute oral toxicity, mutagenicity) did not indicate higher toxicity than beta-cyfluthrin (Table 2.6-47).
Considering the higher levels in rat metabolism studies, the reference values proposed for beta-cyfluthrin are also applicable to the metabolites DCVA, 4-OH-FPB_{acid} and FPB_{acid}.
The metabolite FPB_{ald} was not detected in significant amounts in rat metabolism studies. However, it seems plausible that FPB_{ald} is the precursor of FPB_{acid}. FPB_{ald} was of low toxicity in acute oral, dermal and inhalative toxicity as well as in skin and eye irritation. The Ames test was negative. Therefore, for this metabolite the reference values proposed for beta-cyfluthrin are also applicable.
The remaining metabolites $cyfluthrin_{acid}$, FPB_{alc} and FPB_{amide} were only tested for acute oral toxicity and in the Ames test (not acceptable for $cyfluthrin_{acid}$). It is not obvious that these metabolites are involved in rat metabolism. Furthermore, the toxicological properties upon repeated exposure (e.g. developmental toxicity) cannot be judged. Additionally, the genotoxic testing battery is incomplete.
Neither data demonstrating the occurrence in rat metabolism nor toxicological studies were available for the remaining metabolites (Me-FPB_{acid} and FBP).
Taken together, the toxicological properties of FPB_{alc}, FPB_{amide}, Me-FPB_{acid}, FBP and $cyfluthrin_{acid}$ cannot be evaluated based on the submitted information.

2.6.11.2 Impurities

The evaluation of the relevance of impurities is presented in Vol. 4 section C.1.5.

2.6.11.3 Metabolites predicted to occur in groundwater in concentration of above 0.1 µg/L

There is no metabolite predicted to occur in concentrations >0.1 µg/L in groundwater.

2.6.12 Summary of medical data and information

Skin symptoms (paraesthesia) have been observed in people handling the active ingredient. Skin reactions such as pruritus, tautness and reddening of the facial skin, partial facial paraesthesia and signs of irritation in the oro-pharyngeal cavity or coughing, especially when concomitant with an elevated sensitivity, particularly to touch stimuli, may be signs of dermal contact with or inhalative exposure to cyfluthrin. These symptoms may appear immediately or shortly after contact with the substance, they may last up to 24 (rarely to 48) hours, and it was often reported to be worsened by warmth (e.g. showering). Following inhalative exposure irritation of respiratory mucous membranes (coughing, sneezing) may occur. In order to make the user aware of the need for protection, the designation of STOT-SE 3 H335 ‘May cause respiratory irritation’ according to Regulation (EC) No 1272/2008 was proposed.
The dermal sensations are direct and transitory effects on sensory nerve endings and not the result of a primary skin irritation. This conclusion is supported by the skin irritation study in rabbits ([redacted] 2005, ASB2014-7723). There is no evidence for skin irritation as all mean scores for erythema, eschar formation as well as for oedema formation were 0. Therefore, and according to the “Guidance on the application of CLP criteria” (ECHA, 2012) no classification for skin irritation is needed.
Cases of cyfluthrin intoxication and signs of poisoning after oral ingestion are not known. It can be assumed that observations made after intoxication with other α-cyano-pyrethroids are also applicable to cyfluthrin. As for other α-cyano-pyrethroids, there is no specific effective antidote.

In a human volunteer study (Ruddy et al, 1998, TOX2001-879), 1-h inhalation exposure to approx. 0.1 mg cyfluthrin/m^3 air appeared to be in the range of an irritant threshold concentration for humans since only 2 (of 5) subjects showed very marginal transient signs of irritation of the mucous membranes and symptoms experienced were transient and self-limiting. Slightly higher concentrations caused similar effects of greater intensity in all subjects. No clinically significant or drug related abnormalities in vital signs, EKGs or clinical laboratory tests were observed after 1-h exposure to airborne cyfluthrin concentrations of up to 0.2 mg/m^3.
Based on the results obtained in this study and on the information from the teratogenicity studies with inhalational exposure in rats ([redacted] 1988, TOX9401910, [redacted] 1993, TOX9401829) were respiratory disturbances and bradypnoea due to irritative aerosol concentrations of cyfluthrin occurred, it is proposed to classify beta-cyfluthrin/cyfluthrin for irritating properties as follows:

Classification and labelling for respiratory irritation according to Regulation (EC) No 1272/2008 (GHS):

Specific target organ tox.-single exp., cat. 3 'May cause respiratory irritation'

The applicant disagrees with this proposal and has requested an external consultant to review the existing data package. However, the proposal of STOT-SE cat. 3 *'May cause respiratory irritation'* is based on a human volunteer study, medical data (irritation of respiratory mucous membranes with coughing and sneezing after inhalative exposure to cyfluthrin in workers) and inhalational teratogenicity studies in rats. Due to the irritating properties of the test substance at different dose levels a reflex bradypnoea and respiratory disturbances occurred in the dams. In order to make the user aware of the need for protection, the designation of STOT-SE 3 H335 *'May cause respiratory irritation'* according to Regulation (EC) No 1272/2008 is proposed by the RMS.

A literature search was performed during preparation of the Renewal Assessment Report (RAR) by the RMS from the last 10 years. The information provided is considered acceptable.

2.6.13 Literature research for the Renewal Assessment Report (RAR):

Das et al. (2006, ASB2015-929). "*Worker illness related to ground application of pesticide*", Kern County, California, 2005. Morb Mortal Wkly Rep 55(17):486-488.
Summary:
The Occupational Health Branch (OHB) of the California Department of Health Services (CDHS) conducts surveillance of work-related pesticide illness with support from the National Institute for Occupational Safety and Health (NIOSH) and the U.S. Environmental Protection Agency (EPA). On May 12, 2005, CDHS received a report from the California Department of Pesticide Regulation (CDPR) of a suspected pesticide incident in Kern County involving 27 farmworkers (age range: 21 - 61 years; median: 32.5 years) and six emergency responders (age range: 28 - 51 years; median: 33.5 years). CDHS investigated this incident by conducting a site visit; reviewing medical and meteorologic records; and interviewing affected workers, pesticide applicators, and the farmworker employer. Findings indicated that workers became ill from drift of a pyrethroid pesticide (cyfluthrin) that was being applied in a neighbouring field. Pyrethroid pesticide applicators should always operate in a manner that ensures workers not to be exposed.

Miller (2014, ASB2015-928). "Case Report: Human intravenous injection of beta-cyfluthrin with minimal toxic effects", American Journal of Emergency Medicine 32 (2014) 113e1-113e2.
Summary:
The American Journal of Emergency Medicine (Miller, 2014) reported that a 28-year-old man presented to the emergency department 20 minutes after injecting 20 mL of an insecticide containing 0.05 % beta-cyfluthrin. The cause for the injection remained unknown. The man showed sinus tachycardia as the only symptom and was treated with an intravenous fluid bolus of 2000 mL. After 3 hours he fully recovered.

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

For the initial inclusion of beta-cyfluthrin the proposed ADI of 0.02 mg/kg bw/d was based on the results of the chronic feeding study in rats with a NOAEL of 2 mg/kg bw/d and applying a safety factor of 100.
The ADI of 0.003 mg was eventually based on a pharmacological study in mice ([redacted] 1982, TOX9401943; Report no. R2405) and the endpoint used by EMEA was included in the endpoint list of the Review Report (6841/VI/97-final, 2 December 2002). Like in the original monograph (1996), the study is still considered as supplemental information, due to the lack of standardisation of the tests performed. The RMS still considers this study as inappropriate to derive the ADI.
Beta-cyfluthrin/cyfluthrin was assessed by the JMPR in 2006. The 2006 JMPR established common ADIs and ARfDs for cyfluthrin and beta-cyfluthrin of 0 - 0.04 mg/kg bw/day and 0.04 mg/kg bw, respectively. This value was based on a NOAEL of 1 mg/kg bw for findings of acute neurotoxicity observed in a 4-week study with beta-cyfluthrin administered by gavage, and using a safety factor of 25. The JMPR meeting considered it appropriate to apply a chemical-specific adjustment factor of 25 for this end-point.
The RMS agrees to derive the ADI from the same 4-week repeat-dose study with beta-cyfluthrin ([redacted] 1988, TOX9550271). The acute toxicity/neurotoxicity of beta-cyfluthrin/cyfluthrin is the critical endpoint. This applies also to repeat-dose studies. Due to intensive metabolism and rapid excretion of beta-cyfluthrin/cyfluthrin, daily administrations of beta-cyfluthrin/cyfluthrin are considered to represent a sequence of acute intoxications.
With respect to the occurrence of clinical symptoms, the lowest NOAEL from the repeat-dose studies is 1 mg/kg bw/d. Clinical symptoms were evident at the next higher dose of 4 mg/kg bw/d.

Hence, the RMS proposes:

ADI: 0.01 mg/kg bw
based on a 4-week study in rats, SF 100

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

Based on the relatively high acute toxicity of beta-cyfluthrin the derivation of an acute reference dose is considered necessary.
For the initial inclusion of beta-cyfluthrin/cyfluthrin the proposed ARfD of 0.02 mg/kg bw/d was based on the results of the acute oral neurotoxicity study in rats with a NOAEL of 2 mg/kg bw/d and applying a safety factor of 100.
Taking into account the data obtained for 4-week repeat-dose study with beta-cyfluthrin, the ARfD is derived from the NOAEL of 1 mg/kg bw with an assessment factor of 100. The ARfD of 0.01 mg/kg bw is established at the same level as the ADI. This was also proposed by the 2006 JMPR, which established common ADIs and ARfDs for cyfluthrin.

Hence, RMS proposes:

ARfD: 0.01 mg/kg bw/d
based on a 4-week study in rats, SF 100

2.6.16 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL systemic

For the initial inclusion of beta-cyfluthrin/cyfluthrin the proposed AOEL systemic of 0.02 mg/kg bw/d was based on the results of the 90-day and acute oral neurotoxicity study in rats with a NOAEL of 2 mg/kg bw/d and applying a safety factor of 100.

Taking into account the data obtained for 4-week repeat-dose study with beta-cyfluthrin, the AOEL systemic is derived from the NOAEL of 1 mg/kg bw with an assessment factor of 100. No correction for oral absorption (90 %) is considered necessary.

Hence, RMS proposes:

$AOEL_{syst.}$: 0.01 mg/kg bw/d
based on a 4-week study in rats, SF 100

2.6.17 Toxicological end point for assessment of occupational, bystander and residents risks – AOEL inhalative

A separate AOEL for inhalation was derived for the initial inclusion of beta-cyfluthrin/cyfluthrin. The AOEL inhalation was based on the subchronic inhalation study with cyfluthrin in rats to cover the specific localised toxicity by this route. The study had a NOAEL of 0.09 µg/L (equating to 0.0243 mg/kg bw/day.

Hence, RMS proposes:

$AOEL_{inhal.}$: 0.000243 mg/kg bw/d
based on a subchronic inhalation study in rats, SF 100

In a position paper submitted by the applicant an argumentation supporting the approach of setting two separate AOELs (systemic and inhalation) is provided and the application of an assessment factor of 25 is discussed (Wason, 2014, ASB2014-7900).

The applicant disagreed with the $AOEL_{inhalation}$ and argued that it is overly conservative as it is based on a 13-week inhalation study, where rats were exposure to the active ingredient for 12 weeks for 5 days/week and 6 hours/day. This exposure pattern is in excess of the potential exposure to operators/workers/bystanders and residents, according to the intended use pattern of the formulated products. In addition, the NOAEC on the 13-week inhalation study is based on non-specific disturbed behaviour, associated with upper respiratory tract sensory irritation, which is typical for pyrethroids. This response is an acute transient with no long-term consequences and could be regarded as a physiological adaptive response, rather than an adverse toxicological finding.
The applicant believes that only the $AOEL_{systemic}$ should be used for risk assessment purposes and that this is sufficiently protective to cover exposure via the inhalatory route, according to the intended use pattern of the registered formulated products.
However, the RMS prefers to derive an $AOEL_{inhalation}$ in addition to the $AOEL_{systemic.}$ A safety factor (SF) of 25 as proposed by the applicant in a position paper submitted is not supported by the RMS in the PPP process.

2.6.18 Summary of product exposure and risk assessment

Bulldock 25 EC containing 25 g/L beta-cyfluthrin is an insecticide used for foliar spray application on potatoes and wheat at an application rate of 2 x 0.5 L product/ha and on tomatoes in greenhouses at an application rate of 2 x 0.7 L product/ha. The estimated operator exposure for the field uses is below the systemic AOEL without PPE according to the German model (38 % of the $AOEL_{syst}$) and with gloves during mixing/loading and during application according to the UK POEM (241 % of the $AOEL_{syst}$ without PPE; 37 % with gloves m/l and appl.). For the greenhouse use on tomatoes gloves are required for the operator during mixing/loading (157 % of the $AOEL_{syst}$ without PPE, 91 % with gloves m/l). The worker exposure for re-entry is below the systemic AOEL (max. 43 % of the $AOEL_{syst}$) and bystander and resident exposure does also not exceed the systemic AOEL (max. 2.1 % of the $AOEL_{syst}$). No unacceptable risk was identified for operator, worker, bystander and resident comparing the estimated inhalation exposure with the inhalative AOEL.

Montur Forte FS 230 containing 80 g/L beta-cyfluthrin and 150 g/L imidacloprid is used as an insecticide for the treatment of sugar beet seeds at an application rate of 100 mL product/unit seed (130 mL product/ha). The risk assessment for beta-cyfluthrin in Montur Forte FS 230 according to the Seed

TROPEX model has shown that the estimated inhalation exposure of the worker will exceed the inhalative AOEL even if respiratory equipment is used (1007 % of the $AOEL_{inhal}$ with RPE, 60 kg body weight) whereas the total systemic exposure will be below the $AOEL_{syst}$ if gloves, coverall and respiratory equipment are used (315 % of the $AOEL_{syst}$ without and 34 % of the $AOEL_{syst}$ with PPE/RPE, 60 kg body weight). Nevertheless, data from two exposure studies on beet seed treatment in professional plants show that inhalation exposure will be below the inhalative AOEL if RPE is used during all tasks which are performed by different operators (60 % of the $AOEL_{inhal}$ with RPE). No unacceptable risk was identified for the worker provided that gloves, coverall and respiratory equipment are worn (82 % of the $AOEL_{inhal}$ with RPE, 32 % of the $AOEL_{syst}$ with gloves and coverall, 60 kg body weight). The exposure of bystander and resident is below the systemic AOEL (<1 % of the $AOEL_{syst}$) and the inhalative AOEL (max. 23 % of the $AOEL_{inhal}$).

The detailed calculations are presented in Vol. 3, B.6 (product level).

2.7 Residues

2.7.1 Summary of storage stability of residues

Storage stability investigations for cyfluthrin were performed in different plant matrices covering the categories of high water, oil, starch and acid content as well as on hops and peanut shells (no crop category). For matrices of high water and high starch content as well as peanut shells, stability of cyfluthrin during frozen storage could be demonstrated for 38 months. For other matrices, no data are available or the studies provided do not fulfil the data requirements.
Storage stability investigations with different plant metabolites (DCVA, FPB acid, FPB alcohol, FPB aldehyde) were submitted, however, these data were not considered relevant for the assessment of representative uses following the proposed residue definitions for monitoring and risk assessment (cyfluthrin, sum of constituent isomers).

In animal matrices, stability of cyfluthrin as incurred residues and in fortified control samples was investigated in bovine muscle, fat, milk and kidney tissues. Stability is proven for 3 months in liver, 1 month in kidney, 5 months in fat and muscle, and 11 months in milk (all based on incurred residues). No stability data are available for eggs.

Stability of metabolite FPB aldehyde was investigated in bovine liver, however, these data are not considered relevant for the representative uses.

Commodity category	Test commodity	Stability (months)	Study
Plant matrices			
High water content	Tomato Apple (peel) Head lettuce Corn, wheat (green) Apple, melon, tomato, cucumber, sugar cane raw, molasse	not acc. not acc. **26** **26** **38**	Delk 1988 (RIP9401051) Minor and Freeseman 1989 (RIP9401053) Minor and Freeseman 1992 (RIP9401054, ASB2009-1208) Lenz and Lemke 1996 (ASB2009-1323) [b]
High oil content	Cotton seed Cotton seed Soybean Soybean Corn oil	not acc. not acc. not acc. not acc. not acc.	Grace 1989 (RIP9401052) Minor and Freeseman 1989 (RIP9401053) Grace 1989 (RIP9401052) Minor and Freeseman 1989 (RIP9401053) Lenz and Lemke 1996 (ASB2009-1323) [b]
High protein content	-	-	-
High starch content	Potato Potato leaves Corn, potato, wheat [c]	not acc. not acc. **38**	Delk 1988 (RIP9401051) Minor and Freeseman 1989 (RIP9401053) Lenz and Lemke 1996 (ASB2009-1323) [b]
High acid content	Orange [c]	not acc.	Lenz and Lemke 1996 (ASB2009-1323) [b]
Miscellaneous	Hops Peanut shells	not acc. **38**	Grace 1989 (RIP9401052) Lenz and Lemke 1996 (ASB2009-1323) [b]
Animal matrices			
	Liver (fortified)	**12** **1**	Lemke 1987 (RIP9401049; non-GLP) [redacted] 1983 (ASB2009-1452; non-GLP)
	Liver (incurred)	**3**[d]	[redacted] 1983 (ASB2009-1452; non-GLP)
	Kidney (incurred)	**1**[e]	[redacted] 1983 (ASB2009-1452; non-GLP)
	Muscle (incurred)	**5**	[redacted] 1983 (ASB2009-1452; non-GLP)
	Fat (incurred)	**5**	[redacted] 1983 (ASB2009-1452; non-GLP)
	Milk (incurred)	**11** **39**	[redacted] 1983 (ASB2009-1452; non-GLP) [redacted] 1993 (RIP9401069; GLP)

not acc.: non-acceptable study
[a] covering storage stability of beta-cyfluthrin
[b] comprising reports RIP9401055, RIP9401056 and ASB2009-1322
[c] raw and processed
[d] significant instability (<70 % recovery) for next sampling point (7 months)
[e] significant instability (<20 % recovery) for later samplings (6 months)

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

Metabolism, distribution and expression of residues in plants:
The data package submitted to address the plant metabolism of cyfluthrin isomers after foliar application contains the already submitted studies on apples, tomatoes, potatoes, soybeans, cotton and wheat, which were performed with the 2 diastereoisomeric pairs of cyfluthrin, that are also contained in beta cyfluthrin in different amounts. The metabolism of beta-cyfluthrin is therefore inherently covered by these studies with cyfluthrin. The test compound in metabolism studies was labelled either in the cyclopropyl, fluorophenyl or phenyl ring position. To support the application via seed treatment, two new plant metabolism studies in sugar beet were submitted.

Tomato metabolism (foliar application)
In a greenhouse study, tomato fruit and leaf surfaces were treated by a brush at a rate of 6.1 g cyfluthrin/hL. Unchanged cyfluthrin accounted for >90 % of the TRR in tomato fruit and leaf samples from 1 to 35 days after application. The study shows the low rate of metabolisation of cyfluthrin resulting in only one metabolite detected at low percentages in tomato leaves. A very low translocation of radioactivity (parent only) into the fruit was observed.
Key information on test item, test design and analysis is provided. While the study allows only semi-quantitative estimates of the residue situation, this is not considered to challenge the scientific validity of the study, since only parent compound was detected in fruits with no other metabolite being overlooked, while identification rate is acceptable (97.79 % of applied radioactivity). The minor metabolites in leaves are not considered relevant as candidates for risk assessment when discussing a global residue definition.

Overall, this non-guideline study provides valuable and scientifically meaningful insights into the metabolism of cyfluthrin in tomatoes that are in congruence to other plant metabolism data (GLP and non-GLP). Although the information in this non-GLP report is not challenged, the documentation is not traceable and methods applied are not according to current standards.
This non-guideline is considered as acceptable with limitations.

Apple metabolism (foliar application)
Cyfluthrin was applied at a rate of 30 g as/hL to the surface of outdoor apples. The study shows the low rate of metabolisation of cyfluthrin resulting in only 2 metabolites detected at low percentages, the organosoluble character of all residue compounds, and the diffusion of unmetabolised cyfluthrin from outer surfaces into the peel. The report reflects state-of-the-art of the time the study was conducted. Key information on test item (specific activity; purity, isomeric composition), test design (application, sampling) and analysis (methods of analysis, radioactivity calculation) is provided. However, the study allows only semi-quantitative estimates of the residue situation and metabolites relevance for dietary risk assessment due to the unrepresentative study design (direct treatment of apples at known concentration, but unknown rate per area), and analysis (no reporting of amounts per sample).

Overall, this non-guideline study provides valuable and scientifically meaningful insights into the metabolism of cyfluthrin in apples that are in congruence to other plant metabolism data (GLP and non-GLP). Although the information in this non-GLP report is not challenged, the documentation is not traceable and methods applied are not according to current standards. This non-guideline is considered as acceptable with limitations.

Potatoes (foliar application)
Cyfluthrin was applied at a rate of 100 g as/ha to the surface of greenhouse potatoes 60 days after seeding. Samples of foliage and tubers were collected between 0 and 98 days after application. No significant residues were reported for potato tubers (<0.01 mg/kg TRR). In potato foliage, no individual metabolite exceeded the level of significance (10 % TRR). The study shows the low rate of metabolisation and systemic translocation of cyfluthrin. No major metabolites are likely to be formed by potato plants.

Key information on test item, test design and analysis is provided. The study provides valuable and scientifically meaningful insights into the metabolism of cyfluthrin in potatoes that are in congruence to other plant metabolism data (GLP and non-GLP). Although the information in this non-GLP report is not challenged, the documentation is not traceable and methods applied are not according to current standards. This non-guideline study is considered as acceptable with limitations.

Soybean (foliar application, plant cell suspension)
Cyfluthrin was applied at a rate of 100 g as/ha to the surface of greenhouse soybeans. Whole plants were collected between 4 and 84 days post treatment. Mature soybean samples were collected at harvest stage. The study shows the low rate of metabolisation and systemic translocation of cyfluthrin. No individual metabolite in final harvest products exceeded the level of significance (10 % TRR). Most of radioactivity is located in foliar parts (61 mg/kg), in stalks (2.5 mg/kg) and pods (0.22 mg/kg), while TRR in seeds are low (0.04 mg/kg).
No information on absolute residue levels is provided for immature samples.
In vitro investigations indicated largely similarity of metabolite profiles with *in vivo* data.

Key information on test item, test design and analysis is provided. The study provides valuable and scientifically meaningful insights into the metabolism of cyfluthrin in soybean, that are in congruence to other plant metabolism data (GLP and non-GLP). Although the information in this non-GLP report is not challenged, the documentation is not traceable and methods applied are not according to current standards. This non-guideline study is considered as acceptable with limitations.

Cotton (spray/droplet application)
Cyfluthrin was applied at a rate of 100 g as/ha to the surface of cotton leaves or bolls. The study shows the limited rate of metabolisation of cyfluthrin. No individual metabolite in leaves, or bolls (gin trash; lint) exceeded the level of significance (10 % TRR). The extraction efficiency and identification and characterisation rate is high.

The study provides valuable and scientifically meaningful insights into the metabolism of cyfluthrin in wheat, that are in congruence to other plant metabolism data (GLP and non-GLP). Although the information in this non-GLP report is not challenged, the documentation is not traceable and methods applied are not according to current standards. This non-guideline study is considered as acceptable with limitations.

Wheat (foliar application)
Cyfluthrin was applied at a rate of 100 g as/ha to the surface of greenhouse spring wheat plants. The study shows the limited rate of metabolisation of cyfluthrin. No individual metabolite in intermediate (forage) or final harvest products (straw, grain) exceeded the level of significance (10 % TRR). The extraction efficiency and identification and characterisation rate is high.

The study provides valuable and scientifically meaningful insights into the metabolism of cyfluthrin in wheat, that are in congruence to other plant metabolism data (GLP and non-GLP). Although the information in this non-GLP report is not challenged, the documentation is not traceable and methods applied are not according to current standards. This non-guideline study is considered as acceptable with limitations.

Sugar beets (seed treatment)
Two complementary metabolism studies in sugar beets were performed with [cyclopropane-1-^{14}C] and [fluorophenyl-UL-^{14}C] beta-cyfluthrin.
The metabolism of beta-cyfluthrin was investigated after seed treatment at an application rate of 10 g as/ha conforming to GAP. A seed treatment with an overdose application rate of nominal 100 g as/ha (10N rate) was performed to facilitate the investigation of the nature of the residues.

In the study with [cyclopropane-1-^{14}C] label, unconjugated parent is found in traces and metabolite DCVA is a minor compound in all samples (<10 % TRR, <0.01 mg/kg at 1N and 10N rate). Conjugates represent the largest part of radioactivity (sum 58 – 83 % TRR), however, the low absolute

amounts (<0.01 mg/kg in roots under 1N conditions) do not qualify these metabolites as candidates for the residue definition.
In the study with the [fluorophenyl-UL-^{14}C] beta-cyfluthrin, parent was the main compound, which was identified in sugar beet roots of the 10N application rate. Three minor metabolites (all ≤ 0.004 mg/kg at 10N) were detected. These minor metabolites were only characterised, due to their very low amount of radioactivity. It is noted that conjugates were not identified in the study with the fluorophenyl label. As cleavage was not demonstrated there, no conclusion can be made on whether conjugation in this cyclopropyl-label study occurred prior or post ester cleavage.

The studies on sugar beet are fully acceptable.

Metabolism, distribution and expression of residues in livestock:

Poultry metabolism ([redacted] 1983; RIP9400869)
After administration of [phenyl-U-^{14}C]cyfluthrin at a rate of 5 mg/kg bw/day to laying hens for 5 successive days (530 N rate), most of the residues were found in liver, kidney and gizzard, while residues in other tissues were low (0.1-0.4 mg/kg in muscles, fat) or even very low (≤0.05 mg/kg in eggs). Unextractables (after acid and enzymatic hydrolysis) accounted for 10-33 % TRR. The main residue compounds were fat soluble cyfluthrin (ranging from 9 % in kidney to 75 % in fat), 4-OH-FPBacid (not observed in fat; up to 21 % TRR in heart muscle) and FPBacid (3 % TRR in fat and 26 % TRR in muscle).

Severe limitations are observed in analytical and storage aspects that restrict the general applicability of the study results to additional information only. Together with the poultry feeding study, however, the data set is considered complete (except storage stability data for eggs) to propose a residue definition and perform a dietary risk assessment under conditions relevant for the assessment of representative uses within this RAR. Limitations of the data base are outlined in Vol. 3 B.7.

Goat metabolism ([redacted] 2014; ASB2014-7899)
Two goats were orally dosed for 7 consecutive days with 0.11 and 1.0 mg of [cyclopropane-1-^{14}C] labelled beta-cyfluthrin per kg body weight (11/18N and 100/167N rate for dairy/meat ruminants).
Radioactivity from beta-cyfluthrin is excreted in ruminants mainly via urinary excretion (65 % of AD at 0.11 mg/kg bw/d), but also quantitatively via faecal excretion (20 % of AD at 0.11 mg/kg bw/d). At higher levels (1 mg/kg bw/d; ≥100N rate regarding the representative uses and 3N rate regarding all potential uses as identified by EFSA 2010;8(5):1618), significant inhibition of absorption is noted.
At the low dose, TRR in milk was 0.005 - 0.012 mg/kg (11N rate). The residues in milk reached a plateau within 2 days. In edible tissues, total residues at 18N rate were 0.030 mg/kg (liver), 0.054 mg/kg (kidneys), 0.003 mg/kg (muscle) and 0.009 - 0.017 mg (fat).
The amount of metabolites that could be identified and characterised in urine, faeces, milk fat, renal and omental fat was 77 % of the applied low dose. In addition, non-labelled metabolites of beta-cyfluthrin were identified in the urine and faeces of the low dose goat. The [^{14}C]-labelled metabolites of beta-cyfluthrin excreted with faeces were permethric acid and cyfluthrin-amide (FCR 2978 $CONH_2$-cyfluthrin). The [^{14}C]-labelled metabolites of beta-cyfluthrin excreted with urine were permethric acid, permethric acid glucuronide conjugates and hydroxylated permethric acid. Besides the labelled unknown metabolites also additional metabolites, which do not contain the labelled cyclopropane-ring, were detected in urine; phenol sulphate, phenol glucuronide, OH-FCR 3343, FCR 3145 4'-OH-FPBacid, FCR 3343 hippuric acid, COE 5338-78 FBPacid and FCR 1271.

The study is considered acceptable.

Cow metabolism ([redacted] 1983; RIP9400870)
One dairy cow was treated orally with phenyl-UL-^{14}C-labelled cyfluthrin in a dose of 0.5 mg/kg bw/d for 5 successive days (77 and 23N rate for meat and dairy ruminants, respectively). The maximum detected residue in milk was 0.079 mg/kg. A plateau was reached after approximately 3 days of dosing. Analysis of the milk showed that 98 % of TRR was organosoluble and consisted on parent cyfluthrin only. Total residues for tissues were found in the range of 0.021 (muscle, round) to

0.622 mg/kg (liver). In brain, 0.015 mg/kg were found. Extractability of residues is high (93 – 100 %). Two metabolites were major compounds in heart and kidney ($FPB_{alcohol}$ 29 – 43 %) and liver ($FPB_{aldehyde}$ 14 %), but considered out of quantitative relevance at anticipated 1N level of the representative uses. Based on storage stability investigations with samples obtained from this metabolism study, it cannot be excluded that these metabolites are product of storage degradation.

The study is considered as tentatively acceptable.

Cow metabolism ([redacted] 1993; RIP9401069)
The study quantitatively describes the concentration of cyfluthrin residues in milk fat (cream, butterfat) after feeding a dairy cow over 5 days with phenyl-UL-^{14}C-labelled cyfluthrin at a dose of 0.5 mg/kg bw/d (17 and 45N rate for meat and dairy ruminants, respectively). Whole milk had residues of 0.05 mg/kg. The entire residue was identified as parent cyfluthrin (thereby demonstrating stability of cyfluthrin in milk over the entire storage period of at least 39 months. Following centrifugation of milk, 82 % of TRR was associated with cream, indicating a concentration factor of 26. For butterfat, a concentration factor of 79 was determined. The results are fully in accordance to those of the other livestock metabolism studies ([redacted] 1983, RIP9400870 and [redacted] 2014, ASB2014-7899).

The study is considered acceptable.

Metabolism of beta-cyfluthrin in animals is sufficiently understood (Figure 2.6-2). The metabolic pathway is initiated by hydrolysis of the ester bond to lead to α-OH-FPB-ACN as unstable intermediate, which is assumed to form FPB_{acid} via FPB_{ald} (intermediate; not observed in chicken), and DCVA (permethric acid, free and conjugated; hydroxylated), the main excretion products of the [cyclopropane-1-^{14}C]label observed in goats. FPB_{acid} undergoes hydroxylation at the 4`-position of the phenyl ring to form 4-OH-FPB_{acid} and conjugation or combines with glycine to form hippuric acid derivatives. Acid-cyfluthrin is observed in laying hen tissues only, while the precursor $CONH_2$-cyfluthrin is observed in goat excreta. Additional metabolites were identified in a high dose study in hens (>300.000N rate) that were not yet considered in the metabolic pathway scheme provided.
Beta-cyfluthrin is fat soluble and accumulates in fat tissues and milk fat.
Based on the results of the set of livestock metabolism and feeding studies, it is concluded that at 1N rate of the representative uses in cereals, sugar beet and potato, no individual residues above 0.01 mg/kg are expected in milk and tissues.

Fish metabolism
Fish were repeatedly administered for 14 days via diet with [cyclopropane-1-^{14}C] beta-cyfluthrin or [fluorophenyl-UL-^{14}C]beta-cyfluthrin at an actual concentration measured in the diet of 11.7 mg/kg diet for the cyclopropyl-label and 10.6 mg/kg diet for the fluorophenyl-label.
The fish were sacrificed at approximately 6 hours after the last (14th) administration and liver, muscle (including skin) were collected. Rather low levels of radioactivity were measured for liver (0.078 to 0.083 mg/kg) and muscle (0.053 to 0.073 mg/kg). The radioactivity could be efficiently extracted from liver and muscle. The extracted amounts ranged from 79.4 % to 99.1 % of TRR. The extracted radioactivity could then be partitioned into organic solvents and the samples were analysed by TLC and HPLC. The residues in muscle mainly consisted of unchanged parent compound. Also in liver parent compound was the main component of the extracted radioactivity.
Cyclopropyl specific compounds: In liver, besides parent, DCVA was detected in an amount of 0.016 mg/kg. COOH-cyfluthrin was detected in traces in muscle. Unknown metabolites occurring in liver and muscle ranged from <0.001 to 0.007 mg/kg.
Fluorophenyl specific compounds: In liver, besides parent, FCR 3145 and FCR1260 were detected in small amounts of 0.004 and 0.002 mg/kg, respectively. COOH-cyfluthrin was detected in traces in muscle. Unknown metabolites occurring in liver and muscle ranged from <0.001 to 0.004 mg/kg.
The following metabolic pathway is proposed:

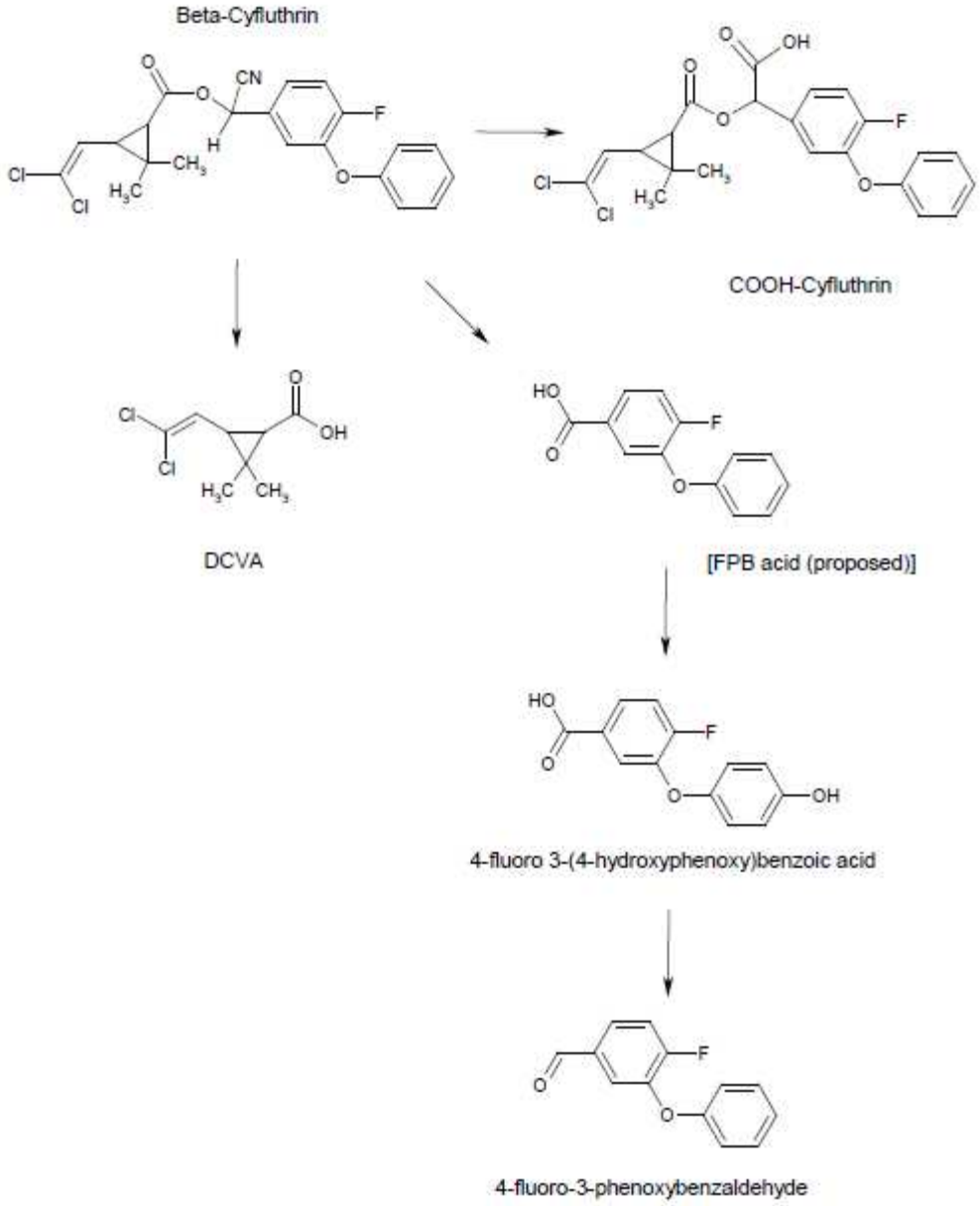


Figure 2.7-1: Proposed metabolic pathway for beta-cyfluthrin in fish

2.7.3 Definition of the residue

Studies of cyfluthrin and beta-cyfluthrin can be both interchangeably used to support the authorisation of either active substance. Slight changes of isomer ratios as observed in some plant and animal studies are not considered to impact the proposal on the residue definition and conditions for dietary risk assessment.

Metabolites detected and quantified in plant and animal metabolism studies are summarised in Table 2.7-1. One unidentified metabolite was detected in significant amounts (>10 % TRR) in a simulated hydrolysis study under conditions representative for tomato processing.

Table 2.7-1: Metabolites identified and quantified in relevant matrices of plant and animal metabolism studies (without cell culture, excreta)

	Plant metabolism	Livestock metabolism	Processing
DCVA Permethric acid	<10 % in primary crops	19 % of TRR in fish liver, 49 % of applied dose in ruminant excreta (free and conjugated); occurrence in poultry not investigated	
FPBald FCR 1260	<10 % in primary crops [a]	up to 14 % in cow liver (non-acceptable study); not detected in new goat metabolism 2 % in fish liver	34 %
FPBalc FCR 1261	<10 % in primary crops [a]	up to 43 % in cow kidney (non-acceptable study); not detected in new goat metabolism	
FPBacid COE 538/78 FCR 2899	<10 % in primary crops [a]	up to 26 % in poultry tissues/eggs	5 %
4-OH-FPBacid FCR 3145	<10 % in primary crops [a]	up to 20 % in poultry tissues/eggs 5 % in fish liver	
Me-FPBacid COE 263/78	<10 % in primary crops [a]		
FPBamide FCR 2947	<10 % in primary crops [a]		
FPB FCR 3030	<10 % in primary crops [a]		
Acid cyfluthrin FCR 2728	<10 % in primary crops [a]	<1 % in fish muscle Up to 6 % in poultry tissues/eggs	

[a] detected after foliar treatment only
[b] permethric acid; common to permethrin and cypermethrin

The metabolites permethric acid (DCVA), FPBald (FCR 1260), FPBacid (FCR 2899) and 4-OH-FPB acid (FCR 3145) can be considered as covered in their toxicological properties by the studies with parent compound (see Vol. 1, 2.6.11.1).

No conclusion can be drawn for metabolites Me-FPBacid (COE 263/78), FPBalc (FCR 1261) FPBamide (FCR 2947), FPB (FCR 3030) and cyfluthrin acid (FCR 2728) regarding their toxicity profile (see 2.6.11.1). However, due to their – apparently – low amounts in plant metabolism studies (<10 %) further toxicological assessment is not considered necessary.
A summary of toxicological data for metabolites is presented in Table 2.6-47.

Plants
The proposed residue definition for monitoring and risk assessment in plants and animals is in accordance to previous assessments:

Cyfluthrin, including other mixtures of constituent isomers (sum of isomers)

Applicability of residue definition: Global residue definition (foliar and seed treatment).

In opposite to representative uses as seed treatment, the proposed residue definition for all uses with foliar treatments is based on previously submitted non-guideline, non-GLP metabolism studies that contain formal and scientific deficiencies at different levels (see assessment under Vol. 3, B.7.2.1).

The proposal for a global residue definition is therefore connected with a high, yet unquantified degree of uncertainty.

Justification - Seed treatment (sugar beet)
Two new metabolism studies in sugar beet after seed treatment equally showed that total residues are very low for both label positions (roots: <0.01 - 0.01 mg/kg at 1N and 0.05 - 0.11 mg/kg at 10N). Limited, but guideline compliant identification efforts revealed that parent is the only identified compound of quantitative relevance (detected above 10 % TRR in one of the two label studies only). Cleavage of parent structure was proven (minimum 5 – 9 % of TRR identified as DCVA trans), but quantification was not complete since for some major unidentified conjugates (individually accounting for up to 44 % of TRR) it could not be clarified whether the cleaved or uncleaved structure was conjugated.
Metabolism rate is apparently low. One identified metabolite (DCVA) appears in root and foliage in quantities <10 % of TRR. Results of the supporting metabolism studies in general confirm these findings (low systemicity; low transformation). The main metabolites from plants were also detected in animal metabolism studies.
Identification rate in sugar beet metabolism studies is acceptable. Overdose rate (10N accompanying 1N investigations) allows for sufficient certainty in identification of potential metabolites. The sum of minor identified metabolites not proposed for inclusion into the residue definition accounts for 8 % of TRR (0.001 mg/kg at 1N) and represents no major uncertainty.
The sum of individual compounds characterised, but not identified, as conjugates (probably parent), accounts for up to 58 % TRR. Due to low amounts (0.008 mg/kg), this is also no major uncertainty. Isomeric changes are not considered as of relevance for the proposal of the residue definition. No further uncertainties are considered to challenge the proposed residue definition.

Justification - Foliar treatment (tomato, potato, wheat, apple, soybean, cotton)
A re-assessment of previously submitted metabolism studies covering foliar applications (potato, wheat, apple, soybean, tomato, cotton) and artificial systems revealed that none of them complies to current standards and the mandatory GLP requirement as expressed in COM Reg. (EU) No. 283/2013. However, they are tentatively considered as acceptable for setting of the residue definition because they have been considered regulatory acceptable for the first evaluation (Germany, 1996, ASB2010-10436), and the scientific arguments of the reports are, although connected with partly severe limitations, overall considered as convincing.
The available set of metabolism studies indicates the likely quantitative non-relevance of metabolites after foliar application (no metabolite in the submitted studies exceeds the level of relevance in RAC at commercial harvest stages or in premature by-products).
The toxicological assessment of metabolites revealed that limited or no information is available for some apparently minor metabolites. Moreover, a higher uncertainty has to be considered for the evaluation of the non-standard and non-GLP studies addressing the plant metabolism after foliar application.
Given the levels reported in the metabolism studies, non-consideration of metabolites for risk assessment and monitoring is indicated.

Animals
In ruminant and poultry metabolism studies, the fate of cyfluthrin and beta-cyfluthrin was elucidated. Parent compound is the quantitatively prominent residue in all commodities (56 – 100 % in cow; 9 – 75 % TRR in laying hen).

Poultry
The phenyl-label metabolism study in poultry was not considered acceptable as a stand-alone-study and no robust residue definition can be derived from the information contained therein. No metabolism study with a cyclopropane label was submitted, although available data indicate the cleavage of beta-cyfluthrin in hen metabolism.
A tentative residue definition can be proposed based on metabolism and feeding studies. Compounds identified at significant levels in the metabolism study were

FPBacid (COE 538/78): 11 – 26 % of TRR in human edible commodities of laying hens
4-OH-FPBacid (FCR 3145): 10 – 20 % of TRR in human edible commodities of laying hens

At the levels identified, these metabolites appear to be absent at levels at or above 0.01 mg/kg even at the dietary burden calculated by EFSA 2010. Limited confirmation is given by the feeding study, where FPBacid was not found in any matrix at the lowest dose level (65N referring to EFSA 2010 dietary burden; analytical method only allows for determination at levels >0.1 mg/kg; linear extrapolation to 1N). It is therefore concluded that at the levels of beta-cyfluthrin (sum of isomers) expected after treatment according to all registered uses (MRL assessment in EFSA 2010), no significant residues of any metabolite are expected in poultry matrices. Potential cleavage compounds bearing the cyclopropane label (e.g. DCVA) are quantitatively covered by this evaluation. Re-assessment of dietary burden with OECD feeding table might require a re-assessment of metabolite relevance (out of the scope of this active substance evaluation).
Both metabolites are considered as toxicological covered by parent compound.

Ruminant
No residue of concern apart from parent compound is identified in a new guideline compliant metabolism study with [cyclopropane-1-^{14}C] labelled beta-cyfluthrin. Cleavage products bearing the label as well as unlabelled cleavage products were identified in urine and faeces only, but not in milk and fat.

In a metabolism study with [phenyl-U-^{14}C] labelled, two metabolites were identified at levels exceeding 10 % of TRR:

FPBaldehyde (FCR 1260): 14 % TRR (0.087 mg/kg) in liver
FPBalcohol (FCR 1261): 29 % TRR (0.011 mg/kg) in heart, 43 % TRR (0.081 mg/kg) in kidney

These compounds are not considered as of quantitative concern at the levels expected at 1N rate from the representative uses (at 77N for beef ruminants, individual metabolites are <0.01 mg/kg). Although the levels may exceed the trigger of relevance (0.01 mg/kg) at higher dietary burdens (e.g. EFSA 2010), the occurrence of both metabolites could not be confirmed in a new metabolism study. Additionally, the study with positive detects of both metabolites is connected with a higher degree of uncertainty (see Vol. 3, B.7.2).

In feeding studies, both metabolites were not found at levels exceeding 0.01 mg/kg up to a dose rate of 0.5 mg/kg bw/d (78N rate equivalent to the metabolism study) and up to 0.05 mg/kg at 1.6 mg/kg bw/d (249N rate). These results are considered sufficient to exclude the presence of levels >0.01 mg/kg even when considering the deficiencies of the analytical method (not validated for determination of levels <0.1 mg/kg).

The proposed residue definition for livestock (monitoring and risk assessment) is:

Cyfluthrin, including other mixtures of constituent isomers (sum of isomers)

Fish
In absence of agreed assessment tools (feeding table, MRL commodity codes, consumption data), the residue definition parent (default) is proposed.

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

The representative uses to be evaluated comprise seed treatment in sugar beets and foliar uses in potato, tomato, and wheat. A sufficient set of residue trials is submitted by the applicants (except wheat S-EU), which complies with the proposed residue definition.

Sugar beet
A guideline compliant residue data set of 10 trials for beta-cyfluthrin in sugar beets is available covering both N-EU and S-EU regions. The analytical method is validated, procedural recoveries are acceptable and storage stability is covered.
No residues above the LOQ (0.01 mg/kg) were found in any of the treated or untreated samples of sugar beet body and sugar beet leaf with root collar sampled 112-197 days after sowing:

Sugar beet root (N-EU): <0.01(6) mg/kg
Sugar beet leaf (N-EU): <0.01(6) mg/kg

Sugar beet root (S-EU): <0.01(4) mg/kg
Sugar beet leaf (S-EU): <0.01(4) mg/kg

Data sets for N-/S-EU can be combined due to the no-residue situation in roots and leaves. No discrepancy is observed to sugar beet metabolism studies.

Tomato
A fully guideline compliant residue data set of 8 trials for beta-cyfluthrin in indoor tomato is available. The analytical method is validated, procedural recoveries are acceptable and storage stability is covered. Residues in ranked order are

Tomato fruit: <0.01(3), 0.011(2), 0.012, 0.014, 0.016 mg/kg

Potato
A guideline compliant residue data set of 15 trials for beta-cyfluthrin in S-EU and N-EU is available with application rates partly outside 25 % of target rate. The analytical method is validated, procedural recoveries are acceptable and storage stability is covered.
Residues of acceptable trials in ranked order are

Potato tuber (N-EU): <0.01(4) mg/kg
Potato tuber (S-EU): <0.01(3) mg/kg

Trials with higher applications are included in acceptable trials. Trials with different samplings all support the findings by showing no residues directly after application as well as at the next sampling point. Number of trials is considered sufficient.

Wheat
A guideline compliant residue data set of 8 trials for beta-cyfluthrin in wheat (N-EU) is available. The analytical method is validated, procedural recoveries are acceptable and storage stability is covered.
Residues in ranked order are

Wheat grain (N-EU): <0.01(3), 0.013, 0.016, <0.02(3) mg/kg
Wheat grain (S-EU): <0.01(4) mg/kg

Wheat straw (N-EU): 0.72, 0.78, 0.24, 0.33, 0.83, 0.85, 0.18, 1.1 mg/kg
Wheat straw (S-EU): 0.43, 0.71, 0.78, 0.42 mg/kg

For S-EU, residue data set with 4 trials is incomplete.

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

The dietary burden resulting from the representative uses is given in Table 2.7-2.

Table 2.7-2: Results of the OECD dietary burden calculation (input values from RAR 2015)

	Maximum dietary burden (mg/kg bw/d)	Median dietary burden (mg/kg bw/d)	Highest contributing commodity	Max dietary burden (mg/kg DM)	Trigger exceeded
Risk assessment residue definition: cyfluthrin, including other mixtures of constituent isomers (sum of isomers)					
Cattle					
Beef	0.006	0.004	Wheat straw	0.27	Yes
Dairy	0.010	0.007	Wheat straw	0.27	Yes
Sheep					
Ram/ewe	0.017	0.012	Wheat straw	0.52	Yes
Lamb	0.022	0.015	Wheat straw	0.51	Yes
Swine					
Breeding	0.001	0.001	Potato	0.03	No
Finishing	0.001	0.001	Potato	0.03	No
Poultry					
Broiler	0.001	0.001	Potato	0.01	No
Layer	0.009	0.006	Wheat straw	0.14	Yes
Turkey	0.001	0.001	Potato	0.02	No

Analytical methods applied in feeding studies
No validated LOQ is available for the feeding studies, but a surrogate LOQ of 0.1 mg/kg can be proposed. Values below this level as reported in feeding studies should be considered as indicative only, and they will not form the basis for subsequent risk assessments.

Poultry
A non-GLP poultry feeding study is available. Cyfluthrin was administered to laying hens at adequate dose levels (range of 0.848 to 8.50 mg/kg bw/d; 94-944N referring to maximum rate). Using analytical methods not satisfying current quality criteria, significant residue levels for parent were only found in the high dose group (0.05 mg/kg). No residues are therefore expected in poultry matrices at the maximum 1N intake levels.

The data set is considered complete (except storage stability data for eggs) under conditions relevant for the assessment of representative uses within this RAR. Limitations of the data base are outlined in Vol. 3, B.7.

Ruminants
A set of GLP and non-GLP cow feeding studies is available. Cyfluthrin was administered to dairy cows at mean levels of 0.163 (7-25N), 0.507 (23-78N) and 1.61 mg/kg bw/d (74-249N; study 1; non-GLP) and at levels of 0.45 (21-70N), 1.5 (69-232N) and 4.5 mg/kg bw/d (206-696N; study 2; GLP).

Residues in ruminant matrices at 1N are constantly expected at levels <0.01 mg/kg except in fat of bovine (0.022 mg/kg) and sheep (0.047 mg/kg).

The studies are, irrespective of severe limitations (see Vol. 3, B.7), considered adequate for the assessment of beta-cyfluthrin within the whole data package of feeding and metabolism studies. The relevant transfer of parent into fat and milk (based on proven concentration in cream and butterfat) and the non-relevant transfer into other matrices can be assessed in a quantitative way. Limitations are considered as additional uncertainties requiring conservative estimates for dietary risk assessment.

2.7.6 Summary of effects of processing

Beta-cyfluthrin is stable to hydrolysis under pH 4/90 °C and pH 5/100 °C. Under pH 6/120 °C (sterilisation; relevant for tomato processing), beta-cyfluthrin is degraded rapidly.
Under study conditions, two fractions were identified as FPB acid, (4.9 % AR) and FPB aldehyde (33.6 % AR). A polar fraction (M7) represented 21.9 % AR. It is stated that the limited amount of radioactivity precluded the identification of the structure of M7. Under realistic conditions residues in commodities subjected to high temperature processing might exceed levels, where formation of the unidentified degradation product M7 exceeds 0.01 mg/kg (potentially relevant for non-representative uses only). However, it is emphasised that the simulated hydrolysis study is not triggered. Therefore, no data requirement on further identification of M7 is proposed.

If the level of residues in RAC is less than 0.1 mg/kg as for the representative uses of beta-cyfluthrin, processing studies shall be carried out if the contribution of the commodity under consideration to the ADI is ≥10 % or if the estimated daily intake is ≥10 % of the ARfD for any European consumer group diet. This is not the case for the evaluated uses of beta-cyfluthrin; therefore no further studies are required. Although the trigger is below the LOQ for potatoes in the respective residue trials, a real no-residue situation is assumed based on the proven non-systemic behaviour of beta-cyfluthrin.

Two quantitative processing studies are available, whereof one is acceptable in terms of GLP, study design, reporting, analytical method and storage stability of raw and processed samples to calculate processing factors for the relevant matrices. Transfer factors in washed tomato (pf 0.81), canned tomato (0.08), raw juice (0.28), raw puree (0.64) and wet pomace (3.14) were calculated.

2.7.7 Summary of residues in rotational crops

The DT_{90} of beta-cyfluthrin in soil has been determined at a level of 359 days in field studies (see Vol. 3, B.8). The relevant trigger of 10 % of the applied active substance 100 days after application is therefore exceeded and rotational crop studies required. However, long-term accumulation of beta-cyfluthrin in soil is not considered relevant due to the high percentage of interception (see PEC_{soil} calculation in Vol. 3, B.8).

One rotational crop metabolism and two field studies were submitted. The available data demonstrate the non-relevance of transfer of residues in rotational crops after treatment according to the representative GAPs (seed treatment and foliar uses).
The data package, although not comprising a stand-alone-study, is considered complete under conditions relevant for the assessment of representative uses within this RAR. Limitations of the data base are outlined in Vol. 3, B.7.

2.7.8 Summary of other studies

No study available and none required for the representative uses of beta-cyfluthrin.

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

The proposed reference values for dietary risk assessment are

ADI: 0.01 mg/kg bw
ARfD: 0.01 mg/kg bw/d

The dietary risk assessment considers residue levels determined in all field studies, the dietary burden resulting from these uses, and the possible transfer from this burden into animal matrices.

Residue input values for the dietary risk assessment are given in Table 2.7-3.

Table 2.7-3: MRL evaluation and residue input data for dietary risk assessment for beta-cyfluthrin resulting from representative uses [a]

Crop groups (representative crops)	MRL (existing)	MRL (RAR proposal)	Residues (beta-cyfluthrin)		Remarks
	MRL	MRL	HR	STMR	
	[mg/kg]	[mg/kg]	[mg/kg]	[mg/kg]	
Sugar beet (root)	0.5	0.01	0.01	0.01	MRL proposal covered by existing MRL
Wheat (grain)	0.02*	0.04	0.020	0.015	MRL proposal covered by existing MRL
Potato	0.04	0.01	0.01	0.01	MRL proposal covered by existing MRL
Tomato	0.05	0.03	0.016	0.011	
Ruminant (cow)[c,d]					proposals covered by existing MRL
Muscle	0.05	0.01*	<0.001	<0.001	
Fat tissue	0.2	0.03	0.022	0.011	
Liver	0.05	0.01*	<0.001	<0.001	
Kidney	0.05	0.01*	<0.001	<0.001	
Edible offal	0.05	0.01*	-		
Other tissues	0.05	0.01*	-		
Milk	0.02*	0.01*	0.002	0.001	
Ruminant (sheep, goat)					
Muscle	0.05	0.01*	n.r. [b]	n.r. [b]	
Fat tissue	0.2	0.05	n.r. [b]	n.r. [b]	
Liver	0.05	0.01*	n.r. [b]	n.r. [b]	
Kidney	0.05	0.01*	n.r. [b]	n.r. [b]	
Edible offal	0.05	0.01*	-	-	
Other tissues	0.05	0.01*	-	-	
Milk	0.02*	0.01*	0.003	0.001	

Crop groups (representative crops)	MRL (existing)	MRL (RAR proposal)	Residues (beta-cyfluthrin)		Remarks
Swine [c]					
Muscle	0.05	0.01*	<0.001	<0.001	
Fat tissue	0.2	0.01*	0.002	0.001	
Liver	0.05	0.01*	<0.001	<0.001	
Kidney	0.05	0.01*	<0.001	<0.001	
Edible offal	0.05	0.01*	-	-	
Other tissues	0.05	0.01*	-	-	
Poultry [c]					
Eggs	0.02*	0.01*	<0.001	<0.001	
Muscle	0.05	0.01*	<0.001	<0.001	
Liver	0.05	0.01*	<0.001	<0.001	
Fat	0.05	0.01*	<0.001	<0.001	

* below LOQ

[a] residue definition (risk assessment, monitoring): cyfluthrin, incl. other mixtures of constituent isomers (sum of isomers)

[b] HR and STMR are not relevant: no reliable consumption data available

[c] HR and STMR are theoretical levels at the calculated 1N rate

[d] covering horse meat

Based on the input values for the representative uses (MRL proposal, plant and animal commodities), no unacceptable acute and/or chronic risk is indicated. The maximum contribution to the proposed ADI of 0.01 mg/kg bw is 6.1 % for NL children. The most critical commodities in terms of acute exposure are tomato (17.4 % of ARfD), potatoes (15.4 %) and cattle milk (12.4 %). The summary of dietary risk assessments is presented in Table 2.7-4 and Table 2.7-5. As no unacceptable risk is indicated at the maximum levels expected after treatment of uses according to GAP, no further refinement is performed. The dietary risk assessment is considered provisional with regard to the uses in wheat, potato and tomato pending outstanding information on metabolism (all) and processing (tomato).

Table 2.7-4: Chronic dietary risk assessment for the representative uses of beta-cyfluthrin (Tier 1; residues at proposed MRL level)

beta cyfluthrin			
Status of the active substance:		Code no.	
LOQ (mg/kg bw):	0,01	proposed LOQ:	
ADI (mg/kg bw/day):	**0,01**	ARfD (mg/kg bw):	**0,01**
Source of ADI:	**RAR**	Source of ARfD:	**RAR**
Year of evaluation:	**2015**	Year of evaluation:	**2015**

Prepare workbook for refined calculations

Undo refined calculations

Explain choice of toxicological reference values.

The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL = pTMRL).
The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment

	TMDI (range) in % of ADI minimum - maximum
	1 6
No of diets exceeding ADI:	---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
6,1	NL child	2,9	Milk and milk products: Cattle	1,9	Wheat	0,6	Potatoes	4,0
5,4	WHO Cluster diet B	3,4	Wheat	0,9	Tomatoes	0,3	Milk and milk products: Cattle	1,0
4,5	UK Toddler	2,3	Sugar beet (root)	1,6	Wheat	0,3	Potatoes	2,7
4,0	WHO cluster diet D	2,6	Wheat	0,5	Milk and milk products: Cattle	0,4	Potatoes	1,1
4,0	ES child	1,8	Wheat	1,2	Milk and milk products: Cattle	0,3	Tomatoes	1,9
3,9	DE child	1,6	Wheat	1,4	Milk and milk products: Cattle	0,3	Tomatoes	1,9
3,5	FR infant	2,6	Milk and milk products: Cattle	0,4	Potatoes	0,3	Wheat	3,2
3,3	SE general population 90th percentile	1,3	Wheat	1,2	Milk and milk products: Cattle	0,4	Potatoes	1,7
3,2	IT kids/toddler	2,7	Wheat	0,4	Tomatoes	0,1	Potatoes	0,1
2,8	WHO regional European diet	1,2	Wheat	0,5	Milk and milk products: Cattle	0,4	Potatoes	1,3
2,8	WHO cluster diet E	1,6	Wheat	0,4	Potatoes	0,3	Milk and milk products: Cattle	1,0
2,7	DK child	2,2	Wheat	0,2	Potatoes	0,2	Tomatoes	0,3
2,7	WHO Cluster diet F	1,4	Wheat	0,4	Milk and milk products: Cattle	0,3	Potatoes	1,1
2,6	UK Infant	1,0	Wheat	1,0	Sugar beet (root)	0,3	Potatoes	1,5
2,4	PT General population	1,6	Wheat	0,5	Potatoes	0,3	Tomatoes	0,5
2,2	FR toddler	1,0	Wheat	0,5	Potatoes	0,2	Tomatoes	0,9
2,1	NL general	0,8	Wheat	0,7	Milk and milk products: Cattle	0,3	Potatoes	1,2
2,1	IT adult	1,7	Wheat	0,3	Tomatoes	0,1	Potatoes	0,1
2,0	ES adult	0,9	Wheat	0,5	Milk and milk products: Cattle	0,2	Tomatoes	0,9
2,0	FR all population	1,3	Wheat	0,3	Milk and milk products: Cattle	0,1	Tomatoes	0,6
1,8	IE adult	0,9	Wheat	0,3	Milk and milk products: Cattle	0,2	Potatoes	0,7
1,6	UK vegetarian	0,8	Wheat	0,4	Sugar beet (root)	0,2	Tomatoes	0,6
1,5	LT adult	0,4	Wheat	0,4	Milk and milk products: Cattle	0,3	Potatoes	0,9
1,4	UK Adult	0,7	Wheat	0,4	Sugar beet (root)	0,1	Potatoes	0,6
1,2	DK adult	0,8	Wheat	0,1	Potatoes	0,1	Tomatoes	0,2
0,7	FI adult	0,4	Wheat	0,1	Tomatoes	0,1	Potatoes	0,1
0,6	PL general population	0,3	Potatoes	0,3	Tomatoes		FRUIT (FRESH OR FROZEN)	0,3

Conclusion:
The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.
A long-term intake of residues of beta cyfluthrin is unlikely to present a public health concern.

Table 2.7-5: Acute dietary risk assessment for the representative uses of beta-cyfluthrin (Tier 1; residues at proposed MRL level)

Acute risk assessment /children	Acute risk assessment / adults / general population

The acute risk assessment is based on the ARfD.

For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the **IESTI 1** calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used.
In the **IESTI 2** calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variabilty factor of 3.

Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.

Unprocessed commodities

No of commodities for which ARfD/ADI is exceeded (IESTI 1):		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 1):**		---	**No of commodities for which ARfD/ADI is exceeded (IESTI 2):**		---
IESTI 1	***)**	****)**	**IESTI 2**	***)**	****)**	**IESTI 1**	***)**	****)**	**IESTI 2**	***)**	**)
Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)
17,4	Tomatoes	0,03 / -	12,6	Tomatoes	0,03 / -	4,6	Tomatoes	0,03 / -	3,7	Tomatoes	0,03 / -
15,4	Potatoes	0,01 / -	12,4	Milk and milk	0,01 / -	3,1	Wheat	0,04 / -	3,1	Wheat	0,04 / -
12,4	Milk and milk	0,01 / -	11,0	Potatoes	0,01 / -	3,0	Potatoes	0,01 / -	2,6	Sugar beet (root)	0,01 / -
6,4	Sugar beet (root)	0,01 / -	6,4	Sugar beet (root)	0,01 / -	2,6	Sugar beet (root)	0,01 / -	2,3	Potatoes	0,01 / -
5,8	Wheat	0,04 / -	5,8	Wheat	0,04 / -	1,7	Milk and milk	0,01 / -	1,7	Milk and milk products: Cattle	0,01 / -
No of critical MRLs (IESTI 1)		---				**No of critical MRLs (IESTI 2)**		---			

Processed commodities

No of commodities for which ARfD/ADI is exceeded:		---			**No of commodities for which ARfD/ADI is exceeded:**		---		
		*****)**					*****)**		
Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)			Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)		
5,2	Tomato juice	0,03 / -			1,8	Bread/pizza	0,04 / -		
4,7	Wheat flour	0,04 / -			0,6	Tomato (preserved-fresh)	0,03 / -		
1,4	Potato puree (flakes)	0,01 / -			0,1	Potato uree (flakes)	0,01 / -		
0,1	Fried potatoes	0,01 / -			0,1	Fried potatoes	0,01 / -		

2.7.10 Proposed MRLs and compliance with existing MRLs

The MRLs proposed for the representative uses are based on the same residue definition as currently established. The maximum residue levels for all crops (except wheat grain) and animal matrices are below the already established MRLs for these commodities (Table 2.7-3).

2.7.11 Proposed import tolerances and compliance with existing import tolerances

No import tolerances are applied and assessed within this RAR.

2.8 Fate and behaviour in the environment

2.8.1 Summary of fate and behaviour in soil

The aerobic degradation in soil was studied in the laboratory in four soils using beta-cyfluthrin radio-labelled in the cyclopropyl- and in the fluorophenyl-moiety. The metabolites requiring further consideration are FPB-acid (maximum 12.7 % after 7 days) and DCVA (maximum 40.5 % after 7 days). The degradation of beta-cyfluthrin is well described by biphasic models (DFOP or FOMC), the geometric mean for normalised DT_{50} is 28.1 days (modelling endpoint, n = 4). The geometric mean for degradation of metabolite DCVA is 3.5 days (n = 3, laboratory studies, parent dosed as test substance) and for metabolite FPB-acid is 1.2 days (n = 4, laboratory studies using both parent and metabolite as test substance).

Four field studies were conducted in S- and N-France, Germany and Spain. The DT_{50} obtained were 3.3 – 45 days (non-normalised).

The anaerobic degradation in soil was studied in the laboratory in one soil using beta-cyfluthrin radio-labelled in the cyclopropyl- and in the fluorophenyl-moiety. No new metabolite was detected.

The photolytic degradation on soil was studied in the laboratory in one soil using beta-cyfluthrin radio-labelled in the fluorophenyl-moiety. No new metabolite was detected. The dissipation of beta-cyfluthrin was very similar in both the irradiatied and the dark control sample. It can be assumed that photo-transformation is not a relevant process.

The adsorption of cyfluthrin to soil was studied in five soils. The $K_{d\ oc}$ is 104491 (geometric mean), hence the active substance can be regarded as immobile in soil. Adsorption of the active substance is not pH-dependent. For the soil adsorption of the major metabolite FPB-acid $K_{f\ oc}$ was determined to be between 39 and 424 (n = 8 soils, Freundlich exponent 1/n between 0.6 and 0.8). For the soil adsorption of the major metabolite DCVA $K_{f\ oc}$ was determined to be between 9 and 356 (n = 8 soils, Freundlich exponent 1/n between 0.743 and 0.957). The adsorption of both metabolites is pH-dependent and mobility in soil is medium to very high.

2.8.2 Summary of fate and behaviour in water and sediment

Cyfluthrin in hydrolytically stable at pH 4, the half-lives are between 160 and 270 days at pH 7 and between 33 and 42 hours at pH 9. The metabolite DCVA is hydrolytically stable at pH 4, 7 and 9.

The photolytic degradation is calculated between 5 and 5.9 days under natural light in spring and summer 40 °Northern latitude.

In water/sediment system the DT_{50} for the whole system is 27.6 days (geometric mean, n = 2), the dissipation $DissT_{50}$ from water is 0.5 days and from sediment 34.1 days. The metabolite DCVA was distributed both in water (36 % applied at 2 days) and sediment (23.7 % at 100 days). The metabolite FPB-acid was distributed in water (29.1 % at day 11) and sediment (24.3 % at day 1). A new metabolite occured in the water/sediment study, FPB-aldehyde: in water (1.1 % at day 1) and sediment (15.7 % at day 1). The rates of degradation in the whole system for the metabolites were: DCVA DT_{50} = 113.8 days (n = 1), FPB-acid DT_{50} = 5.6 days (geometric mean, n = 2) and FPB-aldehyde DT_{50} = 6.6 days. The dissipation from sediment was $DissT_{50}$ = 5.3 days for FPB-acid and $DissT_{50}$ = 5.0 days for FPB-aldehyde. No dissipation from water could be modelled for any metabolite and no dissipation from sediment for DCVA.

2.8.3 Summary of fate and behaviour in air

The vapour pressure of beta-cyfluthrin is between 4.5×10^{-7} Pa (isomer II) and 2.2×10^{-6} (isomer IV) at 20 °C.

The tropospherical half-life of beta-cyfluthrin was calculated to be below one day (17.8 h) using the Atkinson approach.

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

No data available.

2.8.5 Definition of the residues in the environment requiring further assessment

Name and code	Environmental compartment
beta-cyfluthrin	soil water sediment
DCVA	soil water sediment
FPB-acid	soil water sediment
FPB-aldehyde	water sediment

2.8.6 Summary of exposure calculations and product assessment

Soil

The method of calculation of degradation of beta-cyfluthrin in soil is derived from field data (HS-kinetic, k1 = 0.0249 (DT_{50} = 27.8 d), k2 = 0.00485 (DT_{50} = 143 d), t_b = 28 d. The maximum occurrence of metabolites in soil is 12.7 % for FPB-acid (molecular mass 232.2 g/mol) and 40.5 % for DCVA (molecular mass 209.1 g/mol).

The application data for Bulldock EC 25 are given in the following table:

Application rate 2 × 7.5 g/ha as, intervall 14 days			
crop:	winter cereals	spring cereals	potato
application time:	autumn BBCH 11	spring BBCH 11	BBCH 10
crop interception:	25 %	25 %	15 %
soil depth:	5 cm	5 cm	5 cm
soil density:	1.5 g/cm^3	1.5 g/cm^3	1.5 g/cm^3
Application rate 2 × 12.5 g/ha as, intervall 14 days			
crop:	winter cereals	spring cereals	potato
application time:	autumn BBCH 11	spring BBCH 11	BBCH 10
crop interception:	25 %	25 %	25 %
soil depth:	5 cm	5 cm	5 cm
soil density:	1.5 g/cm^3	1.5 g/cm^3	1.5 g/cm^3
Application rate 2 × 17.5 g/ha as, intervall 14 days			
crop:	tomato		
application time:	BBCH 19 and 29		
crop interception:	50 % and 70 %		
soil depth:	5 cm		
soil density:	1.5 g/cm^3		

The application data for Montur Forte FS 230 are given in the following table:

Application rate 1 × 10.5 g/ha as			
crop:	sugar beet		
application time:	BBCH 00		
crop interception:	0 %		
soil depth:	5 cm		
soil density:	1.5 g/cm^3		

Groundwater

Due to very high adsorption of cyfluthrin to soil ($K_{d\ oc}$ 104491, geometric mean) and very quick degradation of metabolites (DCVA: DT_{50} 3.5 days, FPB-acid: DT_{50} 1.2 days) no leaching into groundwater is expected.

The calculation of PECgw following application of Bulldock 25 EC in tomato (2 × 17.5 g/ha as, crop interception 0 % and 50 %) using the models FOCUS Pearl v. 4.4.4 and FOCUS Pelmo v. 5.5.3 gives no value > 0.001 µg/L for beta-cyfluthrin, FPB-acid or DCVA.

Surface water and sediment

Due to the fact that the RAC for use in the aquatic risk assessment is very low (0.067 ng/L beta-cyfluthrin) no FOCUS SW Step 1 and Step 2 calculations were conducted by RMS.

A FOCUS SW Step 3 calculation was conducted by the RMS. The program versions are: SWASH 3.1, MACRO 4.4.2, PRZM 3.1.1, TOXWA 3.3.1 and SWAN 3.0.0. The scenarios in potato are those which meet the lowest PEC in surface water following application of Bulldock 25 EC.

The type and degree of risk mitigation measures accepted and applied in the European Member States are not sufficiently known. As the RMS is of the opinion that 20 m drift buffer zone and 90 % nozzle drift reduction are widely accepted and are applicable in agricultural practice, these parameters are used for FOCUS SW Step 4 calculations.

Other routes of exposure

During sowing of sugar beet treated with Montur Forte FS 230 an active substance containing dust

abraded from the surface of the seed might deposit outside the field.

A PEC 2 D dust ground deposition of beta-cyfluthrin from sugar beet seeds in off-crop areas at 1 m distance from field edge is expected to be 0.007 g as/ha.

A PEC 3 D dust deposition (for three-dimensional structures like hedges or trees) of beta-cyfluthrin from sugar beet seeds in off-crop areas is expected to be 0.09 g as/ha.

2.9 Effects on non-target species

2.9.1 Effect on birds

A number of different avian acute oral, short-term dietary and long-term reproduction studies have been carried out with beta-cyfluthrin and cyfluthrin already evaluated during the initial EU assessment of beta-cyfluthrin.
Additionally, a new acute oral study was submitted. Adverse effects of beta-cyfluthrin to canary birds (*Serinus canaria*) were investigated. ([redacted] 2012).
This study contradicts the results of the study by [redacted] 1979 and the supporting study ([redacted] 1985). The concluded LD_{50} is > 2000 mg/kg bw, although the NOEL concerning sublethal effects and mortality is < 125 mg/kg bw. 1 of 10 birds of every treatment group died shortly after administration. However, the intensity of sublethal effects increased with rising applied amounts of beta-cyfluthrin.
The big difference (factor 40) between endpoints of both studies on the same species cannot be explained by intra species deviation. Due to reasons pointed out in Volume 3 CA chapter B.9.1.1 it is assumed that the exposure of test animals to the active substance was reduced in [redacted] (2012). Thus results are not used for the risk assessment.

Another study testing the acute toxicity of Bulldock to canary bird, shiny cowbirds and eared doves was found in the open literature (Addy-Orduna, L et. al 2011). Results for canary birds support the outcome of [redacted] (1979).

Furthermore, a new acute oral study with bobwhite quail (*Colinus virginianus*) conducted with the representative formulation Bulldock EC 25 is available. However, the maximum tested concentration with regard to the active substance is considerably lower than in the studies with the active substance (please refer to Volume_3_CA B-9). Therefore, it is not possible to compare the toxicity of the active substance alone with the toxicity of the EC 25 formulation.

The following endpoints and effect values were identified as relevant for the quantitative risk assessment according to the current EFSA Guidance Document.

Beta-cyfluthrin:
Acute risk assessment:
Data about the acute toxicity of beta-cyfluthrin to birds are available for four species.
For canary birds, LD_{50} from two valid studies are available. According to the EFSA GD (2009) the endpoint used for the risk assessment is calculated by the geometric mean of LD_{50} for each species.

species	LD_{50} [mg/kg bw)
bobwhite quail	3776 [1)]
Japanese quail	3896 [2)]
hen	3872 [3)]
canary bird	92.2 [4)]
shiny cowbird	2234
eared dove	2271
geometric mean	2939

[1)] based on the LD_{50} geomean of two studies (KIIA8.1.1/01; KIIA 8.1.1/03) each multiplied with 1.888
[2)] based on the geomean of LD_{50} = 2000 mg/kg bw (KIIA8.1.1/02)* 1.518 (one case of mortality) of two studies and LD_{50} = 3000 mg/kg bw (KIIA 8.1.1/07)
[3)] based on the LD_{50} geomean of two studies (KIIA 8.1.1/05; KIIA 8.1.1/06)
[4)] based on the geometric mean of the NOEL = 50 mg/kg bw ([redacted] 1979; according to the EFSA Guidance Document 2009 part 2.1., in absence of information on the amount of regurgitated material, the lowest overall NOEL must be used for the risk assessment. Therefore, the endpoint from this study is the NOEL = 50 mg as/L) and the LD_{50} of170 mg/kg bw (Addy-Orduna, L. et. al 2011; KIIA 8.1.1/11)]

However, as the endpoint for the most sensitive species is lower than geomean-LD_{50}/10 of 293 mg/kg bw for 6 tested species, the geomean LD_{50} of *Serinus canaria* (92.2 mg/kg bw) combined with a safety factor of 1 has to be used in the risk assessment.

Chronic: NOEL = 37.74 mg as/kg bw (mallard duck, *Anas platyrhynchos*)[2]

Representative formulation Bulldock EC25:
Acute: LD_{50} > 2000 mg/kg bw

2.9.2 Effect on other terrestrial vertebrates (wild mammals, amphibians, reptiles)

Acute: LD_{50} = 131.1 mg as/kg bw (geometric mean of LD_{50} -values for male rats and mice):

Species	Rat		Mouse	
Gender	female	male	female	male
Individual LD_{50} in mg/kg bw	651	380	165	91
	336	211	-	-
	77	84	-	-
	200	-	-	-
Geomean for gender	240.9	**188.8**	165.0	**91.0**
Overall geometric mean LD_{50} in mg/kg bw (based on LD_{50} male)	**131.1**			

The overall geometric mean LD_{50} is based on the geometric mean LD_{50} derived for male rats and the LD_{50} value derived for male mice. This approach was chosen as the sensitivity to males appears to be higher than to females. The difference of the geometric means for gender (rats) is 52.1 mg/kg bw. This is 27.6 % of the lower LD_{50} (male) and 21.6 % of the higher LD_{50} (female). The difference between LD_{50} values for male and female mice is 74 mg/kg bw. This is 81.3 % of the lower LD_{50} (male) and 44.9 % of the higher LD_{50} (female). According to the EFSA GD 2009 chapter 2.1.1 the calculating of a geometric mean between the endpoints of genders should be abandoned when "the difference in the LD_{50} value is > 25 %.
The assumption of a higher sensitivity of male mammals is supported by the ADME study of [redacted] (2013b) described in Vol. 3, B.6. Results show that the absorption in male animals is 1.5 fold higher than in female (in case of the highest test concentration 10.1 mg as/kg bw). Thus, the higher sensitivity

[2] The study was conducted with cyfluthrin. In case of toxicity to birds an adjustment of endpoints derived from studies conducted with cyfluthrin is not regarded necessary (for a detailed justification please refer to Volume_3CA_B-9.1).

is based on a higher absorption rate of male rats.

Long-term/reproductive: NOEL = 3**.3 mg as/kg bw** (based on the 2-generation study with rats [(1996), please refer to Volume_3CA _B-6.6.1.).

Representative formulation Bulldock EC25:

Acute toxicity in rats: LD_{50} > 300 mg/kg bw (8.79 mg as/kg bw) < 2000 mg/kg bw (58.6 mg as/kg bw)

Amphibians:

Other than stated by the applicant, it is possible to find information about toxic effects of pyrethroids in general as well as of cyfluthrin in particular to amphibians when searching shortly with SCOPUS. Additionally, it should have been found when using Biosis.
For example, Lambert (2001) described the death of emong tadpoles from tsetse fly control caused by the pyrethroids, cyfluthrin (40 g /ha) in Cameroon, and deltamethrin (12.5 g /ha) and permethrin (11.5 g/ha) in Burkina Faso.

Therefore, an additional extended literature search concerning the toxicity of cyfluthrin and beta-cyfluthrin is required. Biosis, should be searched again. Additionally, other databases should be used, e.g. SCOPUS, PubMed. Furthermore, the applicant should provide a justification for using the selected databases.

The notifier repeated the literature research concerning adverse effects of (beta-)cyfluthrin in scientific databases. As result information on toxic effects of technical beta-cyfluthrin on green frog tadpoles were submitted. Based on these results it is not possible to conclude that the acute risk on tadpoles is covered by information on fish.
There is no information on chronic, sublethal effects to amphibian from public literature. Therefore, the long-term risk for amphibians remains unknown. However, official, appropriate test guidelines for determining the chronic toxicity to amphibians are not available,
Moreover, tadpoles are only the juvenile life stage of amphibians. The adult life stage cannot be assessed or covered by the risk assessment for fish. Adult amphibians spend a big part of their life in terrestrial habitats, e.g. fields. Thus, they are directly exposed to the tank mixtures of pesticides. Due to their very thin and permeable skin, contact toxicity may play a major role concerning the overall toxicity. However, little is known about the toxicity of pesticides to adult amphibian life stages.

As there are neither test guidelines for testing oral and contact toxicity to amphibian nor appropriate exposure models, the risk to amphibians cannot be addressed.

2.9.3 Summary of effects on aquatic organisms

2.9.3.1 Effects on fish

Acute toxicity:

The lowest available acute endpoint from the submitted laboratory studies is derived from . (1994, KIIA 8.2.1/02) performed with rainbow trout (*Oncorhynchus mykiss*) LC_{50} (4 d) = 0.068 µg/L in a flow-through system. Additionally, studies with two other species were conducted [(1994, KIIA 8.2.1/03 and (1988, KIIA 8.2.1/04)] in a flow-through system resulting in the following endpoints: *Lepomis macrochirus* – LC_{50} (4 d) = 0.28 µg/L, *Leucisicus idus melanotus* – LC_{50} (4 d) = 0.331 µg/L, all based on measured concentrations (real).
The geometric mean LC_{50} calculated on the basis of these data is 0.184 µg/L (real) which would lead to a RAC of 1.8 ng/L.
However, considering the fast dissipation of the active substance from the water phase and the exposure in surface waters according to the intended use (dominated by peaks after two spray drift occasions), data derived from flow through systems are considered very conservative, and therefore not the most appropriate to address the acute risk to fish.

Six other acute studies, performed under static conditions (for details please refer to Volume_3CP_Bulldock EC 25_B.9.3.1) were submitted. These include studies with *O. mykiss* and *L. macrochirus*, as for static conditions, plus four other species. LC_{50} values were originally given as nominal concentrations, but were recalculated based on mean measured concentrations (see table below).
These data are in line with the information from a study on the toxicity of the beta-cyfluthrin formulation, Bulldock 25 EC, towards rainbow trout and performed in outdoor ponds ([redacted] 2005, KIIIA1 10.2.2.1/3). Even if the outcome of this study cannot be used to derive directly a relevant endpoint, (please refer to Volume_3CP_Bulldock EC 25_B.9.3.3), it provides additional information supporting the results of the laboratory studies. Indeed the endpoint (LC_{50} = 5 µg/L) from the study report was based on nominal values but the measured concentrations of the active substance in ponds showed a fast decrease (DT_{50} water = 2.9 – 9.3 h). All affected fish (50 %) died at the beginning of the study, i.e. due to acute intoxication.
Therefore, the LC_{50} was recalculated based on the mean measured concentrations of the first four days. The resulting LC_{50} (4 d) is 0.366 µg as/L. It is interesting to note that this value is similar to the LC_{50} (real) = 0.359 µg/L for *O. mykiss* derived from the static laboratory test, although fish used in the outdoor pond study ([redacted] 2005) were bigger and older than in the laboratory study ([redacted] 2006, KIIA 8.2.1/07) and thus possibly less sensitive. This increased sensitivity may be compensated by the influence of other factors that may decrease the effects, so that the resulting effect concentration is similar in pond experiment and in laboratory tests.

Species	**LC_{50} nom [µg/L]**	**LC_{50} real [µg/L]**
O. mykiss	1	0.359
G. aculeatus	2.81	0.837
R. rutilus	1.6	0.513
P. promelas	5.62	1.18
L. macrochirus	3.2	0.87
C. carpio	6	1.5
SSD median HC5	0.82	**0.312**

Based on the mean measured LC_{50} values of the static tests, a geomean of 0.787 µg/L could be calculated and a RAC of 7.87 ng/L would be derived, i.e. 4.4 fold higher than the RAC derived also from a geomean calculation, but under flow through conditions (RAC was 1.8 ng/L). However in case of the static tests, as 6 studies are available, it is possible to perform a SSD; the SSD median HC5 LC_{50} of 0.312 µg/L (real) was determined.
According the new Aquatic Guidance Document (EFSA, 2013) (chapter 2.1.4.2), the RAC based on the SSD approach is calculated by dividing the endpoint by an AF of 9.
Therefore, the final RAC fish acute is 34.6 ng/L (real).

Chronic toxicity:
The lowest available endpoint from the submitted laboratory studies is derived from the early life stage test with rainbow trout (Carlisle, 1985). The derived 56 days LC_{50} of cyfluthrin is 0.069 µg/L (mean measured) and the NOEC is 0.01 µg/L (mean measured).). Endpoints for beta-cyfluthrin adjusted by multiplication with the factor 0.42 which leads to the following values:
LC_{50} (56 d) = 0.029 µg/L
NOEC (56 d) = 0.0042 µg/L
For a detailed reasoning, please refer to Volume_3CA_B.9.3.2 and Volume_3CA_B.9.1.

The submitted fish microcosm study ([redacted] 2005) is considered not appropriate to unburden effects from the ELS study since the introduced fish were too old/big (average weight of 10.3 g) to consider effects to younger life stages including fish embryo. Furthermore, accepting this as higher tier population study can be argued, since only effects to short-term effects on a fish species were tested.

Therefore, the RAC for chronic effects is calculated by the beta-cyfluthrin adjusted NOEC (56 d) of 0.0042 µg/L and an assessment factor of 10. $RAC_{fish,\ chronic}$ = 0.00042 µg/L.

Metabolites:
The metabolites FPB-acid and DCVA of beta-cyfluthrin are formed to a maximum of 44.5 % and 47.6 % of the parent compound in total water systems, respectively. The metabolite FPB-aldehyde is found at 15.7 % of the parent compound only in sediment. Therefore, FPB-acid, DCVA and FPB-aldehyde are regarded as main metabolites. Thus, their ecotoxicological relevance has to be assessed.
Two old studies submitted for the first registration of beta-cyfluthrin address the toxicological effects of FPB-aldehyde ([redacted] 1984; KIIA 8.2.1/06) and DCVA ([redacted] 1984; CA 8.2.1/05, KIIA 8.2.1/05), respectively. Both studies are regarded as valid except for the missing analytic data.
However, DCVA is considered to be stable in the aquatic environment. An LC_{50} (4 d) of > 14.7 mg/L was determined.
The LC_{50} (4 d) of FPB-aldehyde (0.792 mg/L) on rainbow trout can be compared with the nominal LC_{50} of beta-cyfluthrin from the acute study with rainbow trout that was also conducted in a static test system ([redacted] 2006).
As half life times of beta-cyfluthrin and its metabolite FPB-aldehyde are similar (DT_{50} = 2.4 d) according to the water-sediment studies (see Volume_3CA_B.8.2.2), both endpoints can be compared directly. Accordingly, beta-cyfluthrin (LC_{50} = 0.001 mg/L) is 800-fold more toxic than FPB-aldehyde.
A new laboratory study ([redacted] 2010; KIIA 8.2.1/13) was submitted addressing the acute toxicological effects of the metabolite FPB-acid to fish (rainbow trout). This study is considered as valid. The deduced derived LC_{50} (4 d) = 4.06 mg/L.
In conclusion, the acute endpoints for the metabolites FPB-acid, DCVA and FPB-aldehyde are by several orders of magnitude higher compared to those for the active substance, therefore all three main metabolites are considered to be of no ecotoxicological concern for fish.

2.9.3.2 Effects on aquatic invertebrates

Beta-cyfluthrin is very toxic to aquatic invertrabrates. Data for the tiered risk assessment with regard to acute and chronic effects is summarised in the following table.

tier	acute	chronic
1	EC_{50} (4 d, *Hyalella azteca*, mm) = 0.23 ng/L AF (assessment factor) = 100 **RAC_{acute} = 0.0023 ng/L**	NOEC (21 d, *Americamysis bahia*) = 0.41 ng/L AF = 10 **$RAC_{chronic}$ = 0.041 ng/L**
2	Geomean on 4 species of invertebrates [effect values based on real concentrations (ng/L)] *Daphnia magna*: 2d LC_{50} = 75.9 (geomean of LC_{50} = 55 ng/L and 105 ng/L) *A. bahia*: 4d LC_{50} = 1.59 ng/L (geomean of 3 values: 2.22 ng/L; 2.23 ng/L and 0.82 ng/L) *Gammarus pulex*: 4 d-LC_{50} = 4.0 (mean of 2 and 7 d) *Hyallela azteca*: 4 d-LC_{50} = 0.23 **Geomean LC_{50}: 3.25 ng/L** AF = 100 **RAC_{acute} = 0.0325 ng/L**	In a weight of evidence approach the selection of the lowest endpoint from the three invertebrate species tested is possible. Account for a part of the species sensitivity with a reduced AF of 6: *Daphnia magna*: NOEC (21d) = 25 ng/L *A. bahia*: NOEC (21 d) = 0.41 ng/L *Gammarus pulex*: NOEC (21 d) = 0.43 ng/L Relevant endpoint is 0.41 ng/L AF = 6 **$RAC_{chronic}$ = 0.068 ng/L**

3	Based on an overall assessment taking into accout the outcome of microsom studies (Heimbach (2000; KIIIA1 10.2.3/03); Jenkins, W.R. (2014; KIIIA1 10.2.3/05) as well as results from laboratory studies **ETO-RAC is 0.105 ng/L** **ERO-RAC is 1.05 ng/L**

Tier 2 RAC chronic

In addition to the chronic study with *A. bahia*, which is considered in the tier 1, chronic studies on two other invertebrates species have been performed (i.e. *D.magna* and *G. pulex*). The results for the three tested species can not be used to calculate a geometric mean since the endpoints are not all based on same type of endpoints (reproduction for *A. bahia* and *D.magna* and behavior (swimming ability) for *G. pulex).* Indeed similarity of endpoints is one of the conditions to be fulfilled to use the geometric mean approach for refined risk assessment, as mentioned in the Aquatic GD (EFSA Journal 2013; 11(7):3290).

Furthermore, the acute toxicity dataset points out that *Hyallela azteca* is more sensitive than the 3 other species tested (about 7-fold more sensitive than the second most sensitive tested species *A. bahia*). Thus assuming that *Hyallela azteca* is also about 7-fold more sensitive in terms of chronic toxicity, applying the geomean to derive a RAC would not deliver a sufficient level of protection. Thus the alternative is to use a WoE approach by selecting the lowest endpoint from the three invertebrate species tested and account for the part of species sensitivity adressed, by using a reduced AF. In this case, *A.bahia* is used, i.e. a NOEC (21d) = 0,41 ng/L with an AF 6 to deliver a **RAC of 0,068 ng beta-cyfluthrin/L.**

Furthermore the RMS wants to point out that they generally have strong concerns to use the geometric mean approach for chronic data. In the Aquatic GD, it is stated that there is currently limited experience in the use of the Geomean approach for chronic data, hence calibration for this approach is needed (see Aquatic GD, chapter 8.3.2).

The geometric mean approach was developed on the basis of acute toxicity data; indeed it is reported in EFSA 2006[3] (page 39) that ”due to a limited amount of chronic data available, the analyses were restricted to acute toxicity data”. Actually there exists not only no data analysis supporting the use of the geometric mean approach for chronic toxicity data but there is also a scientific reasoning missing that the concept could also be applied to chronic data. Thus it remains to be investigated whether the same (geomean) procedure can be used for chronic toxicity data as well as for acute data. It seems that the arguments for proposing the use of the geometric mean approach on chronic data are based on pure pragmatism rather than on science. However, new approaches proposed for the effect and the risk assessment should be based on the certainty that a suitable level of protection for aquatic ecosystems can be maintained not only on average overall substances but for each single active substance.

Tier 3 RAC:

Summary of outcomes from the outdoor micro- and mesocosm studies of Heimbach (2000, KIIIA1 10.2.3/03) and Jenkins (2014, KIIIA1 10.2.3/05):

Both studies are considered for derivation of an endpoint for aquatic invertebrates for the risk assessment of beta-cyfluthrin.

Information gathered from the mesocosm study of Heimbach (2000, KIIIA1 10.2.3/03) delivers a RAC of 0.25 ng cyfluthrin/L (equivalent to a RAC of 0.105 ng beta-cyfluthrin/L). This is derived from an extrapolated NOEC of 0.54 ng/L (since the study did not deliver a real NOEC, as effects were observed at the lowest concentration tested), associated with an AF of 2 and is based on the most sensi-

[3] *EFSA (European Food Safety Authority), 2006. Opinion of the Scientific Panel on Plant health, Plant Protection Products and their Residues on a request from the EFSA related to the assessment of the acute and chronic risk to aquatic organisms with regard to the possibility of lowering the assessment factor if additional species were tested. The EFSA Journal 2005, 301, 45 pp. doi:10.2903/j.efsa.2006.301.*

tive endpoint namely emergence of *Chaoborus*.
This study (Heimbach, 2000) was evaluated and accepted in the previous EU review under Directive 91/414/EEC. The endpoint for risk assessment was a No Observed Ecologically Adverse Effect Concentration (NOEAEC) of 50 ng as/L which was used in combination with an uncertainty factor (or assessment factor AF) of 2, to derive an Ecologically Acceptable Concentration (EAC) of 25 ng as/L. However, for the current assessment the study was re-evaluated according to the recommendations of the aquatic GD (EFSA 2014). For the ETO-option the NOEC was calculated on the basis of a factor of 20 below the lowest concentration tested, i.e. a factor 10 for extrapolating from substantial effects to negligible effects and an additional factor 2 to account for a higher sensitivity of an earlier life stage. This is equivalent to a NOEC of 0.54 ng cyfluthrin/L. The NOEC is then associated to a standard AF of 2 (AF of 2 to 3 is recommended in the aquatic GD (EFSA 2014)) to derive an ETO-RAC. The ETO-RAC of 0.25 ng cyfluthrin/L is equivalent to an ETO-RAC of 0.105 ng beta-cyfluthrin/L). Applying the ETO-RAC is recommended since the ERO-RAC may not provide a sufficient protection level in terms of the sustainability of the population at risk.

Information gathered from the mesocosm study of Jenkins (2014) delivers a RAC <0.20 ng beta-cyfluthrin/L. This is derived from a NOEC < 0.5 ng beta-cyfluthrin/L associated with an AF of 2.5 and is also based on the most sensitive endpoint namely emergence of *Chaoborus*.
However this study suffers of various short-coming:
1) A large proportion of the *Chaoborus* individuals emerged before the 1st exposure (mean time to emergence for control individuals was 1.34 days). This means that at the time of exposure, the remaining individuals were either at a late stage or already at the pupae stage. It is well known that the (i) earlier larval stages are the most sensitive and (ii) that pupae do not feed and have low metabolic activity. As a result, it can be stated that the contamination is occurring at a stage where *Chaoborus* is least sensitive. Micro- or mesocosm studies should be typically performed with sensitive populations – i.e. preferably either with young individuals or whenever relevant with mixed populations (containing eggs, larvae of different stages, pupae) – to enable good evaluation of the risk for the population of concern.
In the mesocosm study of Heimbach, 2000, on cyfluthrin, the treatment was applied earlier in comparison with the timing of emergence in control ponds compared to the present study, performed in limited size microcosm (mean time to emergence for control individuals was 47 days versus 1.34 days). It can be stated that the NOEC of younger larval stages of *Chaoborus* would certainly be lower than 0.5 ng/L, although the variation of sensitivity of different larval instars of *Chaoborus* towards beta-cyfluthrin is not known.
2) Because the highest abundance of adults (emergence) occurred before the 1st exposure, it is difficult to demonstrate statistically significant effects at low concentrations in such conditions. Furthermore, there is possibly higher variability between replicates towards the end of this emergence process than at the beginning.

The outcomes of the 2 independent studies are in line and similar (factor of about 3 maximum between the 2 RACs), especially considering that:

a) the NOEC leading to the RAC of 0.105 ng beta-cyfluthrin/L from the study of Heimbach (2000) is extrapolated and not observed, and
b) the NOEC leading to the RAC of <0.20 ng beta-cyfluthrin/L from the study of Jenkins (2014) is also linked to uncertainties linked to the shortcomings described above. Therefore the information obtained from this study confirms that the extrapolation made in the study of Heimbach (2000) leads to reliable estimate even if linked to a number of uncertainties.

Consequently, taking all information into account, **we conclude that the RAC to be used for the aquatic risk assessment is equivalent to 0.105 ng beta-cyfluthrin/L**.

Metabolites:

Effects of the main metabolites FPB-acid, DCVA and FPB-aldehyde to aquatic invertebrates are adequately addressed by acute laboratory studies with *Daphnia magna* [FPB-acid: EC_{50} = 39300 µg/L (nom); DCVA: EC_{50} = 25000 µg/L (nom); FPB-aldehyde: EC_{50} = 1300 µg/L (nom)]. Additionally,

possible adverse effects are covered by the microcosm studies evaluated for the risk assessment (Heimbach, 2000 and Kimmel, 2014).
Studies investigating effects of the metabolites to sediment dwellers are not available. FPB-acid and FPB-aldehyde are formed to a maximum of 24 % (1 d) and 16 % (1 d) of the parent compound in sediment, respectively. Therefore, possible toxic effects due to both metabolites are covered by the chronic laboratory studies with *Chironomus riparius* conducted with the parent compound.
The maximum concentration of DCVA (24 %) in sediment peaks out 100 days after application. However, the notifier provided supporting information for the risk assessment of the beta-cyfluthrin metabolite DCVA to sediment dwellers. Based on information about the toxicity of DCVA to *Daphnia magna*, physico-chemical and structural properties and efficacy data, it can be concluded that the toxicity of DCVA is covered by the studies with the parent compound.

Representative formulations:

1. Results with the representative formulation **Bulldock EC 25** reveal a slightly higher toxicity of the formulation (EC_{50} = 55 ng as/L) compared to the active substance (EC_{50} =105 ng as/L).

2. Results with the representative formulation **Montur Forte FS 230** reveal a slightly lower toxicity of the formulation 48 h EC_{50} = 4.2 µg/L than estimated by calculating the additive toxicity of both active ingredients, beta-cyfluthrin and imidacloprid (EC_{50} = 1.42 µg/L).
However, it was shown that other aquatic invertebrate species are more sensitive than *Daphnia magna* towards the active ingredients of the formulation.

When comparing the toxicity of both active substances to the most sensitive organisms *Caenis horaria* (imidacloprid) and *Hyalella azteca* (beta-cyfluthrin), it is also shown that beta-cyfluthrin is by 5 orders of magnitude more toxic than imidacloprid.

Therefore, the acute risk assessment for exposure with the formulation beta-cyfluthrin + imidacloprid FS 230 (Montur Forte FS 230) via dust drift deposition is based on the RACs derived for beta-cyfluthrin.

For the chronic risk assessment of aquatic invertebrates, the RAC (tier3) for beta-cyfluthrin is 0.105 ng/L. The RAC for imidacloprid is of 9 ng/L [HC5 (EC_{10}) of SSD analysis = 0.027 µg/L; AF of 3: see EFSA conclusions on aquatic risk assessment of imidacloprid of Sept. 2014]. Thus, the RAC for beta-cyfluthrin is about 3 orders of magnitude lower. Therefore, the chronic risk assessment for exposure with the formulation beta-cyfluthrin + imidacloprid FS 230 (Montur Forte FS 230) via dust drift deposition is also based on the RACs derived for beta-cyfluthrin.

2.9.3.3 Effects on sediment dwellers

New studies with beta-cyfluthrin (technical) were performed, according to the spiked water and spiked sediment designs (Kimmel, 2014, KIIA 8.5.2/02 and Kimmel, 2014, KIIA 8.5.2/03) which replace the EU agreed endpoints based on formulations (EC 50 g/L and SC 125 g/L) studies for the renewal of approval. Results are summarised in Table 2.9-1 below.

Table 2.9-1: Chronic toxicity of beta-cyfluthrin to *Chironomus riparius* (spiked water)

Sediment dwelling organisms					
Chironomus riparius	Beta-cyfluthrin	28 d/ static/water – sediment system/spiked water	NOEC	0.4 (nom)	KIIA 8.5.2/02 D58720 Kimmel, 2014c M-481015-01-1 R-30154

Chironomus riparius	Beta-cyfluthrin	28 d/ static/water – sediment system/spiked sediment	EC_{10}	170 µg/kg	KIIA 8.5.2/03 D58731 Kimmel, 2014d M-481037-01-1 R-30153
Chironomus riparius	FPB-acid	Toxicity is addressed by the study with the active substance.			
Chironomus riparius	FPB-aldehyde	Toxicity is addressed by the study with the active substance.			
Chironomus riparius	DCVA	DCVA is a main metabolite of beta-cyfluthrin. It is built in sediment up to 23.7 %. The maximum measured concentration is 100 days after application. No study addressing the toxicity of DCVA to sediment dwellers is available. Toxicity is adressed by alternative information replacing experimental studies according EFSA GD (2013). (KIIA 8.2.5.4/04)			

Additionally, a new spiked water study with the representative formulation Montur Forte 230 was performed:

Table 2.9-2: Toxicity of the formulated product beta-cyfluthrin + imidacloprid FS 230 to sediment dwellers

Test substance	Test species		Endpoint	Reference
beta-cyfluthrin + imidacloprid FS 230	Invertebrate, chronic, *C. riparius*	NOEC EC15	15.5 µg form/L 19.9 µg form/L	Bruns (2012) M-432814-01-1 KIIIA1 10.2.2.3

The 28 d endpoints for the active ingredients are:
Beta-cyfluthrin: NOEC = 0.4 µg/L (nom)
Imidacloprid: EC5 = 1.86 µg/L

The calculated additive toxicity for the formulation is: NOEC = 3.86 µg/L.

Hence, the formulation Montur Forte FS 230 is less toxic than predicted. However, the MDR is 0.25 and therefore in the range of 0.2 to 5.

2.9.3.4 Effects on algae

Toxicity of the active substance beta-cyfluthrin to algae was tested by a growth inhibition study with *Scenedesmus subspicatus* (Heimbach 1987, KIIA 8.4/01). Toxic effects of representative formulation Bulldock EC 25 to *Scenedesmus subspicatus* were investigated by Heimbach (1988, KIIIA1 10.2.2.3). Both studies have been evaluated during the initial EU assessment of beta-cyfluthrin.

Beta-cyfluthrin: NOEC $\geq$ 2 µg as/L; EC_{50} > 2 µg as/L

FCR 4545 (Bulldock) EC 25: E_bC_{50} (96 h) = 2.86 mg as/L; E_rC_{50} (96 h) = 3.68 mg as/L,
NOEC (96 h) = 1.0 mg/L

Additionally a new study with the formulation beta-cyfluthrin + imidacloprid FS 230 (80 + 150) G (Montur Forte FS 230 g/L) was submitted (Bruns, 2012, KIIIA1 10.2.1 /02). This growth inhibition

study was conducted with *Pseudokirchneriella subcapitata* and is considered to be valid:
E_rC_{50} (72 h) form > 100 mg form./L, NOE_rC (72 h) is ≥ 100 mg form./L.

The representative formulation Montur forte FS 230 showed no toxicity to algae (96 h E_rC_{50} > 100 mg form/L *P. subcapitata*) in the conducted laboratory test.

2.9.4 Summary of effects on arthropods

2.9.4.1 Summary of effects on arthropods other than bees

Bulldock EC 25:

Existing data on non-target arthropods were assessed during the EU evaluation of beta-cyfluthrin (2002).
However, re-evaluating the studies, many of them turn out to be not valid and/or not plausible.
For detailed reasons please refer to the documentation of the respective study in Volume_3CP_Bulldock EC 25_B.9.5.2.
Two new tier 1 tests on glass plates with *Typhlodromus pyri* and *Aphidius rhopalosiphi* are available (see Volume_3CP_Bulldock EC 25_B.9.5.2.1) as well as three aged residue studies with *Coccinella septempunctata* (see Volume_3CP_Bulldock EC 25_B.9.5.2.2), two in-field studies with the formulation Bulldock 25 EC, two in-field studies with a cyfluthrin-formulation and one off-field study with Bulldock 25 EC (see Volume_3CP_Bulldock EC 25_B.9.5.2.4)

The following laboratory studies are considered valid and appropriate for risk assessment:

Table 2.9-3: Toxicity of Bulldock EC 25 to non-target arthropods (only valid laboratory studies)

Typhlodromus pyri	LR_{50} = 0.0025 g as/ha 20 %, 28 %, 41 %, 82 % and 100 % mortality at 0.3, 0.9, 2.7, 8.1 and 24.3 mg as/ha		KIIIA1 10.5.1/02 FC010TPL Roig, 2014a M-479587-02-1 R-33356	valid for assessing mortality; effects on reproduction were not investigated
Aphidius rhopalosiphi	LR_{50} = 0.163 g as/ha 3 %, 5 %, 25 %, 29 % and 90 % mortality at 20, 40, 80, 160 and 320 mg as/ha		KIIIA1 10.5.1/01 FC011ARL Roig, 2014b M-479582-01-1 R-33355	valid for assessing mortality; effects on reproduction were not investigated
Poecilus cupreus	7.7 g as/ha: Mortality: 0 % Slight effects on food consumption up to 2 days after application		KIIIA1 10.5.1/01 HBF/CA 27 Heimbach, 1990 M-052707-01-1 R-19124	valid
Poecilus cupreus, larvae	Bulldock EC 025 Extended Lab., formulation mixed into soil	LR_{50}> 0.04 mg as/kg soil $LR_{100} \leq$ 0.4 mg as/kg soil NOEC < 0.04 mg/as kg/soil	KIIIA1 10.5.2./02 Neumann (2001) M-080415-01-1	valid

Montur Forte FS 230

Table 2.9-4: Ecotoxicological endpoints for ground dwelling arthropods exposed to beta-byfluthrin (CYB: beta-byfluthrin; IMD: imidacloprid)

Test species	Tested Formulation, study type, exposure	Ecotoxicological Endpoint				Author (Year) Reference	
Poecilus cupreus, larvae	CYB tech. Extended Lab., mixed into soil Control 0.005 mg CYB / kg dry soil 0.010 mg CYB / kg dry soil 0.015 mg CYB / kg dry soil	treat. [mg as/kg dry soil]	Mortality [%]	Effect on body weight [%]	Development time [d]	KIIA 8.8.1.3 Neumann (2002) M-079000-02-1 (amended)	valid
		control	20	-	43.0		
		0.005	25	9.2	42.7		
		0.010	0	8.6	42.9		
		0.015	0	10.9	45.1		
Poecilus cupreus, larvae	CYB tech. + IMD tech. Extended Lab., test item mixed into soil (LUFA 2.1)	treat. CYP/IMD[mg as/kg dry soil]	corr. Mortality [%]	Effect on body weight [%]	Development time [d]	KIIIA1 10.5.2/01 Neumann (1999) M-024650-01-1	valid
		0.005/0.01	-25[1]	8.7	42.2		
		0.01/0.01	0	7.6	42.3		
		0.01/0.02	-18.8[1]	10.0	43.8		
Poecilus cupreus, larvae	CYB+IMD FS 230 (80+150) Aged residue extended lab, sugar beet pills ($1.1x10^5$ pills /ha) in soil, (9.3 g CYB + 15.8 g IMD / ha)		Effect on hatching rate [%]	Effect on body weight [%]		Jans (2013) M-453475-01-1 KIIIA1 10.5.2/02	valid
		1st bioassay (day of drilling)	-11.1[1]	-1.4[1]			
		2nd bioassay (6 weeks aging in the field)	0	1.1			
Aleochara bilineata,	CYB+IMD FS 230 (80+150) Aged residue extended lab, sugar beet pills ($1.1x10^5$ pills /ha) in soil, (9.3 g CYB + 15.8 g IMD / ha)		Effect on Reproduction [%]			Jans (2013) M-465184-01-1 KIIIA1 10.5.2/03	valid (1. Bioassay)
		1st bioassay (day of drilling)	8.1				
		2nd bioassay (4 weeks aging in the field)	25.5				

[1] A negative value indicates a higher feeding rate, higher body weight or lower mortality in the treatment than in the control

* CYB+IMD FS 500 (80+420): studies have been originally submitted, evaluated and are cited in Addendum 1 to the Monograph of 01 October 1996 (starting page 153-155)

2.9.4.2 Summary of effects on bees

Bulldock EC 25:

Hazard quotients

The acute risk to honeybees from the use of Bulldock EC 25 was assessed using the maximum single application rates and the respective LD_{50} values to calculate hazard quotients (HQ) (*EPPO/OEPP, 2003: Environmental risk assessment scheme for plant protection products, Chapter 10: Honeybees (PP 3/10(2)). Bulletin OEPP/EPPO Bulletin 33: 141-145*)) as follows:

Hazard Quotient = max. application rate [g product/ha] / LD_{50} [µg product/bee]

Hazard quotients were calculated for oral exposure (Q_{HO}) and contact exposure (Q_{HC}) to Bulldock 25 EC with the individually applied dose of 12.5 g as/ha in wheat or potatoes and 7.5 g as/ha in tomatoes. The results are shown in Table 2.9.4.2-1. For bumblebees no risk assessment scheme currently exists.

Table 2.9.4.2-1: Risk to bees from exposure to Bulldock 25 EC

Substance	Crop	Application rate [g as/ha]	Exposure route	LD_{50} [µg as/bee]	Hazard quotient
Bulldock 25 EC	Tomatoes	17.5	Contact	0.0337	519
			Oral	0.0164	1067
	Wheat, potato	12.5	Contact	0.0337	371
			Oral	0.0164	762

All hazard quotients are above the trigger value of 50, indicating that the active substances pose a high risk to bees. Therefore, a higher tier risk assessment is presented below.

Toxicity to bee larvae and chronic toxicity to adult honeybees

According to current regulations an acute feeding study on honeybee larvae and a chronic feeding study on adult honey bees were conducted with the representative formulation Bulldock 25 EC.
In both studies the determined LD_{50} value via oral exposure (larvae LD_{50} = 0.020 µg as/larvae; adult chronic LD_{50} = 0.019 µg as/bee/day) was in the same range as the acute oral toxicity for Bulldock 25 EC (LD_{50} = 0.0164 µg as/bee).
Thus, there is no indication of a higher sensitivity of adults from chronic compared to acute exposure and no indication of a higher sensitivity of larvae compared to adults.

Higher tier risk assessment for honeybees

A number of semi-field (tent/tunnel) and field studies is available and is considered in the following risk assessment conclusion on the general safety of beta-cyfluthrin to bees resulting from field applications of Bulldock 25 EC.

Semi-field (tunnel/tent) studies under confined conditions

In seven semi-field studies, 0.15 % Bulldock 25 EC (equivalent to 15 g as/ha, Pinsdorf 1989a, Pinsdorf 1989b, Schulz 1989a, Schulz 1989b) and 0.375 % Bulldock 25 EC (equivalent to 37.5 g as/ha, Stute 1987a, Stute 1987b) was applied on flowering *Phacelia* in the evening after bee flight. At all application rates, bee flight intensity was transiently reduced. In addition, behavioural effects and higher mortality rates were observed during the first 2 days following the evening application. Therefore, higher tier studies are required.

Field studies

In four field studies which had already been assessed during the first EU evaluation of beta-cyfluthrin (2002), 0.15 % Bulldock 25 EC (equivalent to 15 g as/ha) was applied on flowering *Phacelia* fields in the evening after bee flight (Stute 1989a, Stute 1989a, Pinsdorf 1989c, Pinsdorf 1989d). Here the foraging activity was still transiently reduced (refer to semi-field). However the mortality, the colony strength and brood were not affected.
Furthermore two field studies have been assessed during the first EU evaluation to address potential effects of Bulldock 25 EC on bee colonies when applied to flowering crops during bee flight (Nengel 1997, Kleiner 1997). In both studies Bulldock 25 EC was applied at rates of 7.5 and 15 g as/ha to flowering *Phacelia* fields. There were sharp decreases in foraging activity and increased mortality for

up to 3 days after applications at 15 g as/ha. At 7.5 g as/ha foraging activity was decreased for 1 day with a slight increase in mortality. There were no effects on bee brood in both studies for both application rates.
In two new field studies (Sandrock 2014c, Sandrock 2014d) honeybees were monitored after two applications of 17.5 g beta-cyfluthrin as/ha (700 mL Bulldock 25 EC/ha) after daily bee flight onto flowering *Phacelia tanacetifolia* in a 10-day interval. In the first study of Sandrock (2014c) the foraging activity was affected on the day after the second application and no effect on forager mortality was detected. Apparent effects on honeybee behaviour were observed, especially increased nervousness and aggressiveness. Furthermore, during the exposure phase and the post-exposure phase, brood nests decreased more in the test item colonies compared to the control colonies. However, some colonies showed signs of rearing daughter queens in both treatments, including queen supersedure in two test item replicates. Therefore the dataset on colony conditions should be interpreted with caution.
In the second study of Sandrock (2014d) the foraging activity was not affected, but adult mortality slightly increased for 2 days. The colony strength and brood nest area remained in largely the same range over the exposure and post-exposure monitoring period. However, the distance between control and test item field was only 1.6 km in the study 2012, which is considered not sufficient and thus reliability of the test is considered limited. On the basis of the available data, effects on colony conditions cannot finally be excluded.

Overall conclusions of risk to bees

Due to the results of laboratory tests Bulldock EC 25 is considered highly toxic to bees for oral as well as contact toxicity. Hazard quotients are clearly above the trigger of 50 indicating a high potential risk. As observed in semi-field studies on bees, beta-cyfluthrin has adverse effects on bee mortality when applied on flowering crops during daily bee flight. In addition, behavioural effects and slightly increased mortality rates were observed during the first 2 days following the evening application. Therefore, higher tier studies are required.
In the field studies reported for the evaluation in 2002, with application of 15 g as/ha to flowering *Phacelia* fields in the evening after the bee flight activity foraging activity was still transiently reduced and mortality was not increased. However, in field studies conducted during bee flight the flight intensity was reduced and mortality was slightly increased for one day (7.5 g as/ha) or 3 days (15 g as/ha) after application.
In the new field studies (Sandrock 2014c, Sandrock 2014d) with application after daily bee flight and repeated application at 17.5 g as/ha the foraging activity was reduced for 1 day and adult mortality slightly increased for 2 days. Furthermore, effects on brood development and brood termination rate were observed in the test item treatment.
Based on the total set of data, it can be concluded that Bulldock 25 EC has to be classified as hazardous to bees. Therefore it must not be used on plants which are in flower or which are visited by bees; this also applies to weeds and honey dew.

Montur Forte FS 230

Table 2.9.4.2 2 presents a summary of all studies submitted for the risk assessment.

Table 2.9.4.2-2. Endpoints for the beta-cyfluthrin containing seed-treatment product Montur forte 230 FS

Test substance	Test species	Endpoint	Value	Reference
Montur forte 230 FS	adult honeybees	72 h acute oral LD_{50}	0.270 µg product/bee (0.072 µg as/bee)	Schmitzer, S. (2011) Study no.: 64111035 CP 9.5.1.1./01
		96 h acute contact LD_{50}	0.201 µg product/bee (0.054 µg as/bee)	

Due to the results of laboratory tests Montur forte 230 FS is considered to be highly toxic to bees for oral and contact exposure, respectively. However as bees are not exposed to relevant residues

- via nectar and pollen (sugar beets do not flower in commercial sugar beet production, beta-cyfluthrin is virtually non-systemic),
- via seed-treatment dust during the sugar-beet-pill sowing operation (sugar beet pills are very resistant to mechanical abrasion and are predominately sown with mechanical, non-air assisted sowing machines),
- via guttation liquid (beta-cyfluthrin is virtually non-systemic, moreover, sugar beet shows guttation only very rarely [e.g. Joachimsmeier *et. al.*, 2011; M-481776-01-1; MCP 10.3.1; DOI 10.5073 / jki. 2012.437.020]),

it can be concluded that beta-cyfluthrin, when used for the preparation of sugar beet pills, does not pose an unacceptable risk for honey bees.

2.9.5 Summary of effects on non-target soil meso- and macrofauna

Effects on earthworms

An acute study on *Eisenia fetida* with beta-cyfluthrin (technical substance) was submitted and evaluated in the course of the initial Annex I inclusion of beta-cyfuthrin (Heimbach, 1987, KIIA 8.9.1/01).

For the main soil metabolites FPB-acid and DCVA, two acute studies on *Eisenia fetida* and two reproduction studies are available.

Table 2.9-5: Toxicity of beta-cyfluthrin and metabolites FPB-acid and DCVA to earthworms

Species	Test design	LC_{50} (mg as/kg dw soil)	NOEC (mg as/kg dw soil)	Reference	reliability
Beta-cyfluthrin					
Eisenia fetida	14 d acute	>1000 >500 [1]	10 5 [1]	KIIA 8.9.1/01 HBF/RG 83 Heimbach, 1987 M-053564-01-1 R-19143	valid
FPB-acid					
Eisenia fetida	14 d acute	> 63 > 31.5 [1]	< 63 <31.5[1]	KIIA 8.9.1/02 09P11RA Moser and Scheffczyk, 2009 M-354192-01-1 R-27979	valid
Eisenia fetida	56 d chronic	-	5.2 **2.6 (reproduction)[1]**	KIIA 8.9.2/01 kra/Rg-R-143/13 Kratz, 2013a M-468873-01-1 R-34697	valid

DCVA					
Eisenia fetida	14 d acute	122.7 61.35 [1]	< 63 <31.5 [1]	KIIA 8.9.1/03 09P10RA Moser, 2009 M-356435-01-1 R-27978	valid
Eisenia fetida	56 d chronic	184.76 92.38 [1]	5.2 **2.6 (reproduction)[1]**	KIIA 8.9.2/02 kra/Rg-R-157/13 Kratz, 2013b M-468552-01-1 R-34696	valid

Studies shaded in grey have been reviewed as part of the 2002 EU evaluation.
Values in bold: Endpoints used for risk assessment
[1] endpoint corrected/divided with a factor of 2, due to log Pow >2 and peat content of 10 % in study
log Pow results FPB-acid at 23 °C: Log Pow = 2.6 at pH 5, Log Pow = 0.8 at pH 7, Log Pow = -0.5 at pH 9
log Pow results DCVA at 25 °C: Log Pow = 2.5 at pH 5, Log Pow = 0.8 at pH 7, Log Pow = -0.8 at pH 9

New chronic reproduction studies on *Eisenia fetida* with the representative formulations Bulldock EC 25 and Montur Forte FS230 are presented in the table below.

Table 2.9-6: Toxicity of the representative formulations Bulldock EC 25 and Montur Forte FS 230 to earthworms

Species	**Test design**	**LC_{50} (mg as/kg soil dw)**	**NOEC (mg as/kg soil dw)**	**Reference**	**reliability**
Bulldock EC 25					
Eisenia fetida	14 d acute	29.7 14.85[1]	1 0.5[1]	KIIIA1 10.6.2 Heimbach, 1988, M-053588-01-2, HBF/RG 85	valid
Eisenia fetida	56 d chronic	4.06 (reproduction) 2.03 (reproduction)	1.65 (reproduction) **0.83 (reproduction)[1]**	KIIIA1 10.6.3 74484022 Pavic, 2013 M-461275-01-1 R-30148	valid
Montur Forte FS 230					
Eisenia fetida	56 d chronic, test item mixed into soil	-	1.78	Leicher (2011) M-407796-01-1 KIIIA1 10.6.3/02	valid
Eisenia fetida	56 d chronic, exposure via treated sugar beet pills	-	>1,300,000 treated sugar beet pills	Luehrs (2003) M-110969-01-1 KIIIA1 10.6.3/01	valid

[1] corrected by factor of 2 due to lipophilic substance (log P_{ow} > 2) and 10 % peat content in test soil

Effects on non-target soil meso- and macrofauna (other than earthworms)

New studies have been conducted exposing *Hypoaspis aculeifer* and *Folsomia candida* to beta-cyfluthrin. In addition, studies on *Hypoaspis aculeifer* and *Folsomia candida* with the metabolites FPB-acid and DCVA (permethric-acid) are available and summarised below.

Table 2.9-7: Effect of beta-cyfluthrin and metabolites FBP-acid and DCVA to soil macroorganisms other than earthworms

Species	Test design	NOEC (reproduction) (mg as/kg dry soil)	Reference	reliability
Beta-cyfluthrin				
Hypoaspis aculeifer	14 d chronic	**0.97**	KIIA 8.9.2/03 74501089 Pavic, 2012 M-476271-01-1; R-30149	valid
Folsomia candida	28 d chronic	**56**	KIIA 8.9.2/04 FRM-Coll-172/14 Frommholz, 2014 M-475305-01-1; R-34698	valid
FPB-acid				
Hypoaspis aculeifer	14 d chronic	**297**	KIIA 8.9.2/05 P14HR Moser and Scheffczyk, 2005a M-258697-01-1; R-23564	valid
Folsomia candida	28 d chronic	**28**	KIIA 8.9.2/06 FRM-Coll-144/12 Frommholz, 2012a M-440962-01-1; R-34695	valid
DCVA				
Hypoaspis aculeifer	14 d chronic	**≥ 316** **100 (mortality)**	KIIA 8.9.2/07 P15HR Moser and Scheffczyk, 2005b M-259607-01-1; R-23565	valid
Folsomia candida	28 d chronic	**18**	KIIA 8.9.2/08 FRM-Coll-143/12 Frommholz, 2012b M-440379-01-1; R-34694	valid

Values in bold: Endpoints used for risk assessment

For *Folsomia candida*, a study is available with the representative formulation Bulldock 25 EC.
Moreover, new studies were conducted exposing *Hypoaspis aculeifer* and *Folsomia candida* to Montur Forte FS 230.

Table 2.9-8: Toxicity of the representative formulations Bulldock EC 25 and Montur Forte 230 to soil macroorganisms other than earthworms

Species	Test design	NOEC (reproduction) (mg as/kg dry soil)	Reference	reliability
Bulldock 25 EC				
Folsomia candida	28 d chronic	**1.592**	KIII1 10.6.6/01 IRV-13-7 McCormac, 2014 R-33352	valid
beta-cyfluthrin+ imdidacloprid FS 230 (Montur Forte FS 230)				
Hypoaspis aculeifer	14 d chronic, test item mixed into soil	**≥32 mg product/kg dw soil**	Moser & Scheffczyk (2003) M-103032-01-1 KIIIA1 10.6.6 /01	valid
Folsomia candida	28 d chronic, test item mixed into soil	**4.6 mg product/kg dw soil**	Frommholz (2011) M-407864-01-1 KIIIA1 10.6.6 /03	valid
Folsomia candida	28 d, treated pills placed in ca. 2.5 cm depth in the soil	1 seed/vessel (5-fold field rate) or 714 mL product/ha[1]	Lechelt-Kunze (2003) M-111565-01-1 KIIIA1 10.6.6 /02	valid

Values in bold: Endpoints used for risk assessment

A study addressing the toxicity of Bulldock EC 25 to *Hypoaspis aculeifer* is not available. Therefore, the risk assessment is based on data of the active substance.
However, comparing the endpoints (NOEC) of beta-cyfluthrin and Bulldock EC 25 for *Folsomia candida*, a 35 fold higher toxicity of Bulldock EC 25 can be determined.
As TER values for *Hypoaspis aculeifer* divided by 35 (assuming a comparable difference in toxicity) would be below the acceptablity criterion of 5, the toxicity and, therefore, the risk of Bulldock EC 25 to *Hypoaspis aculeifer* can not be sufficiently assessed on the basis of results for the active substance.
Consequently, a chronic *Hypoaspis aculeifer* study with Bulldock EC 25 is needed.
Thus, a data gap is defined.

2.9.6 Summary of effects on soil nitrogen transformation

There are two studies available that were conducted with beta-cyfluthrin. They had been reviewed for the first Annex I inclusion of beta-cyfluthrin.
Additionally, two new studies were performed with one of the representative formulations Bulldock 25 EC and Montur Forte FS 230, respectively.
Two nitrogen mineralisation studies with the two major soil metabolites (i.e. FPB-acid and DCVA) were conducted. Results are presented in the table below.

Table 2.9-9: Effects on soil micro-organisms

Test design	NOEC (reproduction) (mg as/kg dry soil)	Reference	reliability
Beta-cyfluthrin			
Nitrogen mineralisation 28-day study	No significant effects (>25 %) on nitrogen mineralisation by day 28 at 0.018 and **0.18 kg/ha**	KIIA 8.10.1/02 BSI/47987 Blumenstock, 1987 M-054489-01-2 R-19148	valid
Carbon mineralisation 28-day study	No significant effects (>25 %) on microbial respiration by day 28 at 0.018 and **0.18 kg/ha**	KIIA 8.10.1/01 AJO/46887 Anderson, 1987 M-054544-01-2 R-19147	valid
FPB-acid			
Nitrogen mineralisation 28-day study	No significant effects (>25 %) on nitrogen mineralisation at 0.012 mg/kg dry soil and 0.125 mg/kg dry soil, corresponding to 0.009 kg and 0.094 kg test item/ha, respectively	KIIA 8.10.1/03 13 10 48 016 N Schulz, 2013a M-454537-01-1 R-34704	valid
DCVA			
Nitrogen mineralisation 28-day study	No significant effects (>25 %) on nitrogen mineralisation at 0.011mg/kg dry soil and 0.112 mg/kg dry soil, corresponding to 0.008 kg and 0.084 kg test item/ha, respectively	KIIA 8.10.1/04 13 10 48 017 N Schulz, 2013b M-454538-01-1 R-34705	valid
Beta-cyfluthrin 25 EC			
Nitrogen mineralisation 28-day study	No significant effects (>25 %) on nitrogen mineralisation at 0.96 mg/kg dry soil and 9.61 mg/kg dry soil, corresponding to 0.8 L and 8.0 L test item/ha, respectively	KIIIA1 10.7.1 10 48 084 N Schulz, 2011 R-28684	valid
Beta-cyfluthrin + imidacloprid FS 230			
Nitrogen - mineralisation 28-day study	No significant effects (>25 %) on nitrogen mineralisation at 0.98 mg prod./kg dry soil	Schulz (2011) M-416194-01-1 KIIIA1 10.7.1	valid

2.9.7 Summary of effects on terrestrial non-target higher plants

Although beta-cyfluthrin is not an herbicide, a limit test to investigate possible effects on vegetative vigor and seedling emergence was performed with the representative formulation Bulldock 25 EC.

Table 2.9-10: Effects of Bulldock 25 EC to non-target terrestrial plants

Test substance Test type	Most sensitive species	Lowest ER_{50}	Reference
Bulldock 25 EC (formulated product) 21 d seedling emergence	Green cabbage (*Brassica oleracea var. sabellica*) Cucumber (*Cucumis sativa*) Carrot (*Daucus carota*) Lacy phacelia (*Phacelia tanacetifolia*) Sunflower (*Helianthus annuus*) Flax (*Linum usitatissimum*) Onion (*Allium cepa*) Rye grass (*Lolium multiflorum*) Barley (*Hordeum vulgare*) Erect brome (*Bromus erectus*)	ER_{50} (phytotoxicity, seedling emergence, seedling fresh weight) > 60 g as/ha	KIIIA1 10.8.1.3 Marquardt and Siemoneit-Gast, 2012a M-438332-01-1 R-30155
Bulldock 25 EC (formulated product) 21 d vegetative vigour	Green cabbage (Brassica oleracea var. sabellica) Cucumber (*Cucumis sativa*) Carrot (*Daucus carota*) Lacy phacelia (*Phacelia tanacetifolia*) Sunflower (*Helianthus annuus*) Flax (*Linum usitatissimum*) Onion (*Allium cepa*) Rye grass (*Lolium multiflorum*) Barley (*Hordeum vulgare*) Erect brome (*Bromus erectus*)	ER_{50} (phytotoxicity, seedling fresh weight) > 60 g as/ha	KIIIA1 10.8.1.2 Marquardt and Siemoneit-Gast, 2012b M-438396-01-1 R-30156

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

No further studies on effects on other terrestrial organisms were submitted and are required.

2.9.9 Summary of effects on biological methods for sewage treatment

Table 2.9-11: Effects of beta-cyfluthrin and cyfluthrin on biological methods of sewage treatment

Test substance Test type	Test organism	Endpoint [mg/L]	Reference
beta-cyfluthrin (Bulldock)	activated sludge (domestic)	30 min EC_{50} >10000	CA 8.8/01 485 A/94 Caspers and Mueller, 1994a M-053009-01-2 R-34706
cyfluthrin	activated sludge (domestic)	30 min EC_{50} >10000	CA 8.8/02 478 A/94 Caspers and Mueller, 1994b M-021811-01-1 R-19149

2.9.10 Summary of product exposure and risk assessment

2.9.10.1 Birds

According to the proposed use pattern of Bulldock EC 25 the risk assessment is based on the scenario "cereals/potatoes", considering the corresponding indicator species in the screening assessment. All calculated TER values are above the respective acceptability criteria of 10 for acute and 5 for long-term exposure, respectively.
An exposure to birds by the application of Bulldock EC 25 in greenhouses (tomatoes) is not expected. Therefore, the risk to birds is considered acceptable.

The second representative formulation Montur Forte FS 230 is used as seed treatment for sugar beet seeds. According to the EFSA GD (2009) it is assumed that birds may ingest seeds pelleted with Montur Forte FS 230 by mistake as grit. The respective risk assessment is laid out in the scheme presented in section 5.1.2.
As the formulation contains imidacloprid as a second active substance, the acute risk assessment is based on the assumption of effect additivity.
Acceptability criteria of 10 for acute and 5 for long-term exposure are met.
The risk due to the exposure to imidacloprid via ingesting seedlings of the treated sugar beet seeds was assessed in detail in Addendum 7 to the DAR for imidacloprid (January, 2014). The risk assessment also covers the representative use of Montur Forte FS 230 since the application rate of imidacloprid is lower.
The exposure of birds to beta-cyfluthrin via seedlings of the treated sugar beet seeds is considered to be negligible and, thus, the risk acceptable.
Beta-cyfluthrin is a non-systemic insecticide (please refer to Volume3CA_B.3).
When comparing the calculated NAR (30000 – 36000 mg as/kg)/5 (for a loading rate of 0.9 mg/seed) with the measured residues (15.5 mg/kg seedlings) for the systemic, water soluble insecticide imidacloprid [refer to Addendum 7 to the AR for imidacloprid (January, 2014)], it can be definitely assumed that actual residues for the non-systemic, water-insoluble insecticide beta-cyfluthrin are even much lower than for imidacloprid.

Since the intended uses for Bulldock EC 25 and Montur Forte FS 230 g/L do not include critical crops and growth stages for the formation of pools in leaf whorls, only the scenario of puddles formed on soil needs to be considered, in principle, for an assessment of the risk from the uptake of contaminated drinking water. However, as the ratio of highest application rate (25 g as/ha) to lowest relevant endpoint (NOEL = 37.74 mg as /kg bw/d) for beta-cyfluthrin only amounts to 0.66, the risk can be con-

sidered acceptable without the need for further calculations.

Due to the high log P_{OW} = 5.9 of beta-cyfluthrin, an assessment of the risk from possible bioaccumulation in the food chain is necessary. All calculated TER values are above the respective acceptability criteria of 5 for exposure via food chain.
The calculated TER values at tier 1 level is above the respective acceptability criteria of 5 for exposure via food chain for fish eating and for earthworm-eating birds.

Risk of biomagnification in terrestrial food chains
According to the ADME studies (please refer to Volume_3CA _B-6.1) beta-cyfluthrin is not considered to be bioaccumulative, but is quickly excreted. Therefore the risk of biomagnification in terrestrial food chains is low.

Overall, the risk to birds from the intended uses of beta-cyfluthrin is considered acceptable.

2.9.10.2 Terrestrial vertebrates other than birds (mammals)

According to the proposed use pattern of Bulldock EC 25 the risk assessment is based on the scenario "cereals/potatoes". Considering the corresponding indicator species in the screening assessment and/or the generic focal species at tier 1 all calculated TER values achieve the respective acceptability criteria of 10 for acute and 5 for long-term exposure, respectively.

The second representative formulation Montur Forte FS 230 is used as seed treatment for sugar beet seeds. For pelleted seeds, a risk assessment for mammals is not required according the EFSA GD (2009).

The risk due to the exposure to imidacloprid via ingesting seedlings of the treated sugar beet seeds was assessed in detail in Addendum 7 to the DAR for imidacloprid (January, 2014). The risk assessment also covers the representative use of Montur Forte FS 230 since the application rate of imidacloprid is lower.
The exposure of birds to beta-cyfluthrin via seedlings of the treated sugar beet seeds is considered to be negligible and, thus, the risk acceptable.
Beta-cyfluthrin is a non-systemic insecticide (please refer to Volume3CA_B.3).
When comparing the calculated NAR (30000 – 36000 mg as/kg)/5 (for a loading rate of 0.9 mg/seed) with the measured residues (15.5 mg/kg seedlings) for the systemic, water soluble insecticide imidacloprid [refer to Addendum 7 to the DAR for imidacloprid (January, 2014)], it can be definitely assumed that actual residues for the non-systemic, water-insoluble insecticide beta-cyfluthrin are even much lower than for imidacloprid.

Since the intended uses for Bulldock EC 25 and Montur Forte FS 230 g/L do not include critical crops and growth stages for the formation of pools in leaf whorls, only the scenario of puddles formed on soil needs to be considered, in principle, for an assessment of the risk from the uptake of contaminated drinking water. However, as the ratio of highest application rate (25 g as/ha) to lowest relevant endpoint (NOEL = 3.3 mg as/kg bw/d) for beta-cyfluthrin only amounts to 7.6, the risk can be considered acceptable without the need for further calculations.

Due to the high log P_{OW} = 5.9 of beta-cyfluthrin, an assessment of the risk from possible bioaccumulation in the food chain is necessary.
The calculated TER value at tier 1 level is above the respective acceptability criteria of 5 for exposure via food chain for fish eating and earthworm-eating mammals.

Risk of biomagnification in terrestrial food chains
According to the ADME studies (please refer to Volume_3CA _B.6.1) beta-cyfluthrin is not considered to be bioaccumulative, but is quickly excreted. Therefore the risk of biomagnification in terrestrial food chains is low.

Overall, the risk to wildlife mammals from the intended uses of beta-cyfluthrin is considered to be acceptable.

2.9.10.3 Aquatic organisms

Representative uses of Bulldock EC 25

The acute and chronic TER values calculated by the RMS are presented in **Table 2.9-12** to **Table 2.9-19**.
As beta-cyfluthrin is not volatile, exposure of surface water bodies by the representative use in tomatos in greenhouse is not expected. Therefore, the risk to aquatic organisms is deemed to be acceptable.

Table 2.9-12: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) in winter wheat in spring]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella azteca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gibba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC_{10} (µg/kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D1/ditch	0.03350	0.12700	**2.03**	**0.123**	**0.00690**	**0.0122**	11.9	134	59.7	25.1
D1/stream	0.04170	0.40000	**1.63**	**0.100**	**0.00554**	**0.00983**	9.59	425	48.0	20.1
D2/ditch	003880	0.25100	**1.75**	**0.108**	**0.00595**	**0.0106**	10.3	677	51.5	21.6
D2/stream	0.03410	0.17500	**1.99**	**0.123**	**0.00677**	**0.0120**	11.7	971	58.7	24.6
D3/ditch	0.03830	0.15700	**1.78**	**0.110**	**0.00603**	**0.0107**	10.4	1080	52.2	21.9
D4/pond	0.00154	0.03450	**44.2**	**2.73**	**0.15**	**0.266**	260	4930	1300	545
D4/stream	0.03000	0.03260	**2.27**	**0.14**	**0.0077**	**0.0137**	13.3	5210	66.7	28
D5/pond	0.00168	0.03300	**40.5**	**2.50**	**0.138**	**0.244**	238	5150	1190	500
D5/stream	0.03320	0.04430	**2.05**	**0.127**	**0.00696**	**0.0123**	12.0	3840	60.2	25.38
D6/ditch	0.03850	0.17900	**1.77**	**0.109**	**0.006**	**0.0106**	10.4	950	51.9	21.8
R1/pond	0.02500	0.20100	**2.72**	**0.168**	**0.00924**	**0.0164**	16.0	846	80.0	33.6
R1/stream	0.00147	0.03550	**46.3**	**2.86**	**0.157**	**0.279**	272	4790	1360	571
R3/stream	0.03520	0.09630	**1.93**	**0.119**	**0.00656**	**0.0116**	11.4	1770	56.8	23.9
R4/stream	0.02500	0.31100	**2.72**	**0.168**	**0.00924**	**0.0164**	16.0	547	80.0	33.6
TER criterion			100	10	100	10	10	10	10	10

Table 2.9-13: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) in winter wheat in autumn]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella az-teca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gib-ba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC_{10} (µg/Kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D1/ditch	0.03350	0.1450	**2.03**	**0.0290**	**0.00690**	**0.0122**	11.9	1170	59.7	25.1
D1/stream	0.04320	0.4520	**1.57**	**0.00929**	**0.00535**	**0.00949**	9.26	376	46.3	19.4
D2/ditch	0.03860	0.2210	**1.76**	**0.0190**	**0.00598**	**0.0106**	10.4	769	51.8	21.8
D2/stream	0.03290	0.09070	**2.07**	**0.0463**	**0.00702**	**0.0125**	12.2	1870	60.8	25.5
D3/ditch	0.03810	0.1410	**1.78**	**0.0298**	**0.00606**	**0.0108**	10.5	1210	52.5	22.0
D4/pond	0.03270	0.0850	**2.08**	**0.0494**	**0.00706**	**0.0125**	12.2	2000	61.2	25.9
D4/stream	0.00152	0.0340	**44.7**	**0.124**	**0.152**	**0.270**	263	5000	1320	553
D5/pond	0.03530	0.1030	**1.93**	**0.0408**	**0.00654**	**0.0116**	11.3	1650	56.7	23.8
D5/stream	0.001610	0.03530	**42.2**	**0.119**	**0.143**	**0.255**	248	4820	1240	522
D6/ditch	0.03850	0.1950	**1.77**	**0.0215**	**0.006**	**0.0106**	10.4	872	51.9	21.8
R1/pond	0.02490	0.3480	**2.73**	**0.0121**	**0.00928**	**0.0165**	16.1	489	80.3	33.7
R1/stream	0.00170	0.04780	**40.0**	**0.0879**	**0.136**	**0.241**	235	3560	1180	494
R3/stream	0.0350	3.1180	**1.94**	**0.00135**	**0.0066**	**0.0117**	11.4	54.5	57.1	24
R4/stream	0.0250	0.3090	**2.72**	**0.0136**	**0.00924**	**0.0164**	16.0	550	80.0	33.6
TER criterion			**100**	**10**	**100**	**10**	10	10	10	10

Table 2.9-14: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) application in spring cereals]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella azteca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gibba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC10 (µg/Kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D1/ditch	0.03910	0.2450	**1.74**	**0.0171**	**0.00591**	**0.0105**	10.2	694	51.2	21.5
D1/stream	0.03350	0.1200	**2.03**	**0.035**	**0.00690**	**0.0122**	11.9	1420	59.7	25.1
D3/ditch	0.03830	0.1600	**1.78**	**0.0263**	**0.00603**	**0.0107**	10.4	1060	52.2	21.9
D4/pond	0.00150	0.0277	**45.3**	**0.152**	**0.154**	**0.273**	267	6140	1330	560
D4/stream	0.03130	0.0473	**2.17**	**0.0888**	**0.00738**	**0.0131**	12.8	3590	63.9	26.8
D5/pond	0.00170	0.0312	**40**	**0.135**	**0.136**	**0.2412**	235	5450	1180	494
D5/stream	0.03240	0.0365	**2.10**	**0.115**	**0.00713**	**0.0127**	12.3	4660	61.7	25.9
R4/stream	0.02500	0.0316	**2.72**	**0.133**	**0.00924**	**0.0164**	16.0	5380	80.0	33.6
TER criterion			**100**	**10**	**100**	**10**	10	10	10	10

Table 2.9-15: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) application in spring cereals]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella azteca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gibba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC10 (µg/Kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D1/ditch	0.065100	0.408000	**1.045**	**0.0103**	**0.00355**	**0.00630**	**6.14**	417	30.7	12.9
D1/stream	0.055800	0.200000	**1.22**	**0.021**	**0.00414**	**0.00735**	**7.17**	850	35.8	15.0
D3/ditch	0.063800	0.266000	**1.07**	**0.0158**	**0.00362**	**0.00643**	**6.27**	639	31.3	13. 2
D4/pond	0.002490	0.046200	**27.3**	**0.0909**	**0.0928**	**0.165**	161	3680	803	337
D4/stream	0.052200	0.078800	**1.30**	**0.0533**	**0.00443**	**0.00785**	**7.66**	2160	38.3	16.11
D5/pond	0.002830	0.051900	**24.0**	**0.0809**	**0.0816**	**0.145**	141	3280	707	297
D5/stream	0.054000	0.060800	**1.26**	**0.0691**	**0.00428**	**0.00759**	**7.41**	2800	37.0	15. 6
R4/stream	0.041600	0.526000	**1.63**	**0.00798**	**0.00555**	**0.00986**	**9.62**	323	48.0	20.2
TER criterion			**100**	**10**	**100**	**10**	10	10	10	10

Table 2.9-16: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) in winter wheat]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella azteca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gibba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC_{10} (µg/Kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D1/ditch	0.05580	0.2110	**1.22**	**0.0753**	**0.00414**	**0.00735**	**7.17**	806	35.8	15.1
D1/stream	0.06950	0.6660	**0.978**	**0.0604**	**0.00332**	**0.00590**	**5.76**	255	28.8	121
D2/ditch	0.06460	0.4180	**1.05**	**0.0650**	**0.00358**	**0.00635**	**6.19**	407	31.0	13.0
D2/stream	0.05680	0.2920	**1.20**	**0.07392**	**0.00407**	**0.00722**	**7.04**	582	35.2	14.8
D3/ditch	0.06380	0.2670	**1.07**	**0.0658**	**0.00362**	**0.00643**	**6.27**	637	31.3	13.2
D4/pond	0.002560	0.05750	**26.6**	**1.64**	**0.0902**	**0.1605**	156	2960	781	328
D4/stream	0.050	0.05430	**1.36**	**0.084**	**0.00462**	**0.0082**	**8.0**	3130	40.0	16.8
D5/pond	0.00280	0.0550	**24. 3**	**1.50**	**0.0825**	**0.146**	143	3090	714	300
D5/stream	0.05530	0.07380	**1.232**	**0.0759**	**0.00418**	**0.00741**	**7.23**	2300	36.2	15.2
D6/ditch	0.06410	0.2990	**1.063**	**0.0655**	**0.00360**	**0.00640**	**6.24**	569	31.2	13.1
R1/pond	0.04160	0.3350	**1.63**	**0.101**	**0.00555**	**0.00986**	**9.62**	507	48.1	20.2
R1/stream	0.002450	0.05920	**27.8**	**1.71**	**0.0943**	**0.167**	**163**	2870	816	343
R3/stream	0.05870	0.1610	**1.16**	**0.0716**	**0.00394**	**0.00698**	**6.81**	1060	34.1	14.3
R4/stream	0.04170	0.5190	**1.63**	**0.101**	**0.00554**	**0.00983**	9.59	328	48.0	20.1
TER criterion			100	10	100	10	10	10	10	10

Table 2.9-17: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) in autumn/winter wheat]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella azteca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gibba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC_{10} (µg/Kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D1/ditch	0.055580	0.2420	**1.22**	**0.0174**	**0.00416**	**0.00738**	**7.20**	702	36.0	15.1
D1/stream	0.07190	0.7530	**0.946**	**0.00558**	**0.00321**	**0.00570**	**5.56**	226	27.8	11.7
D2/ditch	0.06430	0.3680	**1.06**	**0.0114**	**0.00359**	**0.00638**	**6.22**	462	31.1	13.1
D2/stream	0.05480	0.1510	**1.24**	**0.0278**	**0.00422**	**0.00748**	**7.30**	1130	36.5	15.3
D3/ditch	0.06350	0.2350	**1.07**	**0.0179**	**0.00364**	**0.00646**	**6.30**	723	31.5	13.2
D4/pond	0.05450	0.1420	**1.25**	**0.0296**	**0.00424**	**0.00752**	**7.34**	1200	36.7	15.4
D4/stream	0.002540	0.05670	**26.8**	**0.0741**	**0.0909**	**0.161**	157	3000	787	331
D5/pond	0.05880	0.1720	**1.16**	**0.0244**	**0.00393**	**0.00697**	**6.80**	988	34.0	14. 3
D5/stream	0.002690	0.05880	**25.3**	**0.0714**	**0.0859**	**0.152**	149	2890	743	312
D6/ditch	0.06410	0.3260	**1.06**	**0.0129**	**0.00360**	**0.00640**	**6.24**	521	31.2	13.12
R1/pond	0.04140	0.580	**1.64**	**0.00724**	**0.00558**	**0.00990**	**9.66**	293	48.3	20.3
R1/stream	0.002840	0.07970	24.0	**0.0527**	**0.0813**	**0.144**	141	2130	704	296
R3/stream	0.05830	5.1970	**1.17**	**0.000808**	**0.00396**	**0.00703**	**6.86**	32.7	34.3	14.4
R4/stream	0.04170	0.5150	**1.63**	**0.00816**	**0.00554**	**0.00983**	9.59	330	48.0	20.1
TER criterion			100	10	100	10	10	10	10	10

Table 2.9-18: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) in potatoes]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella azteca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gibba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC_{10} (µg/Kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D3/ditch	0.03140	0.1220	**2.17**	**0.0344**	**0.00736**	**0.0131**	12.7	1390	63.7	26.8
D4/pond	0.00141	0.0280	**48.2**	**0.15**	**0.164**	**0.291**	284	6070	1420	596
D4/stream	0.02640	0.03230	**2.58**	**0.130**	**0.00875**	**0.0155**	15. 2	5260	75.8	31.8
D6/ditch	0.03110	0.09160	**2.19**	**0.0459**	**0.00743**	**0.0132**	12.9	1860	64.3	27.0
D6/ditch	0.03120	0.09930	**2.18**	**0.0423**	**0.00740**	**0.0131**	12.8	1710	64.1	26.9
R1/pond	0.00141	0.03740	**48.2**	**0.112**	**0.164**	**0.291**	284	4550	1420	596
R1/stream	0.02160	0.5150	**3.15**	**0.00816**	**0.0107**	**0.0189**	18.5	330	92.6	38. 9
R2/stream	0.02850	0.5000	**2.39**	**0.0084**	**0.00811**	**0.0144**	14.0	340	70.2	29.5
R3/stream	0.03040	0.2530	**2.27**	**0.0166**	**0.00760**	**0.0135**	13.2	672	65.8	27.6
TER criterion			100	10	100	10	10	10	10	-

Table 2.9-19: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) in potatoes]

Scenario	PEC global max (µg/L)	PECsediment global max (µg/kg)	Fish acute	Fish ELS	Invertebrates acute	Invertebrates prolonged	Sed. dweller prolonged	Sed. dweller prolonged	Algae	Aquat. plant
			Oncorhynchus mykiss	*Oncorhynchus mykiss*	*Hyalella azteca*	*Americamysis bahia*	*Chironomus riparius*	*Chironomus riparius*	*Pseudokirchn. subcapitata*	*Lemna gibba*
			LC_{50} (µg/L)	NOEC (µg/L)	EC_{50} (µg/L)	NOEC (µg/L)	NOEC (µg/L)	EC_{10} (µg/Kg)	E_bC_{50} (µg/L)*	E_rC_{50} (µg/L)
			0.068	0.0042	0.000231	0.00041	0.4	170	>2	> 0.84
FOCUS Step 3										
D3/ditch	0.05230	0.2040	**1.30**	**0.0206**	**0.00442**	**0.00784**	***7.65***	833	38.2	16.1
D4/pond	0.002360	0.04660	**28.9**	**0.0901**	**0.0979**	**0.174**	169	3650	847	356
D4/stream	0.0440	0.05380	**1.55**	**0.0781**	**0.00525**	**0.00932**	**9.09**	3160	45.5	19. 1
D6/ditch	0.05180	0.1530	**1.31**	**0.0275**	**0.00446**	**0.00792**	**7.72**	1110	38.6	16.2
D6/ditch	0.05190	0.1660	**1.31**	**0.0253**	**0.00445**	**0.00790**	**7.71**	1020	38.5	16.2
R1/pond	0.002360	0.06240	28.8	0.0673	**0.0979**	**0.174**	169	2720	847	356
R1/stream	0.0360	0.8590	**1.89**	**0.00489**	**0.00642**	**0.0114**	11.1	198	55.6	23.3
R2/stream	0.04750	0.8340	**1.43**	**0.00504**	**0.00486**	**0.00863**	**8.42**	204	42.1	17.7
R3/stream	0.05070	0.4220	**1.34**	**0.00996**	**0.00456**	**0.00809**	**7.89**	403	39.4	16.6
TER criterion			100	10	100	10	10	10	10	-

Based on the calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 1, 2, 3), the calculated TER values for the acute and long-term risk resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP (field uses) of the formulation Bulldock 25 EC do not achieve the acceptability criteria TER ≥ 100 and TER ≥ 10 for fish and aquatic invertebrates, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2 for long-term and acute effects.

Therefore a refined higher tier risk assessment is conducted and presented below:

Refined risk assessment based on FOCUS STEP 4 calculations

Table 2.9-20: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) in winter wheat, application in spring] (FOCUS STEP 4 - 20 m + 90 % drift reduction measures)

Focus scenario	**Step 4 20 m + 90 % drift reduction**	**Fish acute**	**Fish chronic**	**Invertebrates**
		SSD	***Oncorhynchus mykiss***	***Overall assessment/microcosm***
		median HC5 LC_{50} (µg/L)	**NOEC (µg/L)**	**RAC (µg/L)**
	PEC (µg/L)	**0.312**	**0.0042**	**0.000105**
D1/ditch	0.0003010	1040	14.0	**0.349**
D1/stream	0.00030	1040	14.0	**0.350**
D2/ditch	0.0003070	1020	13.7	**0.342**
D2/stream	0.0003060	1020	13.7	**0.343**
D3/ditch	0.0003030	1030	13.9	**0.347**
D4/pond	0.0001140	2740	36.8	**0.921**
D4/stream	0.0002690	1160	15.6	**0.390**
D5/pond	0.0001250	2500	33.6	**0.840**
D5/stream	0.0002980	1050	14.1	**0.352**
D6/ditch	0.0003050	1020	13. 8	**0.345**
R1/pond	0.0002240	1390	18.8	**0.469**
R1/stream	0.000110	2840	38.2	**0.955**
R3/stream	0.0003170	984	13.2	**0.331**
R4/stream	0.0002830	1100	14.8	**0.371**
TER criterion		9	10	1

Based on calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 4 – 20 m + 90 % drift reduction), the calculated TER values for the acute and long-term risk to fish resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP of the formulation Bulldock EC 25 achieve the adjusted tier 2 acceptability criterion TER ≥ 9 for fish (acute) and acceptability criterion TER ≥ 10 for fish (chronic), but do not achieve the tier 3 RAC for aquatic invertebrates, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2 for long-term effects.

The results of the assessment indicate an unacceptable risk for aquatic organisms due to the intended (representative) use of Bulldock EC 25 in winter wheat in spring according to the label.

Table 2.9-21: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) in winter wheat, application in autumn] (FOCUS STEP 4 - 20 m + 90 % drift reduction measures)

Focus scenario	Step 4 20 m + 90 % drift reduction	Fish acute	Fish chronic	Invertebrates
		SSD	*Oncorhynchus mykiss*	*Overall assessment/microcosm*
		median HC5 LC_{50} (µg/L)	NOEC (µg/L)	RAC (µg/L)
	PEC (µg/L)	**0.312**	**0.0042**	**0.000105**
D1/ditch	0.0003010	1040	14.0	**0.349**
D1/stream	0.0003420	912	12.3	**0.307**
D2/ditch	0.0003060	1020	13.7	**0.343**
D2/stream	0.0002950	1060	14.2	**0.356**
D3/ditch	0.0003020	1030	13.9	**0.348**
D4/pond	0.0002940	1060	14. 3	**0.357**
D4/stream	0.0001130	2760	37.2	**0.929**
D5/pond	0.0003170	984	13.2	**0.331**
D5/stream	0.0001200	2600	35	**0.875**
D6/ditch	0.0003050	1020	13. 8	**0.344**
R1/pond	0.0003360	929	12.5	**0.312**
R1/stream	0.0001270	2460	33. 1	**0.827**
R3/stream	0.0003600	867	11. 7	**0.292**
R4/stream	0.0004890	638	8.59	**0.215**
TER criterion		9	10	1

Based on the calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 4 – 20 m + 90 % drift reduction), the calculated TER values for the acute and long-term risk to fish resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP of the formulation Bulldock EC 25 achieve the adjusted tier 2 acceptability criterion TER ≥ 9 for fish (acute) and acceptability criterion TER ≥ 10 for fish (chronic), but do not achieve the tier 3 RAC for aquatic invertebrates, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2 for long-term effects.

The results of the assessment indicate an unacceptable risk for aquatic organisms due to the intended (representative) use of Bulldock EC 25 in winter wheat in autumn according to the label.

Table 2.9-22: Maximum PECSW values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) in spring wheat, application in spring] (FOCUS STEP 4 -20 m + 90 % drift reduction measures)

Focus scenario	Step 4 20m + 90 % drift reduction	Fish acute	Fish chronic	Invertebrates
		SSD	*Oncorhynchus mykiss*	*Overall assessment/ microcosm*
		median HC5 LC_{50} (µg/L)	NOEC (µg/L)	RAC(µg/L)
	PEC(µg/L)	**0.312**	**0.0042**	**0.000105**
D1/ditch	0.000309	1010	13.6	**0.340**
D1/stream	0.000301	1040	14.0	**0.349**
D2/ditch	0.000303	1030	13.9	**0.347**
D2/stream	0.000111	2810	37.8	**0.946**
D3/ditch	0.000281	1110	14.9	**0.374**
D4/pond	0.0001270	2460	33.1	**0.827**
D4/stream	0.000291	1070	14.4	**0.361**
D5/pond	0.0002820	1110	14.9	**0.372**

Table 2.9-23: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) in winter wheat, application in spring] (FOCUS STEP 4 - 20 m + 90 % drift reduction measures)

Focus scenario	Step 4 20 m + 90 %	Fish acute	Fish chronic	Invertebrates
		SSD	*Oncorhynchus mykiss*	*Overall assessment/ microcosm*
		median HC5 LC_{50} (µg/L)	NOEC (µg/L)	RAC (µg/L)
	PEC (µg/L)	0.312	0.0042	0.000105
D1/ditch	0.0006010	519	**6.99**	**0.175**
D1/stream	0.000330	945	12.7	**0.318**
D2/ditch	0.0003070	020	13.7	**0.342**
D2/stream	0.0006120	510	**6.86**	**0.172**
D3/ditch	0.0003030	1030	13.9	**0.347**
D4/pond	0.0001140	2740	36.8	**0.921**
D4/stream	0.0005390	579	**7.79**	**0.195**
D5/pond	0.0001250	2500	33.6	**0.840**
D5/stream	0.0005960	523	**7.05**	**0.176**
D6/ditch	0.0003050	1020	13. 8	**0.344**
R1/pond	0.0004490	695	**9.35**	**0.234**
R1/stream	0.000110	2840	38.2	**0.955**
R3/stream	0.0006330	493	**6.64**	**0.166**
R4/stream	0.0004710	662	**8.92**	**0.223**
TER criterion		9	10	1

Based on calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 4 – 20 m + 90 % drift reduction), the calculated TER values for the acute and long-term risk to fish resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP of the formulation Bulldock EC 25 achieve the adjusted tier 2 acceptability criterion TER ≥ 9 for fish (acute) and acceptability criterion TER ≥ 10 for fish (chronic), but do not achieve the tier 3 RAC for aquatic invertebrates, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2 for long-term effects.

The results of the assessment indicate an unacceptable risk for aquatic organisms due to the intended (representative) use of Bulldock EC 25 in spring/winter wheat in spring according to the label.

Table 2.9-24: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) in winter wheat, application in autumn] (FOCUS STEP 4 - 20 m + 90 % drift reduction measures)

Focus scenario	**Step 4 20 m + 90 %**	**Fish acute**	**Fish chronic**	**Invertebrates**
		SSD	***Oncorhynchus mykiss***	***Overall assessment/ microcosm***
		median HC5 LC_{50} (µg/L)	**NOEC (µg/L)**	**RAC (µg/L)**
	PEC (µg/L)	0.312	0.0042	0.000105
D1/ditch	0.0006020	518	**6.98**	**0.174**
D1/stream	0.0003420	912	12.3	**0.307**
D2/ditch	0.000306	1020	13.7	**0.343**
D2/stream	0.0005910	528	**7.11**	**0.178**
D3/ditch	0.0003020	1030	13.9	**0.348**
D4/pond	0.0005870	532	**7.16**	**0.179**
D4/stream	0.0001130	2760	37.2	**0.929**
D5/pond	0.0006340	492	**6.62**	**0.166**
D5/stream	0.0001200	2600	35	**0.875**
D6/ditch	0.0003050	1020	13.8	**0.344**
R1/pond	0.0005610	556	**7.49**	**0.187**
R1/stream	0.0001280	2440	32.8	**0.820**
R3/stream	0.000638	489	**6.58**	**0.165**
R4/stream	0.0008140	383	**5.16**	**0.129**
TER criterion		9	10	1

Based on the calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 4 – 20 m + 90 % drift reduction), the calculated TER values for the acute and long-term risk to fish resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP of the formulation Bulldock EC 25 achieve the adjusted tier 2 acceptability criterion TER ≥ 9 for fish (acute) and acceptability criterion TER ≥ 10 for fish (chronic), but do not achieve the tier 3 RAC for aquatic invertebrates, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2 for long-term effects.

The results of the assessment indicate an unacceptable risk for aquatic organisms due to the intended (representative) use of Bulldock EC 25 in winter wheat in autumn according to the label

Table 2.9-25: Maximum PECSW values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) in spring wheat, application in spring] (FOCUS STEP 4 -20 m + 90 % drift reduction measures)

Focus scenario	Step 4 20m + 90 % drift reduction	Fish acute	Fish chronic	Invertebrates
		SSD	*Oncorhynchus mykiss*	*Overall assessment/ microcosm*
		median HC5 LC_{50} (µg/L)	NOEC (µg/L)	RAC (µg/L)
	PEC (µg/L)	0.312	0.0042	**0.000105**
D1/ditch	0.000309	1010	13.6	**0.340**
D1/stream	0.000601	519	**6.99**	**0.175**
D3/ditch	0.000303	1030	13.9	**0.347**
D4/pond	0.000111	2810	37.8	**0.946**
D4/stream	0.000563	554	**7.46**	**0.187**
D5/pond	0.000127	2460	33.1	**0.827**
D5/stream	0.000582	536	**7.22**	**0.180**
R4/stream	0.000470	664	**8.94**	**0.223**
TER criterion		9	10	1

Based on the calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 4 – 20 m + 90 % drift reduction), the calculated TER values for the acute and long-term risk to fish resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP of the formulation Bulldock EC 25 achieve the adjustted tier -2 acceptability criterion TER ≥ 9 for fish (acute) and acceptability criterion TER ≥ 10 for fish (chronic) , but do not achieve tier – 3 RAC for aquatic invertebrates, according to commission implementing regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2. for long-term effects.

The results of the assessment indicate an unacceptable risk for aquatic organisms due to the intended (representative) use of Bulldock EC 25 in spring wheat according to the label.

Table 2.9-26: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 7.5 g as/ha (14 d) in potatoes] (FOCUS STEP 4 - 20 m + 90 % drift reduction measures)

Focus scenario	Step 4 20 m + 90 %	Fish acute	Fish chronic	Invertebrates
		SSD	*Oncorhynchus mykiss*	*Overall assessment/ microcosm*
		median HC5 LC_{50} (µg/L)	NOEC (µg/L)	RAC (µg/L)
	PEC (µg/L)	0.312	0.0042	0.000105
D3/ditch	0.0003020	1030	13.9	**0.348**
D4/pond	0.0001090	2860	38.5	**0.963**
D4/stream	0.0002750	1130	15. 3	**0.382**
D6/ditch	0.0002990	1040	14.0	**0.351**
D6/ditch	0.0003000	1040	14.0	**0.350**

R1/pond	0.0001120	2790	37.5	**0.938**
R1/stream	0.0002250	1390	18. 7	**0.467**
R2/stream	0.0002970	1050	14.1	**0.354**
R3/stream	0.0003180	981	13.2	**0.330**
TER criterion		9	10	1

Based on the calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 4 – 20 m + 90 % drift reduction), the calculated TER values for the acute and long-term risk to fish resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP of the formulation Bulldock EC 25 achieve the adjusted tier 2 acceptability criterion TER ≥ 9 for fish (acute) and acceptability criterion TER ≥ 10 for fish (chronic), but do not achieve the tier 3 RAC for aquatic invertebrates, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2 for long-term effects.

The results of the assessment indicate an unacceptable risk for aquatic organisms due to the intended (representative) use of Bulldock EC 25 in potatoes according to the label.

Table 2.9-27: Maximum PEC_{SW} values and TER values for beta-cyfluthrin [2 x 12.5 g as/ha (14 d) in potatoes] (FOCUS STEP 4 -20 m + 90 % drift reduction measures)

Focus scenario	**Step 4 20 m + 90 %**	**Fish acute**	**Fish chronic**	**Invertebrates**
		SSD	***Oncorhynchus mykiss***	***Overall assessment/microcosm***
		median HC5 LC_{50} (µg/L)	**NOEC (µg/L)**	**RAC (µg/L)**
	PEC (µg/L)	0.312	0.0042	0.000105
D3/ditch	0.0003020	1030	13.9	**0.348**
D4/pond	0.0001090	2860	38.5	**0.963**
D4/stream	0.0005490	568	**7.65**	**0.191**
D6/ditch	0.0002990	1040	14.0	**0.351**
D6/ditch	0.00030	1040	14.0	**0.350**
R1/pond	0.0001150	2710	36.5	**0.913**
R1/stream	0.0004490	695	**9.35**	**0.234**
R2/stream	0.0005930	526	**7.08**	**0.177**
R3/stream	0.0006360	491	**6.60**	**0.165**
TER criterion		9	10	1

Based on calculated concentrations of beta-cyfluthrin in surface water (PEC_{SW} FOCUS Step 4 – 20 m + 90 % drift reduction), the calculated TER values for the acute and long-term risk to fish resulting from an exposure of aquatic organisms to beta-cyfluthrin according to the GAP of the formulation Bulldock EC 25 achieve the adjusted tier 2 acceptability criterion TER ≥ 9 for fish (acute) and acceptability criterion TER ≥ 10 for fish (chronic), but do not achieve the tier 3 RAC for aquatic invertebrates, according to Regulation (EU) No 546/2011, Annex, Part I C, 2. Specific principles, point 2.5.2 for long-term effects.

The results of the assessment indicate an unacceptable risk for aquatic organisms due to the intended (representative) use of Bulldock EC 25 in potatos according to the label.

Refined risk assessments based on roughly estimates of further refinements proposed by the applicant (Ranke, J. 2014)

Conclusion:

Based on roughly estimates of further refinements proposed by Ranke, J. (2014) a safe use of Bulldock EC 25 as a spray application in wheat [spring/autumn application – 2 x 7.5 g as/ha (14 days) and 2 x 12.5 g as/ha (14 days)] and in potatoes [2 x 7.5 g as/ha (14 days) and 2 x 12.5 g as/ha (14 days)] can be demonstrated for one Scenario (R1).
However, the proposed risk mitigation measures are indeed theoretically possible, but not practicable in all EU Member States (e.g. in Germany).

Representative uses of Montur Forte FS 230

Run-off and drainage

The required triggers are not met for surface water organisms such as fish and invertebrates for beta-cyfluthrin when based on worst-case FOCUS Step 2 PECsw values. Therefore, TER calculations based on FOCUS Step 3 PECsw values were calculated.

Table 2.9-28: TER calculations for beta-cyfluthrin based on FOCUS Step 3

Species	Endpoint [µg/L]	PECsw,max [µg/L]	FOCUS scenario	TER	Trigger
Beta-cyfluthrin, sugar beet					
Fish, acute *Oncorynchus mykiss*	LC_{50} 0.068	4.01×10^{-9}	D4 (stream, 1st)	1.70×10^{7}	100
Invertebrate, acute *Hyalella azteca*	LC_{50} 0.000231	4.01×10^{-9}	D4 (stream, 1st)	5.76×10^{4}	100
Fish, chronic *Oncorynchus mykiss*	NOEC 0.0042	4.01×10^{-9}	D4 (stream, 1st)	1.05×10^{6}	10
Invertebrate, chronic *Americamysis bahia*	NOEC 0.00041	4.01×10^{-9}	D4 (stream, 1st)	1.02×10^{5}	10

Based on FOCUS Step 3 PECsw values, the TER_{acute} and TER_{lt} values for the active substance beta-cyfluthrin exceed the required trigger of 100 and 10, respectively.
This indicates an acceptable risk to aquatic organisms by exposure to beta-cyfluthrin via run-off and drainage. The calculations for the worst-case scenario D4 (stream, 1st) cover all other FOCUS scenarios which are relevant for sugar beet.

The PECsw,max step 3 for imidacloprid for Montur Forte FS 230 were not provided by the applicant. Therefore they were estimated on the basis of the values calculated from the formulation Gaucho:
Focus step 3 (please refer to EFSA Journal 2014;12(10):3835)
PECsw max of imidacloprid based on the application of Gaucho:
Maximum run-off scenario: < 0.0005 µg/L
Maximum drainage scenario: FOCUS Step 3: PEC_{sw} = 0.01 µg/L; PEC_{sed} = 0.01 µg/kg

These values correspond with an application rate of 117 g as/ha.
The application rate (imidacloprid) of Montur Forte 230 is 19.5 g as/ha, i.e. 6 fold lower.
Thus, the roughly estimated PECsw values of imidacloprid by the application of Montur Forte FS 230 are::
Maximum run-off scenario: < 0.000083 µg/L
Maximum drainage scenario: FOCUS Step 3: PEC_{sw} = 0.0017 µg/L; PEC_{sed} = 0.0017 µg/kg

Table 2.9-29: TER calculations for imidacloprid based on FOCUS Step 3

Scenario	PEC global max (µg/L)	Fish acute	Fish chronic	Invertebrates acute	Invertebrates prolonged
		C.variegatus	*Oncorhynchus mykiss*	*SSD*	*Tier II RACsw*
		LC_{50} (µg/L)	NOEC (µg/L)	*Tier II RACsw*[2] (µg/L)	*Tier II RACsw*[1] (µg/L)
		161 000	9020	0.098	**0.009**
run-off max	< 0.000083	1.94×10^9	1.09×10^8	1180	108

[1] EFSA Journal 2014;12(10):3835: Nevertheless, as it was agreed at the meeting, in the absence of further data, EFSA considered that the endpoints from Roessink *et al*., (2013) can be used for risk assessment as a conservative approach. The experts also agreed to use the lowest endpoint where several studies on the same species were available.
The HC5 value (and 95 % confidence interval) on the basis of acute toxicity **data for insects** (n = 15, values in bold in Table B1 of Appendix B) was 0.49 (0.098 – 1.38) µg/L. Consequently, for insect taxa the **median HC5 was 0.49 µg/L** and the **lower limit HC5 was 0.098 µg/L**.
The experts discussed the AF by taking into account the criteria in the EFSA PPR Panel (2013). Most of the criteria in the guidance indicate that the appropriate AF should be 6. However, the experts considered that an AF of 5 could be suitable because some criteria triggered the lowest AF recommended in the guidance document and the most sensitive tested species were considered in the SSD.
Therefore, applying an AF of 5 to the median HC5 of 0.49 µg/L, the resulting tier-2B RACsw;ac was 0.098 µg as/L. However, it has to be noted that this **tier-2B RACsw;ac** may only be used as provisional for risk assessment, due to the limitations related to the data set.
[2] EFSA Journal 2014;12(10):3835 :„ A SSD approach was carried out by the Netherlands (NL) based on some literature data (n=10, values in bold in Tables B3 and B4 in Appendix B). EFSA evaluated the NL approach in the **study evaluation notes** (see section 3; EFSA, 2014b). The chronic SSD and the endpoints used to construct this curve were discussed at the Pesticides Peer Review Experts' Meeting 116 (June 2014). The chronic SSD curve provided by the NL and agreed at the meeting has been included in Appendix C of this Conclusion. The **HC5 value** (and 95 % confidence interval) was **0.027** (0.0031 – 0.092) **µg as/L**. The experts agreed to apply an AF of 3 to the median HC5, as recommended by the EFSA PPR Panel (2013). Therefore, the **tier-2B RACsw;ch** was **0.009 µg as/L**. This RAC is more relevant than the **tier-2A,** above. However, as already mentioned, it is noted that this **tier-2B RACsw;ch** may only be used as provisional for risk assessment, due to the limitations related to the data set used to construct the SSD." A data gap concerning the chronic toxicity to aquatic invertebrates was defined. Until now, reliable data addressing these data have not been provided. Thus, in this report, the provisional tier-2B $RAC_{sw;ch}$ of 0.009 µg as/L will be used for risk assessment.

Based on these estimated PEC_{sw} values, the acceptability criteria are met. Thus, the risk to aquatic organisms is considered to be acceptable.

Exposure via dust drift deposition

The TER calculations are based on exposure values given by draft Guidance Document SANCO/10553/2012 (2014) and adjusted to the portion of beta-cyfluthrin:

Table 2.9-30: TER calculations for beta-cyfluthrin based on exposure via dust drift

Species	RAC [ng/L]	$PEC_{sw,max}$ [ng/L]	TER
Fish, acute Tier 2	34.6	**2.345**	14.9
Fish, chronic Tier 1	**0.42**	**2.345**	**0.17**
Invertebrate Tier 3	**0.105**	**2.345**	**0.045**
Sediment dweller, chronic Tier 1	40	**2.345**	16.9

TER values indicate an unacceptable risk for fish (chronic) and aquatic invertebrates due to exposure to beta-cyfluthrin and therefore with Montur Forte FS 230 via dust drift deposition.

2.9.10.4 Non-target arthropods other than bees

Bulldock EC 25

Tier 1 risk assessment for in-field exposure

Table 2.9-31: HQ values for non-target arthropods (Tier-1) for in-field exposure

Species	Intended use	LR_{50} [g as/ha]	Exposure	PER [g as/ha]	HQ
A. rhopalosiphi	Wheat, potato 7.5 g as/ha	0.163	in-field	12.75	78
	Wheat, potato 12.5 g as/ha		in-field	21.25	130
T. pyri	Wheat, potato 7.5 g as/ha	0.0025	in-field	12.75	5100
	Wheat, potato 12.5 g as/ha		in-field	21.25	8500

PER: Predicted environmental rates ; HQ: Hazard quotient

All in-field HQ triggers for Tier 1 are above the trigger value for both indicator species *A. rhopalosiphi* and *T. pyri* indicating an unacceptable risk to non-target arthropods.

Tier 1 risk assessment for off-field exposure

Table 2.9-32: HQ values for non-target arthropods (Tier-1) for off-field exposure

Species	Intended use	L/ER_{50} [g as/ha]	Exposure	$PER^*_{off\text{-}field}$ x correction factor [g/ha]	HQ
A. rhopalosiphi	Wheat, potato 7.5 g as/ha	0.163	off-field	0.01199	0.07
	Wheat, potato 12.5 g as/ha		off-field	0.019975	0.12

T. pyri	Wheat, potato 7.5 g as/ha	0.0025	off-field	0.01199	4.76
	Wheat, potato 12.5 g as/ha		off-field	0.019975	7,99

PER: Predicted environmental rates ; HQ: Hazard quotient; TER: Toxicity to exposure ratio
*PER off–field with risk mitigation: 5 m + 90 % drift reduction (drift factor = 0.00047)

Considering risk mitigation measures (5 m + 90 % drift reduction), the tier 1 off-field HQ for *Aphidius rhopalosiphi* is below the trigger of 2. However, the HQ trigger is not met for *Typhlodromus pyri*. This indicates an unacceptable risk to non-target arthropods.

Higher tier risk assessment for in-field and in- field exposure

Leaf dwelling arthropods:
Due to the lack of valid extended laboratory tests and semi-field tests for leaf dwelling arthropods, a tier 2 risk assessment cannot be performed.
Although several valid aged residue studies with *Coccinella septempunctata* reveal a potential for recolonialisation with regard to this species, they are not appropriate to unburden the results of the tier 1 risk assessment. Based on information from all valid laboratory and extended laboratory studies, *T.* pyri, not *C. septempunctata* turned out to be the most sensitive species.

Soil dwelling arthropods:
Studies on two representative species of this group are available: *Aleochara bilineata* and *Poecilus cupreus*.

The study with *Aleochara bilineata* is classified as not valid (please refer to Volume_3CP_Bulldock EC 25_B.9.5.2.1).

A laboratory study was conducted with Bulldock EC 25 formulation on the adult rove beetle *Poecilus cupreus* (Heimbach, 1990, KIIIA1 10.5.1/03). The beetles were exposed to a rate of 7.7 g as/ha applied on sand. There were no effects on mortality and slight effects on food consumption two days after application. Further semi-field studies were conducted covering rates from 8.0 g as/ha to 12.5 g as/ha. At the lower application rates no effects on mortality and food consumption was observed, for the highest rate of 12.5 g as/ha an effect on food consumption of 100 % was observed. Based on the highest rate tested, an in-field risk cannot be excluded.
A second laboratory test conducted with Bulldock EC 25 on *Poecilus cupreus* larvae (Neumann, 2001, KIIIA1 10.5.2/02) were submitted with the dossier for the second representative formulation Montur Forte FS 230 (but described within this document) revealed an significantly higher sensitivity to larvae (LR_{50}> 0.04 mg as/kg soil; $LR_{100} \leq$ 0.4 mg as/kg soil; NOEC < 0.04 mg/as kg/soil). As the maximum $PECsoil_{accu}$ (potatoes; BBCH 10, 2 x12.5 g/ha) is 0.0242 mg as/kg soil (dw), the risk has to be further addressed in the context of full fauna field studies.

Refined in-field risk assessment based on full fauna field studies

Four in-field studies were submitted. Only one was carried out in cereal fields (Vinall, 2005, R-19598, KIIIA1 10.5.3/03), but was conducted with another formulation (containing cyfluthrin).
Due to this fact and other strong shortcomings this study was considered as non reliable - R3 (according de Jong et al. 2009).
Likewise, the other three in-field studies in alfalfa (Mack, 2013, R-28693, KIIIA1 10.5.3/05) and in orchard (Knäbe, 2013, R-28694, KIIIA110.5.3/06; Vinall, 2006, R-19592, KIIIA1 10.5.4/04) were evaluated as non-reliable - R3 (according de Jong et al. 2009).
For details, please refer to Volume_3CP_Bulldock EC 25_B.9.5.2.4.
Due to their incomparable study design (different crops, different sprayed products) an overall assessment of all four studies is not possible.
Consequently, no reliable data about the toxicity of Bulldock EC 25 to non-target arthropods in-field are available. Accordingly, a higher tier risk assessment cannot be conducted.

Refined off-field risk assessment based on full fauna field studies

The submitted off-field study was conducted to assess the impact of drift rates of Bulldock EC 25 on non-target arthropod fauna in a meadow (Mack, 2014, R-30607, KIIIA1 10.5.3/07).
The reliability of the study was valued according criterias from de Jong et al., 2010.
Due to several strong shortcomings the studies was classified as R3 – not reliable.
For details, please refer to Volume_3CP_Bulldock EC 25_B.9.5.2.4.

Overall conclusions on risk to non-target arthropods other than bees

In-field

As no valid tier 2 studies and no reliable in-field studies are available, the risk assessment remains on tier 1. Based on the endpoints from the laboratory tests with *A. rhopalosiphi* and *T. pyri*, the risk assessment indicates an unacceptable risk to non-target arthropods.

Off-field

As no valid tier 2 studies and no reliable in-field studies are available, the risk assessment remains on tier 1.
When considering maximum risk mitigation measures (5 m + 90 % drift reduction), the tier 1 off-field HQ for *Aphidius rhopalosiphi* is below the trigger of 2. However, the HQ trigger is not met for *Typhlodromus pyri*. This indicates an unacceptable risk to non-target arthropods.

Due to the non-volatile property of beta-cyfluthin, an exposure of the area outside the greenhouse is not expected. Therefore the risk for non-target arthropods after greenhouse applications in tomatoes (17.5 g as/ha, 14 d) is acceptable.

Montur Forte FS 230

In-field risk assessment

Assessment of exposure via coated seeds only

A study was conducted with larvae of *Poecilus cupreus* by mixing beta-cyfluthrin (tech.) and imidacloprid (tech.) into LUFA 2.1 soil (Neumann, P., 1999, KIIIA1 10.5.2/01).
The exposure to imidacloprid (techn.) & beta-cyfluthrin at 0.005 & 0.010, 0.010 & 0.010 and 0.010 & 0.020 mg/kg had no adverse effect on ground beetle larvae compared to the control treatment. Only at 0.010 & 0.020 mg/kg the body weight was statistically reduced by 10 % compared to the control.

These test rates were about 29 % below the maximum PEC_{soil} value that is expected for beta-cyfluthrin from the use of beta-cyfluthrin + imidacloprid FS230 according to the proposed use pattern ($PEC_{soil, max}$: 0.014 mg beta-cyfluthrin/kg soil).

Further studies that were conducted with larvae of *Poecilus cupreus* with application rates of beta-cyfluthrin at 0.015 mg as/kg soil (Neumann, 2002, KIIA 8.8.1.3) and 0.040 mg as/kg soil (Neumann, 2001; KIIIA1 10.5.2./02; please refer to Volume_3CP_Bulldock EC 25_B.9.5.2.2) resulted in no increased mortality indicating that the exposure to beta-cyfluthrin following the application of beta-cyfluthrin + imidacloprid FS 230 will not result in unacceptable adverse effects on larvae of *Poecilus cupreus*.

To confirm the conclusions for *Poecilus cupreus* and to address the risk to a second soil dwelling arthropod, *Aleochara bilineata*, aged residue studies were conducted with *Aleochara bilineata* and lar-

vae of *Poecilus cupreus* (Jans, 2013, KIIIA1 10.5.2/02 and Jans, 2013, KIIIA1 10.5.2/03).
For these studies sugar beet seeds were treated with the representative formulation beta-cyfluthrin + imidacloprid FS 230 (80+150) at a treatment rate of 0.1 L/Unit (1 Unit = 10^5 seeds). In addition a plateau concentration of 0.02 mg imidacloprid/kg dry soil was established in the test soil before introducing the treated sugar beet pills into the soil. The sugar beet pills were introduced into the test containers with a seeding rate of 1.1 x10^5 seeds/ha. A first bioassay was started at the day when the seeds were introduced and a second bioassay was started 4 weeks (for *Aleochara bilineata*) and 6 weeks (for *Poecilus cupreus*) later. The study results confirmed already in the first bioassay that even initial effects will be clearly below 50 %.

It can be concluded that the use beta-cyfluthrin + imidacloprid FS 230 according to the proposed use pattern will not result in unacceptable adverse effects on non-target arthropod species in the in-field area.

Off-field risk assessment

The off-field is exposed by dust abraded and drifted during the drilling.

Risk has to be assessed according the draft guidance document "Authorisation of Plant Protection Products for Seed Treatment" (SANCO/10553/2012; January 2014) chapter 11.5:

Non-target arthropods outside the field sown with treated seeds will be exposed to the active substance through the deposition of abraded dust. Foliar dwelling non-target arthropods have to be considered particularly at risk. It is considered that the realistic worst case exposure for terrestrial invertebrates – especially pollinators – will not be found on the ground but in 3-dimensional spatial structures (e.g. trees, hedges, adjacent crops). Thus, the predicted 3-D exposure data (as listed in chapter 10.5.4 of the draft GD SANCO/10553/2012) will be employed in the assessment of the risk for foliar-dwelling non-target arthropods exposed to contaminated dust. As long as no generic factors are available for every crop, a worst case extrapolation factor of 13 is used to derive 3-D exposure data from 2-D ground deposition data.

Because of the attractiveness of flowers to pollinators, a vegetation dilution factor is deemed to underestimate the risk for species e.g. foraging in the outer part of a flowering hedge. Moreover, pollinators like bees or butterflies will forage from one flower to the next and accumulate high amount of dust. Thus, no vegetation distribution factor should be used to assess the realistic environmental risk for non-target arthropods exposed to contaminated dust deposited in 3-dimensional structures.

The TER-ratio can be calculated as follows:

$$TER_{3D\,dust} = \frac{Ecotoxicological\,Endpoint_{liquid\ formulation}\ \left(g\ a.s./ha\right)}{PEC_{3D\,dust\,deposition}\ \left(g\ a.s./ha\right)}$$

where

TER	=	Toxicity to Exposure Ratio
as	=	active substance
PEC *3D dust deposition*	=	Predicted Environmental Concentration after deposition of abraded dust in adjacent 3-dimensional structures

A TER trigger value of 10 or 5 (Uniform principles; Regulation (EU) No 546/2011) is proposed. These triggers are in line with the ESCORT 2 safety factors of 10 or 5 in the off-field risk assessment based on resp. first tier and extended laboratory tests.

The PEC *3D dust deposition* can be calculated as follows (chapter 10.5.4 of the draft GD SANCO/10553/2012):

$$PEC_{3D\,dust\,deposition}\,(g\,a.s./ha) = PEC_{2D\,ground\,dust\,deposition}\,(g\,a.s./ha) \times 3D\,extrapolation\,factor$$

where

PEC	=	Predicted Environmental Concentration
as	=	active substance
3D factor	=	extrapolation factor was determined in field studies with dif ferent crop types to be **13**.

The 3D extrapolation factor describes the ratio between dust deposition in 3D structures (measured in gauze netting) and 2D structures (measured in Petri dishes).

According to chapter 10.5.4 of the draft GD SANCO/10553/2012 the PEC 3-D for dust deposition in off-crop areas can be assumed to be 0.26 g as*/ha (* as a sum for all active substances in the formulation).

However, studies testing the toxicity of Montur Forte FS 230 on leaf dwelling arthropods (*Aphidius rhopalosiphi, Typhlodromus pyri*) were not submitted.

Therefore, a risk assessment referring exposure in the off-field area cannot be carried out.
A data gap is defined.

2.9.10.5 Non target soil meso- and macrofauna

Bulldock EC 25

Table 2.9-33: TER values for earthworms and other soil macro- and mesofauna (Tier-1), wheat, 2x7.5 g as/ha, interception: 25 %, 14 d

Species	Test item	Time scale	Endpoint [mg/kg as soil dw]	Max. PEC_{SOIL} [mg/kg soil dw]	TER
Eisenia fetida	beta-cyfluthrin (Bulldock 25 EC)	Chronic	0.83	0.0128	64.8
	FPB-acid	Chronic	2.6	0.0009	2890
	DCVA	Chronic	2.6	0.0025	1040
Folsomia candida	beta-cyfluthrin	Chronic	56	0.0128	4380
	FPB-acid	Chronic	28	0.0009	31100
	DCVA	Chronic	18	0.0025	7200
	beta-cyfluthrin (Bulldock 25 EC)	Chronic	1.592	0.0128	124
Hypoaspis aculeifer	beta-cyfluthrin	Chronic	0.97	0.0128	75.8
	FPB-acid	Chronic	297	0.0009	330000
	DCVA	Chronic	100	0.0025	40000

Table 2.9-34: TER values for earthworms and other soil macro- and mesofauna (Tier-1), wheat, 2x12.5 g as/ha, interception: 25 %, 14 d

Species	Test item	Time scale	Endpoint [mg/kg soil dw]	Max. PEC_{SOIL} [mg/kg soil dw]	TER
Eisenia fetida	beta-cyfluthrin (Bulldock 25 EC)	Chronic	0.83	0.0213	39.0
	FPB-acid	Chronic	2.6	0.0014	1860
	DCVA	Chronic	2.6	0.0042	619
Folsomia candida	beta-cyfluthrin	Chronic	56	0.0213	2630
	FPB-acid	Chronic	28	0.0014	20000
	DCVA	Chronic	18	0.0042	4290
	beta-cyfluthrin (Bulldock 25 EC)	Chronic	1.592	0.0213	74.7
Hypoaspis aculeifer	beta-cyfluthrin	Chronic	0.97	0.0213	45.5
	FPB-acid	Chronic	297	0.0014	212000
	DCVA	Chronic	100	0.0042	23800

Table 2.9-35: TER values for earthworms and other soil macro- and mesofauna (Tier-1): potato, 2x7.5 g as/ha, interception: 15 %, 14 d

Species	Test item	Time scale	Endpoint [mg/kg soil dw]	Max. PEC_{SOIL} [mg/kg soil dw]	TER
Eisenia fetida	beta-cyfluthrin (Bulldock 25 EC)	Chronic	0.83	0.0143	58.0
	FPB-acid	Chronic	2.6	0.001	2600
	DCVA	Chronic	2.6	0.0028	929
Folsomia candida	beta-cyfluthrin	Chronic	56	0.0143	3920
	FPB-acid	Chronic	28	0.001	28000
	DCVA	Chronic	18	0.0028	6430
	beta-cyfluthrin (Bulldock 25 EC)	Chronic	1.592	0.0143	111
Hypoaspis aculeifer	beta-cyfluthrin	Chronic	0.97	0.0143	67.8
	FPB-acid	Chronic	297	0.001	297000
	DCVA	Chronic	100	0.0028	35700

Table 2.9-36: TER values for earthworms and other soil macro- and mesofauna (Tier-1), potato, 2x12.5 g as/ha, interception: 15 %, 14 d

Species	Test item	Time scale	Endpoint [mg/kg soil dw]	Max. PEC_{SOIL} [mg/kg soil dw]	TER
Eisenia fetida	beta-cyfluthrin (Bulldock 25 EC)	Chronic	0.83	0.0242	34.3
	FPB-acid	Chronic	2.6	0.0016	1630
	DCVA	Chronic	2.6	0.0047	553
Folsomia candida	beta-cyfluthrin	Chronic	56	0.0242	2310
	FPB-acid	Chronic	28	0.0016	17500
	DCVA	Chronic	18	0.0047	3830
	beta-cyfluthrin (Bulldock 25 EC)	Chronic	1.592	0.0242	65.8
Hypoaspis aculeifer	beta-cyfluthrin	Chronic	0.97	0.0242	40.1
	FPB-acid	Chronic	297	0.0016	186000
	DCVA	Chronic	100	0.0047	21300

Table 2.9-37: TER values for earthworms and other soil macro- and mesofauna (Tier-1): tomatoes greenhouse, 2 x 17.5 g as/ha, interception: 50 %, 14 d)

Species	Test item	Time scale	Endpoint [mg/kg soil dw]	Max. PEC_{SOIL} [mg/kg soil dw]	TER
Eisenia fetida	beta-cyfluthrin (Bulldock 25 EC)	Chronic	0.83	0.0152	54.6
	FPB-acid	Chronic	2.6	0.0010	2600
	DCVA	Chronic	2.6	0.0030	867
Folsomia candida	beta-cyfluthrin	Chronic	56	0.0152	3680
	FPB-acid	Chronic	28	0.0010	28000
	DCVA	Chronic	18	0.0030	6000
	beta-cyfluthrin (Bulldock 25 EC)	Chronic	1.592	0.0152	105
Hypoaspis aculeifer	beta-cyfluthrin	Chronic	0.97	0.0152	63.8
	FPB-acid	Chronic	297	0.0010	297000
	DCVA	Chronic	100	0.0030	33300

The TER_{LT} values exceed the relevant decision-making criterion of 5 for earthworms and other soil macro- and mesofauna. Therefore, it can be concluded that the chronic risk to earthworms and other soil macro- and mesofauna for beta-cyfluthrin from the use of Bulldock 25 EC in all crops according to the proposed good agricultural practice will be acceptable.

A study addressing the toxicity of Bulldock EC 25 to *Hypoaspis aculeifer* is not available. Therefore, the risk assessment is based on data for the active substance.
However, comparing the endpoints (NOEC) of beta-cyfluthrin and Bulldock EC 25 for *Folsomia candida*, a 35 fold higher toxicity of Bulldock EC 25 can be determined.

As TER values for *Hypoaspis aculeifer* divided by 35 (assuming a comparable difference in toxicity) would be below the acceptablity criterion of 5, the toxicity and, therefore, the risk of Bulldock EC 25 to *Hypoaspis aculeifer* cannot be sufficiently assessed on the basis of results fort he active substance. Consequently, a chronic *Hypoaspis aculeifer* study with Bulldock EC 25 is needed.
Thus, a data gap is defined.

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Table 2.9-38: TER values for earthworms and other soil macro- and mesofauna (Tier-1), seed treatment sugar beets

Species	Test item	Time scale	Endpoint [mg/kg soil dw]	Max. PEC_{SOIL} [mg/kg soil dw]	TER
Eisenia fetida	beta-cyfluthrin + imidacloprid FS 230	Chronic	1.78	0.196	9.08
	FBP-acid	Chronic	2.60	0.003	867
	DCVA (permethric acid)	Chronic	2.60	0.001	2600
Folsomia candida	beta-cyfluthrin		56.00	0.014	4000
	beta-cyfluthrin + imidacloprid FS 230		4.60	0.196	23.5
	FBP-acid		28.00	0.003	9330
	DCVA (permethric acid)		18.00	0.001	18000
Hypoaspis aculeifer	beta-cyfluthrin		0.97	0.014	69.3
	beta-cyfluthrin + imidacloprid FS 230		32.00	0.196	163
	FBP-acid		297.00	0.001	297000
	DCVA (permethric acid)		100.00	0.003	33300

[A] Product PECsoil based on a product density of 1.13 kg/L and standard soil parameters (soil layer of 5 cm with a bulk density of 1.5 g/cm^3)

TER_{LT} values for earthworms and other soil macro- and mesofauna exceed the trigger of 5.

Therefore, it can be concluded that the chronic risk for earthworms and other soil macro- and mesofauna than earthworms from the use of Montur Forte FS 230 as treatment of sugar beet seeds according to the proposed good agricultural practice will be acceptable.

2.9.10.6 Soil nitrogen transformation

Bulldock EC 25

Table 2.9-39: Risk on soil micro-organisms

Test substance	Endpoint	Value	$PEC_{soil,max}$ [mg/kg]	Max. field application rate of Bulldock 25 EC
Bulldock 25 EC	Nitrogen transformation	No negative effects up to 9.61 mg test item/kg dry soil (equivalent to 216 g as/ha) after 28 days	0.0242 mg/kg soil dw	0.5 L prod./ha 12.5 g as/ha

Bulldock 25 EC had no significant effect on soil micro-organisms at 9.61 mg Bulldock 25 EC/kg, equivalent to 0.24 mg as/kg dry soil. This is approximately 8.9 times higher than the maximum PECs of 0.027 mg as/kg dry soil following the worst-case application to potatoes. This supports the conclusion that under field conditions the use of Bulldock 25 EC at the proposed rates poses no unacceptable risk to non-target soil micro-organisms. The metabolites FPB-acid and DCVA had no significant effect on soil micro-organisms at soil concentrations up to 0.125 mg/kg dry soil and 0.112 mg/kg dry soil, respectively. As this is 25 times higher for FPB-acid and approximately 18 times higher for DCVA than the maximum PECs no unacceptable effects are to be expected.

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Table 2.9-40: Risk assessment for soil micro-organisms

Test substance	Endpoint	Value	$PEC_{soil,max}$ [mg/kg]
Beta-cyfluthrin + imidacloprid FS 230	Nitrogen transformation	No negative effects up to 0.98 mg test item/kg dry soil after 28 days	0.916[A]

[A] worst-case PEC_{soil} for the product taking into account the maximum application rate of 10.4 g as/ha, a product density of 1.13 kg/L, a soil bulk density of 1.5 g/cm³ and a distribution at soil layer of 0-5 cm

According to regulatory requirements the risk is acceptable, if the effect on nitrogen transformation at the maximum PECsoil values is < 25 % after 100 days.
In no case, deviations from the control exceeded 25 % after 28 days, indicating low risk to soil micro-organisms.

2.9.10.7 Terrestrial non-target higher plants

Beta-cyfluthrin is an insecticide and is therefore not expected to have any significant herbicidal activity. Studies on possible pre- and post-emergence effects on non-target higher plants showed no effects on any of the species tested at a limit rate of 2.4 L Bulldock 25 EC/ha. The calculated maximum $PER_{off\text{-}field}$ of 13.85 mL product/ha (wheat and potatoes), equivalent to 0.346 g as/ha is far below the

level found to have no effects on non-target plants. The resulting TER values are given in the following table.

Table 2.9-41: Bulldock 25 EC: TERs for 10 terrestrial non-target terrestrial plants based on $PER_{off\text{-}field}$ and ER_{50} from a 21 d vegetative vigour test and 21 d seedling emergence test (>60 g as/ha)

Crop	Application rate [g as/ha]	Maximum drift at 1 m distance (%)	Off-field drift rate ($PER_{off\text{-}field}$) [g as/ha]	Endpoint [g as/ha]	TER	Trigger value
Wheat, potato	7.5	2.77	0.208	>60	>289	5
Wheat, potato	12.5	2.77	0.346	>60	>173	5

Bulldock 25 EC will not pose a risk to non-target terrestrial plants because realistic exposure rates are far below the No Observed Effect Rate in both vegetative vigour and seedling emergence test. TERs based on maximum drift at 1 m distance significantly exceed the trigger of 5.

2.9.10.8 Biological methods for sewage treatment

Based on the two studies about effects on activated sludge, adverse effects on biological methods for sewage treatment are not expected.

2.10 Classification and labelling

Table 2.10-1: Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures

Active Substance

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				Not relevant
2.3.	Flammable aerosols				Not relevant
2.4.	Oxidising gases				Not relevant
2.5.	Gases under pressure				Not relevant
2.6.	Flammable liquids				Not relevant
2.7.	Flammable solids				Conclusive but not sufficient for classification.
2.8.	Self-reactive substances and mixtures				Data/statement lacking
2.9.	Pyrophoric liquids				Not relevant

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.10.	Pyrophoric solids				Data/statement lacking
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				Not relevant
2.14.	Oxidising solids				Conclusive but not sufficient for classification.
2.15.	Organic peroxides				Not relevant
2.16.	Substance and mixtures corrosive to metals				Data/statement lacking
3.1.	Acute toxicity - oral	H300		H300	
	Acute toxicity - dermal				Conclusive but not sufficient for classification.
	Acute toxicity - inhalation	H330		H330	
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				Data lacking.
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	Lact. H362			
3.8.	Specific target organ toxicity - single exposure	Cat. 3, H335			
3.9.	Specific target organ toxicity - repeated exposure				Conclusive but not sufficient for classification.

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
3.10.	Aspiration hazard				Conclusive but not sufficient for classification.
4.1.	Hazardous to the aquatic environment	H400 H410	M = 1000000 M = 100000		
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive or conclusive but not sufficient for classification

Justification: for GHS09/H400/H410: acute toxicity to aquatic invertebrates (96 h EC_{50} = 0.000231µg/L, *Hyalella azteca*) and fish (96 h LC_{50} = 0.0068 µg/L, *O.mykiss*) and chronic toxicity to aquatic invertebrates (21 d NOEC = 0.00041µg/L, *Americamysis bahia*), fish (21 d NOEC = 0.0042 µg as/L, *Oncorhynchus mykiss*) as well as sediment organisms (28 d NOEC = 0.0004 mg/L, *Chironomus riparius*).

Precautionary statements:

Proposed notes assigned to an entry:
Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

Bulldock 25 EC

According to Regulation (EC) No. 1272/2008 the following classification is proposed for the preparation:

Symbol:	GHS09
Signal word:	Danger
Hazard class, category:	Acute Tox. 4, Asp. 1, Skin Irrit. 2, Eye Dam. 1, STOT SE 3, Aquatic Acute 1, Aquatic Chronic 1
Hazard statement:	302-304-315-318-332-336-400-410

Justification: for GHS09/H400/H410: acute toxicity toto aquatic invertebrates (48 h EC_{50} = 4.2 µg/L, *Daphnia magna*), data on toxicity to fish are not available

Montur Forte FS 230

According to Regulation (EC) No. 1272/2008 the following classification is proposed for the preparation:

Symbol:	GHS09
Signal word:	Warning
Hazard class, category:	Acute Tox. 4, Lact. , Aquatic Acute 1, Aquatic Chronic 1
Hazard statement:	302-362-400-410

Labelling
'Contains 1,2-benzisothiazole-3(2H)-one. May produce allergic reactions.' [EUH208]
'Contains 5-chloro-2-methyl-2H-isothiazole-3-on and 2-methyl-2H-isothiazole-3-one. May produce allergic reactions.' [EUH208]

Justification: for GHS09/H400/H410: acute toxicity to aquatic invertebrates (48 h EC_{50} = 1.97 µg/L, *Daphnia magna*)

2.11 Relevance of metabolites in groundwater

There is no metabolite predicted to occur in concentrations > 0,1 µg/L in groundwater. An assessment of the relevance is therefore not triggered.

2.12 Consideration of isomeric composition in the risk assessment

2.12.1 Identity and physical chemical properties

Beta-cyfluthrin is a mixture of four diasteromeric pairs with two enantiomers each. The main diastereomers are diastereomer II (300 - 400 g/kg) and diastereomer IV (570 - 670 g/kg).
Physical and chemical properties which are required for pure active substance have been provided seperately for diastereomer II and diastereomer IV. For details see the evaluation in Vol. 3, Part B.2.

2.12.2 Methods of analysis

Four diastereoisomeric pairs are separated by the applied analytical methods. It could be shown that the ratio of diastereoisomers changes after application in plants (Bonarius, 2004, ASB2014-7873). Enantiomeric pairs are not separated in most studies.

2.12.3 Mammalian toxicity

Regarding the data requirement on "consideration of isomeric composition in the risk assessment – mammalian toxicity", the applicant stated in its dossier (Anon, 2014, ASB2014-7869):
"*As no guidance document is currently available that details how questions concerning stereoisomers might be dealt with, it is the opinion of the applicant that it is not appropriate to address this issue until such guidance is available. Therefore the risk assessment should be conducted in accordance with the current published guidelines. All information relevant to beta-cyfluthrin stereoisomers can be found in the respective sections of the dossier.*"

In summary, no evaluation is possible in addition to the evaluations presented in section 2.6 and in Vol. 3, section B.6.

2.12.4 Operator, worker, bystander and resident exposure

Currently, no assessment of operator, worker, bystander and resident exposure taking into account the isomeric composition is possible.

2.12.5 Residues and consumer risk assessment

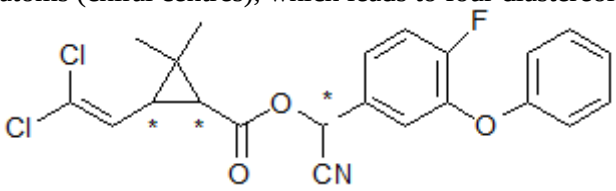
No separate assessment of the role of isomers for dietary risk assessment is performed and none is considered necessary. Please refer to the discussions in Vol. 3, B.6 and B.7.

2.12.6 Environmental fate

The data for degradation in soil were conducted with beta-cyfluthrin which consists of isomers II + IV. The data for degradation in water/sediment system were conducted with cyfluthrin (isomers I – IV), but are recalculated for mixture of isomers II + IV. The data for adsorption were conducted with cyfluthrin. No new findings relevant for risk assessment are expected from new batch studies using beta-cyfluthrin.

2.12.7 Ecotoxicology

The common molecular structure of cyfluthrin and beta-cyfluthrin shows three asymmetric carbon atoms (chiral centres), which leads to four diastereoisomers each consisting of an enantiomer pair.



Thus, cyfluthrin and beta-cyfluthrin are mixtures of eight isomers.
Four of the isomers are considered active: diastereoisomer II (1R,3R,1S + 1S,3S,1R = 1:1; cis) and diastereoisomer IV (1R,3S,1S + 1S,3R,1R = 1:1; trans).

The proportion of diastereoismer pairs in cyfluthrin and beta-cyfluthrin is shown in the table below.

Table 2.12-1:

Diastereomer	**Cyfluthrin**	**Beta-cyfluthrin**
I (1R-3R-R+1S-3S-S = 1:1;cis) CAS: 86560-92-1	23 - 27 %	< 2 %
II **(1R-3R-S + 1S-3S-R = 1:1, cis)** **CAS: 86560-93-2**	**17 - 21 % (mean 19 %)**	**30 - 40 % (mean 35 %)**
III (1R-3R-R + 1S-3R-S = 1:1;trans) CAS: 86560-93-2	32 - 36 %	< 3 %
IV **(1R-3S-S + 1S-3R-R = 1:1; trans)** **CAS:** **CAS: 86560-95-4**	**21 - 25 % (mean 22 %)**	**57 - 67 % (mean 62 %)**
Sum of active diastereoismers	~ 41 %	~ 97 %
Relation of II/IV	0.86	0.56

Active diastereoismers are in written in **bold**.

Therefore, cyfluthrin is 42 % active isomers when compared to beta-cyfluthrin (41/97 = 42).
Therefore, the assumption is that the toxicity endpoints for beta-cyfluthrin should be 42 % of the cyfluthrin endpoints.
However, the relation of the two diastereoisomers II/IV is different for cyfluthrin and beta-cyfluthrin:
II/IV (cyfluthrin) = 0.86
II/IV (beta-cyfluthrin) = 0.56
The relative activity/toxicity of diastereoisomers II and IV is unknown so far.
The assumption that toxicity endpoints for beta-cyfluthrin are 42 % of the cyfluthrin endpoints can be verified either by analysing available information about the eight isomeres (four diastereoisomers) or by comparing empirical (endpoints derived from studies with beta-cyfluthrin) and predicted toxcitiy endpoints (endpoints derived from studies with cyfluthrin and transferred into beta-cyfluthrin endpoint by multiplying with 0.42) for non target organisms.

Aquatic organisms:

Acute toxicity to fish

The lowest measured acute toxicity of beta-cyfluthrin to fish (rainbow trout): LC_{50} (4 d) = 0.068 µg/L (flow –trough)
[For details see Volume3_CA_B.9.2.5.1]
Measured acute toxicity of cyfluthrin to fish (rainbow trout): LC_{50} (4 d) = 0.209 µg/L (flow-through)
[This study was not submitted by the applicant. The endpoint is derived from the US-EPA database ECOTOX.
Source: [redacted] (1994) Acute Toxicity of (Carbon 14)-Cyfluthrin to the Rainbow trout (*Oncorhynchus mykiss*) Under Flow-Through Conditions: Lab Project Number: BD812201: 106778. Unpublished study prepared by Miles Incorporated. 33 p.]

Therefore, the ration between measured LC_{50} values (4 d) of beta-cyfluthrin and cyfluthrin is 0.32 which is only slightly below the assumed factor of 0.42.

Chronic toxicity to fish

No reliable long-term study conducted with beta-cyfluthrin is available. The previous endpoint derives from an ELS-study (flow-trough) examining the toxicity of cyfluthrin to rainbow trout:
NOEC (56 d) = 0.01 µg/L
Thus, the predicted endpoint for beta-cyfluthrin is: NOEC (56 d) =0.0042 µg/L.
The RMS considers the application of the factor 0.42 for calculating the NOEC for beta-cyfluthrin acceptable. The observed effects in the ELS study (mortality, kyphosis, scoliosis reduced activity or erratic swimming and reduced growth) are in line with the known neurotoxic mode of action of pyrethroids. Hence, the same isomers of cyfluthrin may be responsible for acute as well as for chronic effects.

Aquatic invertebrate (chronic, acute)

Liu et al. 2005 examined the acute toxicity of every cyfluthrin isomer to *Ceriodaphina dubia* after separating by enantioselective high-performance liquid chromatography (HPLC). The study author states that the testing procedure followed the current EPA guideline (Weber CI. Methods for measuring the acute toxicity of effluents and receiving waters to freshwater and marine organisms. Cincinnati, OH: U.S. Environmental Protection Agency; 1995.). However, the article reveals no information about the measured concentration of isomers during the course of the study. Thus, endpoints are based on nominal values.

Table 2.12-2: Table of results (LC_{50} values in µg/L) copied from Liu et al. 2005:

	1*R-cis*-α*R*	1*S-cis*-α*S*	1*S-cis*-α*R*	1*R-cis*-α*S*	1*R-trans*-α*R*	1*S-trans*-α*S*	1*S-trans*-α*R*	1*R-trans*-α*S*
Cypermethrin	>7.5	>7.5	>7.5	0.775 ± 0.063	>7.5	>7.5	>7.5	0.995 ± 0.089
Cyfluthrin	>10	>10	>10	0.104 ± 0.018	>10	>10	>10	0.214 ± 0.018

Considering the results for cyfluthrin it becomes obvious that only two isomers (1R-cis-αS and 1R-trans-α-S) are responsible for the toxicity to *C. dubia*.
Each of both isomers belongs to one of the two diastereoisomers II and IV, respectively.
Assuming a 1:1 distribution of enantiomers in the racemic mixures II and IV, the following proportion of the active isomers in cyfluthrin and beta-cyfluthrin is deducible:
Cyfluthrin consists of 19 % diastereomer II and 22 % diasteromer IV and consequently of 9.5 % of 1R-cis-α-cis and 11 % 1 R-trans-αS.
Beta-cyfluthrin consists of 35 % diasteromer II and 22 % diastereomer IV and consequently of 17.5 % 1R-cis-α-cis and 31 % of 1 R-trans-αS.
When assuming additive toxicity it is possible to calculate the toxicity of cyfluthrin and beta-cyfluthrin based on these portions and LC_{50} values of the two toxic isomers.

cyfluthrin: $\frac{1}{LC50} = \frac{0.095}{0.104} + \frac{0.11}{0.214}$

LC_{50} = 0.700 µg/L

beta-cyfluthrin: $\frac{1}{LC50} = \frac{0.175}{0.104} + \frac{0.31}{0.214}$

LC_{50} = 0.319 µg/L

$\frac{LC50\ beta\text{-}Cyfluthrin}{LC50\ Cyfluthrin} = \mathbf{0.46}$

Therefore, the calculated ratio is in line with the assumed 0.42.
Acutally, the LC_{50} values should be compared with real measured LC_{50} values for *Ceriodaphina dubia*. However, no data about toxicity of beta-cyfluthrin to *C. dubia* are available. Endpoints found in the ECOTOX database regarding toxic effects of cyfluthrin to *C.dubia* are very inhomogeneous as derived from studies using different water qualities. Thus, they do not provide reliable endpoints.
However, as the conditions for toxicity testing decribed in Liu et al. 2005 are assumed to be similar the relative toxicity of both active isomeres and consequently the LC_{50} ratio of cyfluthrin and beta-cyfluthrin should be reliable.

Comparing acute toxicity endpoints of cyfluthrin and beta-cyfluthrin to the marine invertebrates *Mysidopsis bahia* the assumed ratio is not fully supported. In fact, the latter [LC_{50} (4 d, beta-cyfluthrin) = 0.0022 µg/L; Machado, 1994 b, is only slightly lower compared to the cyfluthrin endpoint [LC_{50} (4 d, Cyfluthrin) = 0.0024; Surprentant (1987). This is maybe due to deficiencies in former analytical methods. In Surpretant (1987) no limit of quantification is given. However, as two analytical methods were used (LSC and GC/ECD) results from both methods could be compared. Deviations from 27 % - 35 % were determined. However, since LC_{50} values empirically derived for cyfluthrin and beta-cyfluthrin are within the same order of magnitude, the assumed ratio of 0.42 is still regarded as acceptable.

U.S. Environmental Protection Agency. 20XX (use current year). ECOTOX User Guide: ECOTOXicology Database System. Version 4.0. Available: http:/www.epa.gov/ecotox/

Terrestrial vertebrates (endotherms):

The toxicity of beta-cyfluthrin and cyfluthrin for terrestrial vertebrates deviates significantly from toxicity to aquatic organisms (invertebrates, fish). Moreover, there is evidence that toxicity of beta-cyfluthrin and cyfluthrin to terrestrial vertebrates is in the same range. Thus, an adjustment factor is not applied.

Birds

The acute toxicity of cyfluthrin [LD_{50} > 2000 mg/kg bw; *Colinus virginianus*; [redacted] (1983), LD_{50} = 170 mg/kg bw, *Serinus canaria*, Addy-Orduna,L (2011) see B.9.1.1.1/KIIA 8.1.1/03 and B.9.1.1.1/KIIA 8.1.1/06, respectively] and the acute toxicity of beta-cyfluthrin [LD_{50} > 2000 mg/kg bw, *Colinus virginianus*, [redacted] (1994)/, LD_{50} =50 mg/kg bw, *Serinus canaria*, [redacted] 1985 B.9.1.1.1/KIIA8.1.1/01 and B.9.1.1.1/KIIA8.1.1/06] to birds is within the same range. Studies about effects on reproduction were only submitted for cyfluthrin. The lowest ecotoxicological available endpoint is consistent with the old LoEP of the first inclusion [NOEAL of 37.74 mg/kg KG/d or NOEC = 269 ppm ([redacted] 1990)].

Mammals:

Please refer to 2.12.3.

Other groups of organisms

Non –target arthropods:

Laboratory studies used for the risk assessment were conducted with the representative formulations containing beta-cyfluthrin. Therefore, the composition of isomers is not further considered.
Nevertheless, the diastereomeres II and IV are known to be the active as well as the diastereomeres I and III are known to be inactive regarding the toxicity to arthropods.

Non-target soil meso- and macrofauna:

Laboratory studies used for the risk assessment were conducted with the representative formulations containing beta-cyfluthrin. Therefore, the composition of isomers is not further considered in respect to their effect on non-target soil meso- and macrofauna.

Effects on soil nitrogen-transformation:

Laboratory studies used for the risk assessment were conducted with the active substance beta-cyfluthrin and the representative formulations containing beta-cyfluthrin. Therefore, the composition of isomers is not further considered in respect to their effects on soil nitrogen-transformation.

2.13 Residue definitions

2.13.1 Definition of residues for exposure/risk assessment

To be specified for the following matrices:

Food of plant origin:
Cyfluthrin, including other mixtures of constituent isomers (sum of isomers)

Food of animal origin:
Cyfluthrin, including other mixtures of constituent isomers (sum of isomers)

Soil: beta-cyfluthrin

Groundwater: beta-cyfluthrin

Surface water: beta-cyfluthrin

Sediment: beta-cyfluthrin

Air: beta-cyfluthrin

2.13.2 Definition of residues for monitoring

To be specified for the following matrices:

Food of plant origin:
Cyfluthrin, including other mixtures of constituent isomers (sum of isomers)

Food of animal origin:
Cyfluthrin, including other mixtures of constituent isomers (sum of isomers)

Soil: beta-cyfluthrin

Groundwater: beta-cyfluthrin

Surface water: beta-cyfluthrin

Sediment: beta-cyfluthrin

Air: beta-cyfluthrin

Table 2.13-1: Overview about metabolites

Code	**Active substance**	**Soil**		
	beta-cyfluthrin			
Metabolites		**Occurrence**	**Risk Assessment**	
Code	**Structural formula**		Persistence, succeeding crops	Ecotoxicology
DCVA		aerob: max. 40,5 % $DT_{50,lab}$: 3,5 d $DT_{50,field}$: – anaerob: max. 75,7 % soil photolysis: –	no relevance	no relevance
FPB-acid		aerob: max. 12,7 % $DT_{50,lab}$: 1,2 d $DT_{50,field}$: – anaerob: max.63,9 % soil photolysis: max. 22,3 %	no relevance	no relevance

Code	**Active substance**	**Ground water**			
	beta-cyfluthrin				
Metabolites		**Occurrence**	**Risk Assessment**		
Code	**Structural formula**		Pesticidal activity	Toxicology	Ecotoxicology
DCVA		FOCUS-PEARL: 0,001 µg/L	Relevance assessment not triggered	Relevance assessment not triggered	Relevance assessment not triggered
FPB-acid		FOCUS- PEARL: < 0,001 µg/L	Relevance assessment not triggered	Relevance assessment not triggered	Relevance assessment not triggered

Code	Active substance	Surface water and sediment	
	beta-cyfluthrin		
Metabolites		**Occurrence**	**Risk Assessment**
Code	**Structural formula**		Ecotoxicology
DCVA		hydrolysis: main metabolite photolysis: – w/s-study: water: max. 36 % sediment: max.23.7 %	no relevance in water layer
FPB-acid		hydrolysis: – photolysis: – w/s-study: water: max. 24.3 % sediment: max.29.1 %	no relevance
FPB-aldehyde		hydrolysis: – photolysis: – w/s-study: water: max. 1.1 % sediment: max.15.7 %	no relevance

Level 3

beta-cyfluthrin

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		Based on the given information about the active substance and its metabolites, only the representative use of Bulldock EC 25 in tomatoes in greenhouse can be supported so far.

3.1.1.2 Submission of further information

		Yes	No	
i)	It is considered that a complete dossier has been submitted		X	See data gaps in the list of studies to be generated.
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.	X		Yes: but only for the greenhouse application of Bulldock EC 25 in tomatoes due to negligible exposure of areas outside the greenhouse. Therefore, the risk to non-target organisms is regarded acceptable, although reliable data about toxicity are not available so far. For all uses in open field (spray-application, seed treatment), the risk can either be not addressed due to the lack of studies: 1. risk to aquatic organisms due to the exposure with active ingredients of Montur Forte FS 230 via run-off and drainage: - a FOCUSsw PEC calculation for imidacloprid is required; 2. risk to non-target-arthropods in the off-field due to the exposure with Montur Forte FS 230 via dust drift deposition: - laboratory studies with the representative formulation Montur Forte FS 230 and leaf dwelling arthropod standard species *Aphidius*

				rhopalosiphi and *Typhlodromus pyri* are required; 3. risk to soil meso- and macro- fauna: - due to the 35-fold higher toxicity to *Folsomia candida* of Bulldock EC25 compared to beta-cyfluthrin, the toxicity and, thus, the risk of Bulldock Forte EC 25 to *Hypoaspis aculeifer* cannot be assessed on toxicity data on beta-cyfluthrin, therefore a chronic study testing the toxicity of Bulldock EC25 to *Hypoaspis aculeifer* is required; or an unacceptable risk is concluded based on the available (lower tier) data: off-field and in-field-risk to non-target arthropods following the representative spray applications of Bulldock EC 25: due to the lack of valid and reliable higher tier data – the risk assessment is based on tier 1 laboratory studies with *Aphidius rhopalosiphi* and *Typhlodromus pyri.*

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.			(a) Only uses in greenhouse may be authorised. (b) The minimum degree of purity of the active substance Minimum purity: 965 g/kg 300 - 400 g/kg for diastereomer II 570 - 670 g/kg for diastereomer IV

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		
	It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes	X		The residue definition for plants and the resulting dietary risk assessment (with regard to foliar uses) is connected with high uncertainty

	(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: (a) permits any residue of concern to be defined; (b) reliably predicts the residues in food and feed, including succeeding crops (c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing; (d) permits a maximum residue level to be defined and to be determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			due to severe scientific limitations of metabolism studies in terms of study design, performance, and reporting. None of these non-guideline and non-GLP metabolism studies investigating the fate after foliar application can be considered as a stand-alone study.
	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 data gaps in the list of studies to be generated.
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		Authorisation have been granted in nearly all Member states for Bulldock 25 EC/SC. Montur forte is also authorised in several Member States for seed treatment of beets.
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		Applicable for the proposed residue definitions.
Composition				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities	X		Data concerning the identity address sufficiently the requirements of Regulation (EU) No 283/2013.

	and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.			From toxicological point of view only the new proposed specification can be supported and it is proposed that this should be the new reference specification for the active substance beta-cyfluthrin.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	X		FAO 482/TC (1999) Minimum purity : 965 g/kg Ratio of Isomers: Diastereomer I: max. 2.0 % Diastereomer II: 30.0 – 40.0 % Diastereomer III: max. 3.0 % Diastereomer IV: 57.0 – 67.0 %
	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.		X	From toxicological point of view only the new proposed specification can be supported. The specified values for diasteromers II and IV are in compliance with the FAO-specification while the specified values for diastereomers I and III are lower than the FAO-specification. However, it has not been evaluated whether the specification really needs to be stricter than the FAO specification.
Methods of analysis				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	X		Sufficiently validated methods for the determination of the active substance in the technical material are available. Validated methods for the determination of diastereomers I and III and impurities in the technical material are available.
	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	For residues in all types of plant and animal products and for residues in soil, drinking water, air as well as for residues in body fluid and tissues sufficiently validated analytical methods and confirmatory methods are available. Primary and confirmatory methods are missing, which allow the determination of 0.0002 µg/L beta-cyfluthin in surface water.

	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		
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		ADI The RMS derived the ADI from the same 4-week repeat-dose study with beta-cyfluthrin (Heimann and Majeed, 1988, TOX9550271). The acute toxicity/neurotoxicity of beta-cyfluthrin/cyfluthrin is the critical endpoint. This applies also to repeat-dose studies. Due to intensive metabolism and rapid excretion of beta-cyfluthrin/cyfluthrin, daily administrations of beta-cyfluthrin/cyfluthrin are considered to represent a sequence of acute intoxications. With respect to the occurrence of clinical symptoms, the lowest NOAEL from the repeat-dose studies is 1 mg/kg bw/d with an assessment factor of 100. ADI = 0.01 mg/kg bw. ARfD Based on the relatively high acute toxicity of beta-cyfluthrin the derivation of an acute reference dose is considered necessary. Taking into account the data obtained for 4-week repeat-dose study with beta-cyfluthrin, the ARfD is derived from the NOAEL of 1 mg/kg bw with an assessment factor of 100: ARfD = 0.01 mg/kg bw. $AOEL_{syst.}$ Taking into account the data obtained for 4-week repeat-dose study with beta-cyfluthrin, the AOEL systemic is derived from the NOAEL of 1 mg/kg bw with an assessment factor of 100. No correction for oral absorption (90 %) is considered necessary. $AOEL_{syst.}$ = 0.01 mg/kg bw.

				$AOEL_{inhal.}$ A separate AOEL for inhalation was derived for the initial inclusion of beta-cyfluthrin/cyfluthrin. The AOEL inhalation was based on the subchronic inhalation study with cyfluthrin in rats to cover the specific localised toxicity by this route. The study had a NOAEL of 0.09 µg/L (equating to 0.0243 mg/kg bw/day. $AOEL_{inhal.}$ = 0.000243 mg/kg bw. See chapter 2.6.14 – 2.6.17
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	No, beta-cyfluthrin is devoid of a genotoxic potential (see 2.6.5).
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, classification and labelling for carcinogenicity is not warranted. There are no relevant data from epidemiological studies submitted by the applicant indicating a carcinogenic potential to humans. Long-term dietary toxicity studies were conducted in rats and mice. There was no increase in tumour incidences in either study. See section 2.6.6 for justification that classification is not needed.
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			n.a.

	or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
Impact on human health – proposed 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	No classification and labelling for this endpoint is needed (see 2.6.7). Fertility: There are no epidemiological data to evaluate effects on fertility. The RMS sees no evidence for adverse effects on reproduction and therefore, proposes no classification. No effects on fertility were noted in a 2-generation study in rats. Hence no classification for fertility according to CLP regulation is proposed. Developmental toxicity: There are no appropriate epidemiological studies available on developmental effects in humans. The prenatal developmental toxicity of beta-cyfluthrin and cyfluthrin was investigated in rats and rabbits and the studies were considered acceptable. In inhalational teratogenicity studies in rats with cyfluthrin, the increased frequency of malformations (microphthalmia, anophthalmia, bone malformations) in the offspring at 11.9, 12.8 (with oxygen supplement), and 23.7 mg cyfluthrin /m³ air was considered to represent a secondary effect due to hypoxic conditions in the dams (Renhof and Pauluhn, 1988, TOX9401910; Holzum, 1993, TOX9401829). Due to the irritating properties of the test substance at these dose levels a reflex bradypnoea occurred in the dams which was compensated by hypothermia and a reduction in metabolic activity. In addition, an increased incidence of resorptions occurred at a dose level of 23.7 mg/m^3 (Renhof and Pauluhn, 1988, TOX9401910). It can be

				assumed that the occurrence of the mentioned malformations, especially microphthalmia, in the offspring does not represent a direct toxic effect of the test substance. This assumption is supported by reproductive toxicity studies with orally administered beta-cyfluthrin/cyfluthrin where no treatment-related malformations were observed. It is therefore proposed not to classify cyfluthrin for embryotoxic effects in the presence of maternal toxicity (cat. 2). Even though some of the observed findings in the dams were severe findings (such as clinical signs, motor disturbances and/or gait abnormalities), they were considered to represent acute toxic/neurotoxic effects of beta-cyfluthrin/cyfluthrin. Due to intensive metabolism and rapid excretion of beta-cyfluthrin/cyfluthrin, daily administrations of beta-cyfluthrin/cyfluthrin are considered to represent a sequence of acute intoxications. A proposal for classification for acute effects is already made. Manifestations of developmental toxicity seen in rats and rabbits were accompanied by maternal toxicity. Abortion was observed in two (top dose) rabbits, and one dam resorbed its implants completely (Roetz, 1983, TOX9401914). From 60 mg/kg bw/d an increase in the number of post-implantative resorptions was the only observed change in rabbits interpretable as a sign of reproduction toxicity (Becker and Biedermann, 1992, TOX9401915). Taken together, based on the small number of animals affected, these findings are considered not severe enough to justify a classification in Category 2 (H361d). An increased incidence of coarse tremors and the decreased pup body weight observed during the lactation phase (as early as lactation day 5 and ceased by lactation day 18 after weaning) in F_1 and F_2 pups at and above 125 ppm (19 and 59 mg/kg bw/d) occurred in the presence of maternal toxicity (Eigenberg & Elcock, 1996, TOX2001-1771). The excretion of cyfluthrin in rat milk has not been determined but it can be concluded that the presence of adverse effects in the offspring at 125 ppm was due to transfer of cyfluthrin or of its metabolite(s) in the milk during the lactation period. This conclusion is supported by the absence of adverse treatment effects on prenatal or peri-natal litter parameters. Cyfluthrin exposure through the milk is considered to be

				the main determinant of offspring neurotoxicity and it is proposed to classify beta-cyfluthrin as reproductive toxicant in category for effects via lactation (Lact. H362 *'May cause harm to breast-fed children'*). See chapter 2.6.7.2
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			n.a.
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	See above. No classification for carcinogenicity or reproductive toxicity is proposed.
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	Designated studies on endocrine disrupting properties of beta-cyfluthrin have not been conducted by the applicant. The examined endpoints in reproduction toxicity studies did not indicate specific disrupting properties of beta-cyfluthrin. The available fertility studies showed no effects on male or female fertility. The developmental neurotoxicity study (Sheets and Lake, 2003, ASB2007-2856) did not reveal effects on developmental landmarks or sexual maturation. Anyhow it should be noted that male animals were examined less extensively than female animals. Male animals were treated with beta-cyfluthrin only in generational/fertility studies. They were not treated in the teratogenicity studies and data on sperm parameters (number, motility, morphology) and spermatogenesis were not provided in either study on rats and dogs. In addition, based on the information provided, effects on hormone-sensitive tissues like

				reproductive organs, thyroids and pituitary were not reported in the available repeat-dose toxicity studies. Please refer to 2.6.10
iii)	Linked to either i) or ii) immediately above. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			n.a.
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	DT_{50} in water/sediment system 27.6 days for whole system and 0.5 days for water phase (geometric mean n = 2). DT_{50} in soil 28.1 days (laboratory, geometric mean n = 4)
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	<u>P-criterion:</u> DT_{50} in water/sediment system 27.6 days for whole system and 0.5 days for water phase (geometric mean n = 2). DT_{50} in soil 28.1 days (laboratory, geometric mean n = 4) Therefore beta-cyfluthrin does not fulfill the criteria of a persistent substance. <u>B-criterion:</u> Based on the available bioconcentration study with *Lepomis macrochirus* (Burri, 2014), the lipid-normalised steady-state BCF_{SSL} (parent) is 2295. However, the calculation of the $BCF_{steady\ state}$ directly relies on the concentration of the test substance at the steady state in fish and water. It is not possible to determine this concentration at the

				steady state within the new study without a high level of uncertainty. Therefore, we propose to consider the $BCF_{steady\ state}$ as additional information only. The kinetic BCF_k does not depend on measured concentrations. Thus, it provides a more reliable result than the $BCF_{steady\ state.}$ The lipid- and growth corrected kinetic **BCF is 1822**. Therefore, beta-cyfluthrin does not fulfil the B-criterion according to Regulation (EC) No. 1107/2009 Annex II Section 3.7.2.2. <u>T-criterion:</u> Beta-cyfluthrin fulfils the T-criterion according to Regulation (EC) No. 1107/2009 Annex II Section 3.7.2.3 in regard to its toxicity to aquatic invertebrates (21 d NOEC = 0.00041µg/L, *Americamysis bahia*), fish (21 d NOEC = 0.0042 µg as/L, *Oncorhynchus mykiss*) as well as sediment organisms (28 d NOEC = 0.0004 mg/L, *Chironomus riparius*).
Very persistent and very bioaccumulative substance (vPvB)				
		Yes	No	
	It is considered that the active substance **FULFILS** the criteria of a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		X	DT_{50} in water/sediment system 27.6 days for whole system and 0.5 days for water phase (geometric mean n = 2). DT_{50} in soil 28.1 days (laboratory, geometric mean n = 4). Thus, the criterion of a very persistent substance is not met. As the lipid- and growth corrected kinetic BCF derived from the bioconcentration study with *Lepomis macrochirus* (Burri, 2014) is 1822 and, thus, is lower than 5000, the criterion of a very bioaccumulative substance (vB) according to Regulation (EC) No. 1107/2009 Annex II Section 3.7.3.2 is not fulfilled.
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		X	The acute and long-term risk to birds was assessed as acceptable for all intended uses on the tier-1 level. The acute and long-term risk to small mammals was assessed as acceptable for all intended uses. Risk to aquatic organism: The RAC in surface water bodies is defined by the toxicity of 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.			active substance to aquatic invertebrates. The RAC is derived by a stepwise approach. The resulting RAC tier 3 is documented in 2.9.3.2. For the open field spray applications of Bulldock EC 25, the risk to aquatic organisms was assessed to be unacceptable based on FOCUS Step 3 and FOCUS Step 4 PEC calculations (20 m buffer zone and 90 % drift reduction). However, since the maximum acceptable and applied drift buffer zone as well as the nozzle drift reduction in Europe is not known, a calculation considering a higher degree of risk mitigation measures was not performed, but may result in acceptable concentrations. For the representative application of Montur Forte FS 230 as seed treatment for sugar beet seeds, the risk for both active ingredients beta-cyfluthrin and imdiacloprid has to be assessed. Comparing the laboratory data of both active ingredients, beta-cyfluthrin is by 5 orders of magnitude more toxic to aquatic invertebrates than imidacloprid. Therefore, the risk assessment is based on beta-cyfluthrin only. This, however, does not apply for the entry via run-off and drainage into surface water as predicted concentrations of imidacloprid are considerably higher than PECs for beta-cyfluthrin due to the different adsorptive properties in soil of both active substances. The exposure of surface water bodies is via run-off and drainage (PECs calculated by FOCUSsw) and via dust drift deposition (PECs derived from draft SANCO/10553/2012 Rev. 1). The risk based on FOCUSsw Step 3 calculation (entry via run-off and drainage only) was shown to be acceptable for beta-cyfluthrin. However, a FOCUSsw calculation for imidacloprid was not provided. Therefore, a rough estimate of PECs was made referring to FOCUSsw calculations for the formulation Gaucho in assessment report Volume 3, B.9 for imidacloprid. As the resulting TER value was at the edge of acceptability for aquatic invertebrates, the applicant is requested to provide FOCUSsw calculations for imidacloprid considering the representative use of Montur Forte FS 230. PEC in surface water bodies resulting from dust drift depositon were taken from draft SAN-

				CO/10553/2012 Rev. 1. These PECs result in an unacceptable risk for aquatic organisms. Bees: Representative uses of Bulldock EC 25: Bulldock 25 EC has to be classified as hazardous to bees. Therefore it must not be used on plants which are in flower or which are visited by bees; this also applies to weeds and honey dew. Montur Forte FS 230: The use for the preparation of sugar beet pills, does not pose an unacceptable risk for honey bees. Non-target arthropods other than bees: Representative uses of Bulldock EC 25: In-field As no valid tier 2 studies and no reliable in-field studies are available, the risk assessment remains on tier 1. Based on the endpoints from the laboratory tests with *A. rhopalosiphi* and *T. pyri*, the risk assessment indicates an unacceptable risk to non-target arthropods. Off-field As no valid tier 2 studies and no reliable in-field studies are available, the risk assessment remains on tier 1. When considering maximum risk mitigation measures (5 m buffer zone + 90 % drift reduction), the tier 1 off-field HQ for *Aphidius rhopalosiphi* is below the trigger of 2. However, the HQ trigger is not met for *Typhlodromus pyri*. This indicates an unacceptable risk to non-target arthropods. Due to the non-volatile property of beta-cyfluthin, an exposure of the area outside the greenhouse is not expected. Therefore the risk for non-target arthropods after greenhouse applications in tomatoes (17.5 g as/ha, 14 d) is acceptable. Representative use of Montur Forte FS 230: In-field:

				Based on the provided data about the toxicity of the formulation to soil dwelling arthropods, it can be concluded that the use beta-cyfluthrin + Imidacloprid FS 230 according to the proposed use pattern will not result in unacceptable adverse effects on non-target arthropod species in the in-field area. Off-field: The PEC values in the off-field resulting from the exposure by the active ingredients of Montur Forte FS 230 via dust drift deposition are taken from the draft guidance document "Authorisation of Plant Protection Products for Seed Treatment" (SANCO/10553/2012; January 2014) chapter 11.5. However, studies testing the toxicity of Montur Forte FS 230 on leaf dwelling arthropods (*Aphidius rhopalosiphi, Typhlodromus pyri*) were not submitted. Therefore, a risk assessment referring to exposure in the off-field area cannot be carried out. A data gap is defined. Non-target soil meso- and macrofauna: Bulldock EC 25: The TER_{LT} values exceed the relevant decision-making criterion of 5 for earthworms and other soil macro- and mesofauna. Therefore, it can be concluded that the chronic risk to earthworms and other soil macro- and mesofauna from the use of Bulldock 25 EC in all crops according to the proposed good agricultural practice will be acceptable. However, a study addressing the toxicity of Bulldock EC 25 to *Hypoaspis aculeifer* is not available. Therefore, the risk assessment is based on data of the active substance. However, comparing the endpoints (NOEC) of beta-cyfluthrin and Bulldock EC 25 for *Folsomia candida*, a 35 fold higher toxicity of Bulldock EC 25 can be determined. As TER values for *Hypoaspis aculeifer* divided by 35 (assuming a comparable difference in toxicity) would be below the acceptablity criterion of 5, the toxicity and, therefore, the risk of Bulldock EC 25 to *Hypoaspis aculeifer* can not be sufficiently assessed on the basis of

				results for the active substance. Consequently, a chronic *Hypoaspis aculeifer* study with Bulldock EC 25 is needed. Thus, a data gap is defined. Montur Forte FS 230: TER_{LT} values for earthworms and other soil macro- and mesofauna exceed the trigger of 5. Soil nitrogen transformation: Bulldock 25 EC had no significant effect on soil micro-organisms at 9.61 mg Bulldock 25 EC /kg, equivalent to 0.24 mg as/kg dry soil. This is approximately 8.9 times higher than the maximum PECs of 0.027 mg as/kg dry soil following the worst-case application to potatoes. This supports the conclusion that under field conditions the use of Bulldock 25 EC at the proposed rates poses no unacceptable risk to soil micro-organisms. The metabolites FPB-acid and DCVA had no significant effect on soil micro-organisms at soil concentrations up to 0.125 mg/kg dry soil and 0.112 mg/kg dry soil, respectively. As this is 25 times higher for FPB-acid and approximately 18 times higher for DCVA than the maximum PECs no unacceptable effects are to be expected. Montur Forte According to regulatory requirements the risk is acceptable, if the effect on nitrogen transformation at the maximum PECsoil values is < 25 % after 100 days. In no case, deviations from the control exceeded 25 % after 28 days, indicating low risk to soil micro-organisms Sewage treatment: A risk to biological sewage treatment is not expected.
	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	According to the given information on non-target organisms beta-cyfluthrin does not have endocrine disrupting properties.

	Linked to the consideration of the endocrine properties immediately above. It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.			n. a.
	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		Representative uses of Bulldock EC 25: Based on the total set of data, it can be concluded that Bulldock 25 EC has to be classified as hazardous to bees. Therefore it must not be used on plants which are in flower or which are visited by bees; this also applies to weeds and honey dew. Representative use of Montur Forte FS 230: The use for the preparation of sugar beet pills, does not pose an unacceptable risk for honey bees.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	X		The residue definition for plants and the resulting dietary risk assessment (with regard to foliar uses) is connected with high uncertainty due to severe scientific limitations of metabolism studies in terms of study design, performance, and reporting. None of these non-guideline and non-GLP metabolism studies investigating the fate after foliar application can be considered as a stand-alone study.
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		The calculation of PECgw following application of Bulldock 25 EC in tomato (2 × 17.5 g/ha as, crop interception 0 % and 50 %) using the models FOCUS Pearl v. 4.4.4 and FOCUS Pelmo v. 5.5.3 gives no value > 0.001 µg/L for beta-cyfluthrin, FPB-acid or DCVA.

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	

3.1.3 Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	It is considered that the active substance **shall be considered of low risk.** In particular it is considered that the substance **should NOT be classified or proposed for classification** in accordance with Regulation (EC) No 1272/2008 as at least one of the following: — carcinogenic, — mutagenic, — toxic to reproduction, — sensitising chemicals, — very toxic or toxic, — explosive, — corrosive. In addition it is considered that **the substance is NOT**: — persistent (half-life in soil more than 60 days), — has a bioconcentration factor higher than 100, — is deemed to be an endocrine disrupter, or — has neurotoxic or immunotoxic effects.		X	Beta-cyfluthrin is no low risk substance. For human health toxicological properties, see sections 2.6. For ecotoxicalogical properties, see section 2.9.

3.1.4 List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to	Study status		
		No confirma-	Study on-	Study

	representative use(s)	tion that study available or on-going	going and anticipated date of completion	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				
Montur Forte FS 230: Determination of adhesion to seeds for the storage stability tests of the formulation at elevated and ambient temperature.	All uses.	X		
Montur Forte FS 230: Determination of suspensibility before and after storage of the formulation at ambient temperature.	All uses.	X		
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				
Primary and confirmatory methods, which allow the determination of 0.0002 µg/L beta-cyfluthin in surface water.				
3.1.4.6 Toxicology and metabolism				
An acceptable study to address the phototoxic potential.	All uses.	X		
In case detailed toxicological assessments of metabolites reported in residues are necessary, further data and information might be needed. Where relevant, this could in-	All uses.	X		

clude proposals for grouping / bridging / read-across established in line with the relevant GD by ECHA and OECD.				
3.1.4.7 Residue data				
Storage stability data for eggs	Wheat, potato (feed relevant uses)	X		
Four residue trials in wheat (SEU) to complete the data set.	Wheat	X		
3.1.4.8 Environmental fate and behaviour				
3.1.4.9 Ecotoxicology				
Laboratory studies with the representative formulation Montur Forte FS 230 and leaf dwelling arthropod standard species *Aphidius rhopalosiphi and Typhlodromus pyri*	Studies are needed for a reliable risk assessment (for the representative use of Montur Forte FS 230) for non-target arthropods in off-field areas.	X		
A chronic laboratory study testing the toxicity of the representative formulation Bulldock EC 25 to *Hypoaspis aculeifer*.	A study addressing the toxicity of Bulldock EC 25 to *Hypoaspis aculeifer* is not available. Therefore, the risk assessment was based on data of the active substance. Comparing the endpoints (NOEC) of	X		

	beta-cyfluthrin and the Bulldock EC 25 for *Folsomia candida*, a 35 fold higher toxicity of Bulldock EC 25 can be determined. As TER values for *Hypoaspis aculeifer* divided by 35 (assuming a comparable difference in toxicity) would be below the acceptablity criterion of 5, the toxicity and, therefore, the risk of Bulldock EC 25 to *Hypoaspis aculeifer* can not be sufficiently assessed on the basis of results fort he active substance.			

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)**
No evaluation and assessment of phototoxic potential of beta-cyfluthrin possible.	For all uses.
Reference for statement given in the MSDS that new co-formulant in Bulldock 25 EC is non-sensitising.	For all uses (Bulldock 25 EC).
Explanation for the fact that the previous formulation of Bulldock 25 EC was tested in 2010 while the new formulation MCW-5976 was already tested in 2007.	For all uses (Bulldock 25 EC).
Risk assessment for non-target organisms	All field uses
Risk to non-target arthropods (other than honey bees)	Seed treatment (Montur Forte FS 230)

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)**
Risk to aquatic organisms	All field uses
Risk to non-target arthropods (other than bees)	All open-field uses (Bulldock 25 EC) Seed treatment (Montur Forte FS 230)

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		Seed treatment (Montur Forte FS 230)	Foliar use field (Bulldock 25 EC)	Foliar use greenhouse (Bulldock 25 EC)
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		X	
	Assessment not finalised	X		
Risk to aquatic organisms	Risk identified	X	X	
	Assessment not finalised			
Groundwater exposure active substance	Legal parametric value breached			
	Assessment not finalised			
Groundwater exposure metabolites	Legal parametric value breached			
	Parametric value of 10 µg/L(a) breached			
	Assessment not finalised			
Comments/Remarks				

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

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

3.1.8 Area(s) where expert consultation is considered necessary

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

Area(s) where expert consultation is considered necessary	Justification
See chapters 3.1.5 and 3.1.6	

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
none		

3.2 Proposed decision

[redacted]

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 risk identified

Proposed condition/risk mitigation measure	Relevance in relation to representative use(s)
[redacted]	[redacted]

4 Appendices

4.1 Guidance documents used in this assessment

European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals on request
from EFSA. EFSA Journal 2009; 7(12):1438. doi:10.2903/j.efsa.2009.1438. Available online: www.efsa.europa.eu

European Food Safety Authority; Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters on request from EFSA. EFSA Journal 2013;11(7):3290

FOCUS (2006) "Guidance Document on Estimation 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.

de Jong, F.M.W, Bakker, F.M., Brown, K., Jilesen, C.J.T.J., Posthuma-Doodeman, C.J.A.M., Smit, C.E., van der Steen, J.J.M, van Eekelen, G.m.A. 2010. Guidance for summarising and evaluating field studies with non-target arthropods - A guidance document of the Dutch Platform for the Assessment of Higher Tier Studies. Published by the National Institute for Public Health and the Environment. Available online: ww.rivm.nl/bibliotheek/601712006/pdf

Candolfi, M.P., Barrett, K.L.; Campbell, P.J., Forster, R., Grandy, N., Huet, M-C, Lewis, G. Oomen, P.A., Schmuck, R. and Vogt, H. 2000."Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods – From the ESCORT 2 workshop"

Barrett. K. L.. Grandy. N.. Harrison. E. G.. Hassan. S..and Oomen. P. (1994). Guidance document on regulatory testing procedures for pesticides with non-target arthropods. Report No: M-001914-01-1. SETAC

Draft Guidance Document on the authorisation of plant protection products for seed treatment 2014 (SANCO/10553/2012 Rev. 1)

Guidance document (GD) for terrestrial ecotoxicology (SANCO/10329/2002)

J Boesten. A Helweg. M Businelli. L. Bergstrom. H Schaefer. A Delmas. R Kloskowski. A Walker. K Travis. L Smeets. R Jones.V Vanderbroeck. A Van Der Linden. S Broerse. M Klein. R Layton. O-S Jacobsen. D Yon. 1997. "Soil persistence models and EU registration - The final report of the work of the Soil Modelling Work group of FOCUS" Available online: http://ec.europa.eu/food/plant/protection/evaluation/guidance/soil_en.pdf

Toxicology and metabolism of the active substance (B.6; human health):

ECHA: Guidance on the application of the CLP criteria; Version 3.0; November 2012 (ECHA-12-G-14-EN)

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

European Commission: Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009; SANCO/10597/2003 –rev. 10.1; 13 July 2012

European Commission: 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

B.7 Residue data

OECD: Guidance document on residues in livestock (ENV/JM/MONO(2013)8)
OECD: Guidance document on the definition of the residue (ENV/JM/MONO(2009)30)
OECD: Guidance document on overview of residue chemistry studies (ENV/JM/MONO(2009)31)
OECD: Guidance document on crop field trials (ENV/JM/MONO(2011)50)
European Commission: Guidance document Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs; SANCO 7525/VI/95 – rev.9, March 2011

5 Reference list

Review Report (beta-cyfluthrin, 6841/VI/97-final, 2 December 2002)

Opinion of the scientific Committee on Plants regarding the inclusion of beta-cyfluthrin in Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market expressed by the Scientific Committee on Plants, 28 January 2000

beta-cyfluthrin (Monograph), 1996