

European Food Safety Authority



Peer Review Report on trinexapac

- Comments on the assessment report
 - Reporting table
- Pesticides peer review meeting reports
 - Evaluation table
- Comments on the additional information assessment
 - Comments on the draft EFSA conclusion

March 2018

TABLE OF CONTENTS

	Document
00	Cover page
01	Comments on the assessment report
02	Reporting table
03	Pesticides peer review meeting reports
04	Evaluation table
05	Comments on the additional information assessment
06	Comments on the draft EFSA conclusion

Comments on the renewal assessment report on substance (AIR III)

RMS LT

End of commenting period: 18.07.2017 (MS; APPL; EFSA)

Date	Supplier	File
12.07.2017	FR	01 Trinexapac-ethyl FR comments on RAR 2017-07-12.doc
17.07.2017	NL	02 Trinexapac-ethyl NL comments on RAR 2017-07-17.zip
17.07.2017	DE	03 Trinexapac-ethyl comments DE RAR 2017-07-17.doc
18.07.2017	NO	06 Trinexapac-ethyl comments NOR RAR 2017-07-18.doc
18.07.2017	LV	07 Trinexapac-ethyl comments LV RAR 2017-07-18.doc
18.07.2017	APPL	08 Trinexapac-ethyl comments Task Force RAR 2017-07-18.doc
18.07.2017	APPL	09 Trinexapac-ethyl Confidential comments Syngenta RAR 2017-07-18.doc
18.07.2017	EFSA	10 Trinexapac-ethyl EFSA comments on RAR 2017-07-18.doc.doc
18.07.2017	EURLs	11 Trinexapac-ethyl comments EURLs RAR 2017-07-18.doc

Comments of France on the assessment report on Trinexapac

(06.07.2017) 1/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Vol4 C.1.2.2 (syngenta)	FR: Please specify and report clearly that old specifications of the first inclusion are not any more covered by new toxicological evaluation. Technical specification of the reference proposed for renewal of the active substance should be covered by batches used in key (eco)toxicity studies.	
	Vol4 C.1.1.2 (Cheminova Helm ADAMA)	FR: please specify if the manufacture process is the same as the first inclusion of the active substance (addendum 2005) or the same as in reports on the equivalence of technical material (Cheminova source1, 2014 – source 2, 2012 Helm source1, 2016 - source 2, 2013 ADAMA Max Rudong 2014 - Huifeng 2011).	
	Vol4 C.1.2.4.2 Method for determination of impurities (Cheminova source1 and 2)	FR: In method VAM 152-01 for the determination of impurities trinexapac acid (REF 346), trinexapac methyl (REF 375) and ac-trinexapac (REF 376) in technical substance and in method VAM 160-01 for the determination of CPCA (CER 374) in technical substance, the range of linearity tested does not contain the LOQ, (see table C.1.2.4-4) please clarify.	
	Vol4 C.1.2.2(Helm/Adama)	FR: Technical specifications proposed for sources should be covered by batches used in key (eco)toxicity studies.	
	Vol4 C.1.2.1.1 (Helm)	FR: The specification set at 2g/kg for impurity trinexapac methyl (M238) at the Jiangsu Huifeng Agrochemicals Co. Ltd. site should be justified, in representative batches this impurity is found	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 2/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		below 0.5 g/kg.	
	Vol4 C.1.2.4.1 (Helm)	FR: In analytical method for the determination of impurities (trinexapac acid [M224], [M238] impurity III [M320] and ethanol) in technical active substance of source 1, the LOQ should be in linearity range. For the validation of accuracy, the number of samples analysed per fortification level should be indicated for each impurity. The number of samples analysed for the repeatability should be indicated.	
	Vol4 C.1.2.4.1 (Helm)	FR in table C.1.2.4.1-1, the name of impurity II [M238] is trinexapac methyl. For more clarity, please reported it	
	Vol4 C.1.2.4.2 (Helm)	FR: the specification proposed for impurity II [M320] in source 2 (0.5%) is not in the linearity range of method, please clarify	
	Vol4 C.1.2.4.3 (Helm) p44	FR: For the validation of method AM110819E-B for the determination of organic impurities, the number of samples at fortification level should be indicated for impurity [M320].	
	Vol4 C.1.1.1 ADAMA	FR: The source from Max (Rudong) Chemical Co Ltd was evaluated in equivalence report by the Neverland, 2014. Please specify if the manufacturer address of Max (Rudong) Chemical is the same as the plant location indicated in the equivalent report. The address of the plant location from source 2 is not exactly the same as the one evaluated in an	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 3/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		equivalence report (France 2011) This point should be clarified.	
	Vol4 C.1 ADAMA	FR: please indicate if the manufacturing process is the same as the one reported in the equivalence report for source 2.	
	Vol4 C.1.2.3.1 ADAMA	FR: analytical profile of batches from source 1 (Max (Rudong)) should be provided. Batches provided in the equivalence report were manufactured in 2010, for more than 5 years. New batches more recent or a quality control data should be provided to demonstrate that batches are still representative of the production. Specification proposed for trinexapac ethyl manufactured by Max (Rudong) should be indicated in this RAR.	
	Vol4 C.1.2.3.2 Adama p14	FR: there are typos errors in the last sentence of this page. Please modify in "Impurity ethanol used in the third step of the manufacture has not been analysed in the technical grade trinexapac-ethyl."	
	Vol4 C.1.2.4.2.2 ADAMA	FR: In analytical method ABCTM -2012-03-04 for the determination of impurity I (trinexapac acid) and method ABCTM-2012-03-03 for the determination of impurity III, the linearity range should include the LOQ (1.5848 mg/L for impurity I and 5.2734 mg/L for impurity III)	
	Vol4 C.1.2.4.2.2 ADAMA	FR: the analytical method used for the analysis of impurity II and validation data should be reported.	

Physical and chemical properties of the active substance

Comments of France on the assessment report on Trinexapac

(06.07.2017) 4/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Vol3 CA B2.1.10 P6 Spectra for active substance in 3 solutions	FR: pH of acidic solution and basic solution used should be indicated FR characteristics of other spectra should be provided: IR, MS and H-NMR spectra	
	Solubility in organic solvents (p7)	FR: A method CIPAC MT 181 should be used, instead of method CIPAC MT 157.3	
	Vol 3CA B2.9-01b flammability	FR: The applicant should determine auto-flammability according to CLP regulation.	
	Vol 3CA B2.11/01 p11	FR: Explosive properties should be performed UN RTDG method, in accordance with CLP regulation.	
	Vol 3CA B.2.13/01b	FR: Oxidising properties should be performed UN RTDG method, in accordance with CLP regulation.	

Physical and chemical properties of the plant protection product			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CP B.2.2/01	FR: Explosive properties should be performed UN RTDG method, in accordance with CLP regulation	
	Vol. 3 CP B.2.3/01	FR: The applicant should determine flash point with UN RTDG method, according to CLP regulation.	
	Vol3 B.2.7 storage stability	FR agrees with RMS, concentrations tested of 0.75% and 0.1% are acceptable for use concentrations at 0.125% to 0.8%.	

Data on application and efficacy

Comments of France on the assessment report on Trinexapac

(06.07.2017) 5/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: No comment	

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: No comment	

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol3CA B5.1.2	FR: Extraction efficiency should be determined for each method in pre-registration.	
	Vol3CA B.5.2.1 Extraction efficiency in method for trinexapac ethyl residues in plant.	FR: In analytical method of Richter S (2015), the validation data of extraction efficiency should be reported in detail (study No 20120098 and study no 20120173). Please report in this part B5 details for the validation of the extraction efficient (in % TRR) from (study No 20120098 and study no 20120173, provided in metabolismes studies.) In study 20120173 (Piskorski R. (2015) (B.7) : Please clarify the composition of solvent used, ratio of acetonitrile and water with hexane should be detailed. There is 67.4% of extractable radioactive residues (with 21.8% of trinexapac acid), please specify if trinexapac acid is in unextracted fraction for the validation of extraction efficiency. In study 20120098 (Piskorski R. (2015a) :	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 6/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		Please clarify the composition of solvent used, ratio of acetonitrile and water should be detailed. There is 64.8% of extractable radioactive residues (with 21.8% of trinexapac acid) in grain or straw, please specify if trinexapac acid is in unextracted fraction for the validation of extraction efficiency.	
	Vol3CA B.5.2.2 Method for trinexapac residues in animal matrices	FR: in study KCA 4.2/04 Richter S., 2015a, extraction efficient should be provided.	
		FR: title of table "Method for products of plants" is not in accordance with point B.5.2.2, about method for products of animals matrices.	
	Vol3CA B.5.2.3 Method for the determination of residues in soil	FR: The residue definition proposed in Trinexapac ethyl and trinexapac (acid) only for monitoring in soil, i.e without esters and its salts. The analytical method GRM020.04A is not in accordance with residue definition of Trinexapac in soil. Samples are heated at reflux in ultra-pure water, there is a hydrolyse step. Sum of trinexapac acid, ester and its salts are determined with this method, expressed as trinexapac acid. It should be precised that this method would overestimate the content of trinexapac	
	Vol3CA B.5.3.2 Methods for the determination of residues in water	FR: The residue definition proposed in Trinexapac ethyl and trinexapac (acid) only for monitoring in water, i.e without esters and its salts. The analytical method GRM020.02A and its ILV for the determination of trinexapac ethyl and trinexapac (acid) in water, is not specific to trinexapac acid	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 7/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		only, it is not in accordance with residue definition of trinexapac ethyl in water. A step of hydrolyse is performed with HCl for analyse trinexapac (acid). This method quantifies trinexapac, its esters and its salts. Please specify that the method determines sum of trinexapac acid, its ester and its salt, expressed as trinexapac (acid). It should be precised that this method would overestimate the content of trinexapac For the determination of trinexapac ethyl, no hydrolyse is performed, the method is specific to trinexapac ethyl	
	Vol3 CA B.5.2.5 Methods for the determination of residues in air	FR: Trinexapac (acid) is includes in residue definition of trinexapac ethyl in air for monitoring, an analytical method should be provided for the determination of trinexapac acid in air.	
	Vol3 CA B.5.4	An analytical method should be provided for the renewal of the active substance for the determination of Trinexapac ethyl residues in body fluid and tissues, according to Reg (EU) 283/2013.	

Other comments			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)		FR: No comment	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 8/185

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: Section not reviewed, no comment	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 9/185

Section 3 – Residue data

3. Residue data

Storage stability of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 B7, B.7.1.1	FR: in the study K-CA 6.1/01, calculations of the % of recoveries in stored samples should be further detailed. Moreover, a detail of minor deficiencies of this study might be welcome. An example might be added to the "footnote *" of the Table B.7.1.1-1.	

Metabolism, distribution and expression of residues in plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol3CA B.7.2.1 metabolism study in spring wheat	FR: In the study 7 (Piskorski R. (2015a)), extractability at 64.8% TRR in straw indicated in RMS comments and conclusion does not correspond to extractable radioactivity specified in table B.7.2.1-11 for straw. Please clarify.	

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)		FR: No comment	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 10/185

Section 3 – Residue data

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1 level2, 2.7.3 LOEP	FR: considering the available metabolism studies the residue definition proposals might be restricted to cereals and oilseeds groups only. Additional metabolites might be included in residue definition in case further uses are intended in the future.	
	Vol. 3 B7, B.7.3 (table B.7.3.2-4) Vol. 1.2.7.3	FR: Calculations of the proposed CF might be further detailed in these sections.	
	Vol. 3 B7, B.7.3.2 (table B.7.3.2-4) LOEP p22	FR: The monitoring RD for plant and also for animal should specify that only "free" trinexapac acid is included to avoid any confusion.	

Residue trials in plants and identification of critical GAP			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 B7, B.7.3.1 barley and B.7.3.2 wheat	FR: In table B.7.3.1-3 and table B.7.3.2-3, CF are proposed to estimate residue level of OH-CGA179500, CGA300405, CGA275537. It is mentioned in the text above "Values in the grey cells are residue levels estimates calculated using trinexapac acid (free) data and conversion factors (refer to Appendix I for details)". Nevertheless no paragraph explaining the CF calculation was found.	
	Vol. 3 B7, B.7.3.1 barley and B.7.3.2 wheat	FR: in table B.7.3.1-3 and table B.7.3.2-3, it was noticed that for some residue trials the residue level measured for CGA179500 (free) were above the	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 11/185

Section 3 – Residue data

Residue trials in plants and identification of critical GAP			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		residue level measured for CGA179500 (free and conjugated). As this case is not consistent, a justification (regarding sample or analytical method) will be welcome.	
	LOEP p22 and p31	FR: the CF mentioned for grain and straw to convert residue level from monitoring RD to Risk RD seem overestimated compared to the estimated CF proposed in Vol. 3 B7, B.7.3.1 barley and B.7.3.2 wheat table B.7.3.1-3 and table B.7.3.2-3. The detail of the proposal CF value should be added.	

Feeding studies in poultry, ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.1 2.7.5 (Table 2.7.5-1 Table 2.7.5-2) and LoEP p28 and LoEP p29	FR: in the tables presenting "Inputs for animal burden calculations", please add the residue definition used for DB calculation (plant RA: Sum of CGA179500 (free & conj.) and OH-CGA179500). in the tables "Residues from livestock feeding studies", please added the residue definition (animal RA: CGA179500 (<u>free</u>)).	

Effects of processing			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Comments of France on the assessment report on Trinexapac

(06.07.2017) 12/185

Section 3 – Residue data

Effects of processing			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
	LOEP p22 and p32	FR: in Vol.1 is stated that the RD for processed commodities is in line with the RD for raw commodities. So it is concluded that no specific RD is proposed for processed commodities. This information should clearly be mentioned in LOEP (p22 and p32).	

Residues in rotational crops			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		FR: No comment	

Summary of other studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: No comment	-

Estimation of the potential and actual exposure through diet and other sources			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
	Vol.1 2.7.5 (Table 2.7.10-1)	FR: in the tables, please add the residue definition considered.	

Proposed MRLs and compliance with existing MRLs

Comments of France on the assessment report on Trinexapac

(06.07.2017) 13/185

Section 3 – Residue data

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol.1 2.7.5 (Table 2.7.10-1) LOEP p34	FR: in the tables, please add the residue definition considered.	

Proposed import tolerances and compliance with existing import tolerances

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: No comment	

Other comments

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: No comment	

Comments of France on the assessment report on Trinexapac

(06.07.2017) 14/185

Section 4 - Environmental fate and behaviour

4. Environmental fate and behaviour

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: Section not reviewed, no comment	

Section 5 - Ecotoxicology

5. Ecotoxicology

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		FR: Section not reviewed, no comment	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl (17-07-2017)

16/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
-	-	NL: No comments	

Physical and chemical properties of the active substance			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, Physical and chemical properties of the active substance, p. 4-12, general comment.	NL: Please state if the provided studies were accepted or not accepted by the reviewer, this is however no always clear.	

Physical and chemical properties of the plant protection product			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CP, Shelf life following storage at ambient temperature B.2.7/03, p.10.	NL: If the decrease of the active substance after storage > 5% (compared to the initial content), information on degradation products (or a sufficient justification by the applicant) should be provided. It is not sufficient to compare the after storage results with a different stored sample.	

Data on application and efficacy			

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl (17-07-2017)

17/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
-	-	NL: No comments	

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3 CA, B.5.1.1 Methods for the analysis of the relevant impurities as manufactured, p.5.	NL: No section for the analytical methods for the determination of the relevant impurities in trinexapac-ethyl technical, or information on the absence of these analytical methods or reference to the confidential part Vol. 4. have been provided. Please include this information under B.5.1.1.	
(2)	Vol. 3 CA, KCA 4.1.2/03a-b, KCA 4.1.2/04a, KCA 4.1.2/05a-b, KCA 4.1.2/06a-c, p.23-34.	NL: Please specify in the conclusion by the reviewer the guidance document to which the analytical methods are fully validated, SANCO/3029/99 rev. 4 and/or SANCO/825/00 rev. 8.1.	
(3)	Vol. 3 CA, KCA 4.1.2/07-08, p.36-40.	NL: The criteria of SANCO/3029/99 rev.4 are not met, however it is unclear if the reviewer accept or does not accept the analytical methods, please clarify.	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl (17-07-2017)
18/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(4)	Vol. 3 CA, KCA 4.1.2/091-10, p.40-44	NL: Please indicate if the analytical methods are complaint with SANCO/3029/99 rev. 4 and/or SANCO/825/00 erv. 8.1 and are accepted or not accepted by the reviewer, based on the provided information.	
(5)	Vol. 3 CA, KCA 4.1.2/13-14, p.49-54	NL: Please indicate if the analytical methods are accepted or not accepted by the reviewer and are complaint with SANCO/3029/99 rev. 4 and/or SANCO/825/00 erv. 8.1.	
(6)	Vol. 3 CA, KCA 7.1.2.1/01, p.63-65	NL: Please indicate if the analytical method was accepted and is validated in compliance with SANCO/3029/99 rev. 4 or fit for the intended purpose, this is not clear from the comments/conclusions made by the reviewer.	
(7)	Vol. 3 CA, KCA 4.2/19, p.124-126	NL: Please indicate if the analytical method was fully validated according SANCO/825/00 rev. 8.1 and or SANCO/3029/99 rev. 4.	

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
-	-	NL: No comments	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 19/185

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, in vitro metabolism	NL: we agree with the data requirement set in Volume 1 level 3 for an in vitro metabolism study.	

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, B.6.2.4, skin irritation	NL: we agree with the RMS that no further studies are needed on skin irritation. This is line with the current data requirements which state that when no skin irritation was observed in the acute dermal toxicity at the limit dose of 2000 mg/kg bw than this shall be used to waive the need for any dermal irritation study.	

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, B.6.4.1	NL: it would be informative to have detailed results table on the results from the in vitro genotoxicity studies in the RAR.	
(2)	Vol 3 CA, B.6.4.2	NL: Although it has not been definitively shown that the bone marrow was reached we agree with the RMS that based on the ADME studies it is likely that bone marrow was reached.	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 20/185

Section 2 – Effects on human and animal health

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, B.6.5.1, combined chronic toxicity and carcinogenicity in rats	NL: Regarding the squamous cell carcinoma we do not agree with the argument that this finding has little if any biological relevance to humans. The CLP guidance states that while humans do not have forestomach, they do have comparable squamous epithelial tissue in the oral cavity and the upper two-thirds of the oesophagus and that it cannot be ruled out that the substance could cause similar tumours of comparable cell/tissue origin. However, considering the low incidence and the lack of related non-neoplastic findings we do agree that the squamous cell carcinoma can be regarded as incidental.	

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 3 CA, B.6.8.3 Studies on endocrine disruption	NL: Could the RMS provide a more detailed summary of the Böhmler et al. 2006 study.	
(2)	Vol 3 CA, B.6.8.3 Studies on endocrine disruption	NL: Based on the available information it does seem likely that the effects on uterus weight in the 1-year dog study are due to differences in oestrus cycle stage between the dose groups and not by a specific endocrine effect. However, the ToxCast data should be submitted to support this. We therefore agree with the RMS that further clarification is needed.	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 21/185

Section 2 – Effects on human and animal health

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, B.6.8.1.4.3 study 4, in vivo micronucleus	NL: Pending the outcome of validation of the analytic method used, relatively high values of metabolite CGA329773 were found in the plasma (172-245 µg/ml). Considering that bone marrow is highly perfused we do consider it likely that the bone marrow was reached.	
(2)	Vol. 3 CA, B.6.8.1.5 Hydroxylated CGA179500	NL: CGA179500 was considered to be covered by the parent based on the rat metabolism study. Could a similar conclusion be drawn for hydroxylated-CGA179500 based on structural similarity to CGA179500.	

Toxicological end points: ADI, ARfD, AOEL			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, 2.6.11-2.6.13, reference values	NL: the references values proposed by the RMS are supported.	

Product exposure and risk assessment, including dermal absorption			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CP, B.6.4.2.1 bystander exposure	NL: Although it is recognized that there is no EU agreement on which drift values to use for bystander and resident exposure we would prefer a first tier assessment with the German model	

Comments of The Netherlands on the CA and CP assessment report on trinexpac-ethyl(17-07-2017) 22/185

Section 2 – Effects on human and animal health

Product exposure and risk assessment, including dermal absorption			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		applying the drift values for 1 m distance (2.77%) instead of the currently used 10 m (0.29%).	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 23/185

Section 3 – Residue data

3. Residue data

Residue trials in plants and identification of critical GAP			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 3, B.7.3	NL: conversion factors should not be derived from metabolism studies, but from supervised residue trials. A reference is made to Appendix I, but Appendix I contains the literature search and no information on conversion factors.	
	Vol. 3, table 7.3.1-3 and 7.3.2-3	NL: the levels of relevant metabolites from supervised residue trials should not be calculated/estimated using conversion factors.	
	Vol 3, B.7.3.2, study 3	NL: although recoveries in grain for the analytical method used are within the limits reported in the guideline, they are overall low (62-85%), possibly resulting in an underestimation of residue levels in grain.	

Other comments			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B7, paragraph 5	NL: it is reported in the text that the literature search is provided in Appendix III, but in reality this is Appendix I.	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 24/185

Section 4 - Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, 8.1.2.1.1 Aerobic degradation of the active substance	NL: In Table 8.1.2.1.1-5 (page 75), should SFO be considered acceptable for trinexapac acid ?	
(2)	Vol. 3 CA, 8.1.2.1.1 Aerobic degradation of the active substance	NL: In Table 8.1.2.1.1-8 (page 77), the results of DFOP fitting for trinexepac-ethyl can be removed since FOMC is rejected and SFO is acceptable.	
(3)	Vol. 3 CA, 8.1	NL: as a general comment, it is noted that no acidic soil has been selected in the degradation test. Is the soil selection criterion in accordance with the relevant recommendations in OECD 307?	

Adsorption, desorption and mobility in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)		NL: no comments	

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)		NL: no comments	

Fate and behaviour in air			

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 25/185

Section 4 - Environmental fate and behaviour

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		NL: no comments	

PEC in soil

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		NL: no comments	

PEC in surface water and ground water

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		NL: no comments	

PEC from airborne transport and other routes of exposure

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		NL: no comments	

Definition of the residues

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		NL: no comments	

Other comments incl. available monitoring data

Comments of The Netherlands on the CA and CP assessment report on trinexpac-ethyl(17-07-2017) 26/185

Section 4 - Environmental fate and behaviour

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		NL: no comments	

Comments of The Netherlands on the CA and CP assessment report on trinexpac-ethyl(17-07-2017) 27/185

Section 5 - Ecotoxicology

5. Ecotoxicology

Regulation (EC) No 1107/2009 requires a search of the scientific peer-reviewed open literature

Birds and other terrestrial vertebrates			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.9 CA, CA 8.2.1/05, p. 38.	NL: Why 60 mg/L has been chosen as an endpoint? Low effects on survival were observed at 80 and 130 mg/L. In addition, the symbol "<" next to the endpoint seems not to belong there.	
(2)	Vol. 3, B.9 CA, CA 8.2.6/01, p. 96.	NL: <i>A. flos-aquae</i> does not belong to the group of green algae, please amend (conclusion part).	

Bees and non-target arthropods			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 28/185

Section 5 - Ecotoxicology

Earthworms and other non-target soil macro- and mesofauna			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Soil nitrogen transformation			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Terrestrial non-target higher plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Other non-target terrestrial organisms (flora and fauna)			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Biological methods for sewage treatment			

Comments of The Netherlands on the CA and CP assessment report on trinexepac-ethyl(17-07-2017) 29/185

Section 5 - Ecotoxicology

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	NL: no comments.	

Comments of The Netherlands on Vol. 4 (ADAMA) on trinexepac-ethyl

(17-07-2017) 30/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 4, Information on the source 1 (general), different annex points.	NL: For completeness purposes it would be helpful if the results/data and or conclusions made in the equivalence report of the source 1 Max (Rudong) Chemicals Co. Ltd. would be (briefly) summarized under the different annex point in the confidential part volume 4.	
(2)	Vol. 4, C.1.2.4.2.2. Methods for determination of impurities in the technical active substance, p. 23-25 (method ABCTM-2012-03-03).	NL: It is unclear if the analytical method ABCTM-2012-03-03 is used for the determination of impurity II, III or both. Principle of the method is for impurity III, however the analytical method for the determination is used for impurity II, validation is for impurity III, conclusion is for impurity I and II. Please clarify.	

Comments of The Netherlands on Vol. 4 (CHEMINOVA SOURCE 1) on trinexapac-ethyl (17-07-2017) 31/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 4, C.1.2.3.1. Information on five batch analysis of technical trinexapac-ethyl, p. 18.	NL: It is unclear what the trinexapac-methyl results within brackets are, those results are lower than the LOQ. Additionally, the LOQ of trinexapac-ethyl is 0.14%, which higher than the set criteria of 0.1% for significant impurities. Therefore, it is not shown that trinexapac-methyl is not present below 0.1%, and therefore trinexapac-methyl should be set in the proposed specification as 0.1% (or 1 g/kg). Although the measured results are all < 0.1% (or 1 g/kg), these results are below LOQ and therefore not in the validated range of the method and not reliable.	

Comments of The Netherlands on Vol. 4 (CHEMINOVA SOURCE 2) on trinexepac-ethyl (17-07-2017) 32/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 4, C.1.2.3.1. Information on batch analysis of technical trinexapac-ethyl, conclusion p. 18.	NL: The minimum purity of the active substance trinexapac-ethyl, based on the 5-batch analysis and QC-data 2014-2015, should be set at a higher purity (e.g. 965 g/kg), and therefore the proposed specification by the applicant should be adjusted by the RMS. This was also concluded by the reviewer ('it would seem reasonable to slightly increase the minimum purity of the active substance specified in compliance to the analysis results'), however the proposed specification was not adjusted. Please clarify why this was not changed.	

Comments of The Netherlands on Vol. 4 (HELM) on trinexapac-ethyl

(17-07-2017) 33/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 4, C.1.2.3.1. Information on five batch analysis results of technical trinexapac-ethyl (source 1), p.20. + P.26	NL: The specification of the reference source of impurity III [M320] is set at 20 g/kg, however according to the table C.1.2.3.1-2: Comparison of source 1 trinexapac-ethyl specification to the EU approval active substance on p.22-23 + P.30-31, this impurity was not present, please explain.	

Comments of The Netherlands on Vol. 4 (Syngenta) on trinexepac-ethyl

(17-07-2017) 34/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 4, Table C.1.2.3-6 : Comparison of trinexapac-ethyl of Monthey source specifications (Annex I inclusion, provisional specification and the new reference specification), p.33-34.	NL: Agree with the new reference specification of the source.	

Comments of Germany on the assessment report on trinexapac

(17.07.17) 35/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B.5.2, extraction efficiency of monitoring method in plants	DE: The statements on extraction efficiency in plant material are a little bit too general. The extraction procedure of QuEChERS method (homogenisation with acetone/trile/water (1/1, v/v) containing 1 % acetic acid) seems to be not completely comparable to the different extraction procedure used in metabolism studies. It should be at least stated, which amount of trinexapac is extracted after initial extraction. We would also appreciate a justification for adding acetic acid to the extraction solvent.	
(2)	Vol. 1, 5.2.5, Vol. 1, 2.13.2 and list of endpoints, residue definition for monitoring purposes	DE: In different parts of the RAR different residue definitions for monitoring in air are given. In Vol. 1, 2.13.2 trinexapac acid is also included whereas in the list of endpoints the parent compound is mentioned only. Please check and harmonise the residue definition.	

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.1.1, p. 5	DE: Data gap: The <i>in vitro</i> metabolism study has not been conducted.	

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.3.1.1, p. 27 Oral 28-day study in rats	DE: Exposure to all tested doses of trinexapac-ethyl resulted in a statistically significant dose-related effect on liver weight (up to 75 %). It is stated that this effect is due to higher glycogen content in the livers in response to differences in feeding conditions between the control and treated groups. Could you please give more detail what are the differences in the diet?	
(2)	Vol. 3, B.6.3.2.1, p. 30 Oral 90-day study in rats	DE: The cumulative body weight gain in females was decreased (11.1 %) at the highest dose (20000 ppm). At this dose also a significant increase in the relative pituitary weight (33.3 %) and kidney weight (13.2 %) was detected. Furthermore a strong increase in neutrophils could be observed for females in the two highest dose groups (93 % and 66.9 %); is there any explanation for these haematologic findings? Due to the observed effects on organ weights, 20000 ppm should be regarded as LOAEL rather than NOAEL in females.	

Section 2 – Effects on human and animal health

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(3)	Vol. 3, B.6.3.2.3, p. 46 ff Oral 1-year study in dogs	DE: A significant reduction of absolute and relative uterus weight was observed at 1000, 10000 and 20000 ppm. Concurrently it could be observed that in these dose groups more or all females were in the middle/late metoestrus cycle. Historical control data for the uterus weight was not available. The explanation of synchronisation of oestrus cycle stages of females in the highest dose groups due to housing conditions is not sufficient as this should also affect the control group. Even though the data on oestrus cycle might explain the alterations in uterus weight, it cannot be excluded that the alterations in oestrus cycle are substance related. In addition a significant decrease of testes weight could be observed at dose levels 1000, 10000 and 20000 ppm and the weight of ovary was also reduced at these dose levels. Altogether these effects are considered as adverse. Due to the effects seen in on the uterus, ovary and testes weight as well as on the oestrus cycle DE is of the opinion that the dose of 31.6 mg/kg bw/d should be regarded as a LOAEL and the dose of 1.4 mg/kg bw/d as NOAEL This should be taken into account for the establishment of the ADI.	

Comments of Germany on the assessment report on trinexapac

(17.07.17) 38/185

Section 2 – Effects on human and animal health

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.8.3, p. 51	DE: DE supports the opinion of the RMS that in the absence of further data on the effect of trinexapac-ethyl on the oestrus cycle and weight of reproductive organs an endocrine disrupting potential cannot be excluded. Further data are needed (e.g. suitable studies from the OECD Endocrine Disruptor Screening Program).	

Toxicological end points: ADI, ARfD, AOEL			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.11, p. 67, Vol. 3, B.6.3.2.3, p. 46 ff	DE: Because of the effects seen in the 1 year dog study it is proposed to regard 31.6 mg/kg bw/d as a LOAEL and the dose of 1.4 mg/kg bw/d as NOAEL ADI = NOAEL / SF = 1.4/100 = 0.014 mg/kg bw/d	
(2)	Vol. 1, 2.6.13, p. 68	DE: The AOEL proposed by the RMS is supported	

Product exposure and risk assessment, including dermal absorption			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.4.3, Worker exposure	DE: Worker exposure is acceptable even without workwear using a TC value of 12500 cm ² /h according to EFSA guidance. This information should be added to the results.	

Section 3 – Residue data

3. Residue data

Metabolism, distribution and expression of residues in plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.2, spring wheat metabolism Table B.7.2.1-4, p. 29	DE: It is not clear to us what is the amount of conjugates included in the residue fraction of CGA179500 (and others).	
(2)	Vol. 3, B.7.2, rice metabolism Table B.7.2.1-5, p. 34	DE: It is not clear to us what is the amount of conjugates included in the residue fraction of CGA179500 (and others).	
(3)	Vol. 3, B.7.2, grass metabolism Table B.7.2.1-7, p. 39	DE: It is not clear to us what is the amount of conjugates included in the residue fraction of CGA179500 (and others).	
(4)	Vol. 3, B.7.2, grass metabolism	DE: The sentence " <i>Considering that amenity grass is not intended for livestock feeding, no intake of CGA 165935 residues via amenity grass by livestock is anticipated</i> " should be deleted, as grass is representative for cereals.	

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.7.3, p. 77 residue definition	DE: It is written by RMS that the residue definition for plants (monitoring and risk assessment) was changed during the review of Art. 12 assessment in 2012. Please note that the original proposal in EFSA Scientific Report (2005) 57, 1– 70 was already " <i>Trinexapac and its salts in food of plant</i>	

Section 3 – Residue data

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		<i>(cereals, only)</i> '. Only in the LoE the simplified wording " <i>Trinexapac</i> (CGA 179500)" is used.	
(2)	Vol. 1, 2.7.3, p. 77 residue definition	DE: As residue definition for monitoring we would prefer the wording " <i>Sum of trinexapac acid and its salts, expressed as trinexapac acid</i> ". The residue analytical method does not discriminate, so results obtained cover the acid plus their salts.	
(3)	Vol. 1, 2.7.3, p. 77 residue definition for risk assessment	DE: We agree to the approach of the RMS to consider on a tentative basis the hydroxylated acid by a conversion factor in absence of definitive structural elucidation and synthesis of 1-OH reference material and to consider toxicological expert judgement for risk assessment. Indicative residue trials might give confirmation on the proposed quantitative non-relevance.	

Section 4 - Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, CP, B.8.1.2.1.1, Aerobic degradation, KCA 7.1.2.1.1/01 KCA 7.1.2.1.1/02 KCA 7.1.2.1.2/02 Vol. 3, 8.2.2.3 Water/sediment studies, KCA 7.2.2.3/02	DE: The t-test or confidence intervals should not be applied to alpha or beta values of a FOMC fit.	FOCUS Deg. Kin.: <i>"Note that this application of the t-test, while applicable for rate constants, may not be appropriate for all model parameters. For example, with FOMC smaller values of beta indicate more rapid degradation, and alpha only indicates the shape of the curve and has nothing to do with the rate of degradation."</i> Recently, the application of the t-test has also been criticised for other kinetics. See Ranke & Lehmann (2015) (poster on conference in Piacenza; link: chem.uft.uni-bremen.de/ranke/posters/piacenza_2015.pdf)
(2)	Vol. 3, CP, B.8.1.1.3, Soil photolysis, KCA 7.1.1.3/02	DE: We support the classification by the RMS, that CGA275537 and CGA300405 are relevant photolysis transformation products according to the data in Adam (2015).	Both under dry and moist conditions, CGA275537 had lower occurrences in the dark control (max. 2.6 % and 0.8 %, respectively) than under irradiated conditions (max. 10.8 % and 6.5 %, respectively). Hence, CGA275537 can be regarded as a relevant photolysis transformation product. Under dry conditions, CGA300405 had lower occurrences in the dark control (max. 1.2 %) than under irradiated conditions (max. 12.5 %). Hence, CGA300405 can be regarded as a relevant photolysis transformation product. Under moist conditions, CGA300405 had low occurrences both in the dark control (max. 1.5 %) and under irradiated conditions (1.5 %). This might be due to biodegradation of CGA300405 under moist conditions.

Comments of Germany on the assessment report on trinexapac

(17.07.17) 42/185

Section 4 - Environmental fate and behaviour

Adsorption, desorption and mobility in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, CP, B.8.1.2.2.2, Adsorption and desorption of the active substance, KCA 7.1.3.1.1/01	DE: In the previous DAR (2003) it was concluded that sorption is pH dependent. The evaluation with the statistical Kendall Test of the German "Input Decision 3.4" did not confirm this conclusion, maybe due to the small number of data. On the other hand the diagrams of Input Decision suggest that sorption is slightly pH dependent.	Further adsorption studies with soil pH >7 were required by EFSA in 2003 already. Since such studies are still lacking, EFSA recommends to use the worst case K _{foc} values from the soil pH>7 as modelling endpoints for trinexapac-ethyl and trinexapac (See EFSA Scientific report 82005) 57, 1-70). PEC groundwater modelling is required with K _{foc} values for acidic and alkaline soils, due to pH dependence. However, therefore further adsorption studies with soil pH>7 are required.

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, CA, B.8.1.4, Estimation of concentrations in groundwater, KCP 9.1.4/01	DE: It was concluded that the sorption is pH dependent. If this is the case PEC groundwater modelling is required with K _{foc} values for acidic and alkaline soils.	Due to the small number of values, using minimum K _{foc} as it represents a worst-case is useful. Nevertheless further adsorption studies with soil pH >7 were required by EFSA in 2003 already.
(2)	Vol. 3, CA, B.8.1.4, Estimation of concentrations in groundwater, KCP 9.1.4/02	DE: We appreciate the consideration of photodegradates in the groundwater assessment in Bramley (2016).	FOCUS-PELMO 5.5.3 can simulate both the biodegradation and the photodegradation of an active substance, along with its metabolites and photodegradates. This is an optional higher tier 2. However, it is important to know that the tiered approach (PEC _{gw,tier1} > PEC _{gw,tier2}), in comparison to the lower tier 1 presented here, is only guaranteed, if in the lower tier a maximum occurrence of 100 % is used. As all concentrations in Bramley (2016) are < 0.001 µg/L, it can be safely assumed, that also maximum occurrences of 100 % would give concentrations < 0.1 µg/L.

Section 5 - Ecotoxicology

5. Ecotoxicology

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 CA, B.9.2, Effect on aquatic organisms	DE: KCA 8.2.4.1/01 The acute toxicity study for aquatic invertebrates by Smith et al. (1990) is considered to be not valid because up to 467 mg acetone/L have been added as solvent. However, this endpoint is not driving the risk for aquatic organisms.	
(2)	Vol. 3 CA, B.9.2, Effect on aquatic organisms	DE: The study on toxicity for algae (<i>Anabaena-flos-aquae</i>) caused by trinexapac (acid) by Grade (2001b; KCA 8.2.6.2/04) with an $ErC_{50} = 17.5$ mg a.s./L is classified as "not valid", because no exponential growth could be observed. The control group has a lag phase of 24h. In addition, biomass has been determined by fluorescence, the evaluation in this case is not plausible as the test substance seems to have great influence on fluorescence. In the highest test-concentrations fluorescence is in almost all measurements smaller than fluorescence of control medium. A discussion of these findings was not conducted. In this case an inappropriate method for determination of algae biomass has been used.	
(3)	Vol. 3 CA, B.9.2, Effect on aquatic organisms	DE: The study by Hoberg (1992, CGA163935/279) on the toxicity for <i>Lemna</i> which has also been evaluated in the DAR reports a NOEC (14 d) of 0.018 mg a.i./L and an EC_{50} (14 d) of 0.19 mg a.i./L.	

Section 5 - Ecotoxicology

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		However, the toxicity of trinexapax-ethyl towards <i>Lemna gibba</i> does not drive the risk for aquatic organisms as fishes as well as aquatic invertebrates are more sensitive towards the active substance. Also, there is another endpoint (EyC ₅₀ = 0.2 mg a.s./L <i>Myriophyllum spicatum</i>) for the risk assessment of aquatic higher plants.	
(4)	Vol. 3 CA, B.9.2, Effect on aquatic organisms, Table B.9.2-1 to Table B.9.2-3:	DE: Chronic endpoints: EC ₁₀ and EC ₂₀ values have been calculated. Please provide all chronic endpoints (NOEC, EC ₁₀ and EC ₂₀ values) and also a reasoning for the chronic endpoint to be used in risk assessment (NOEC or EC ₁₀).	
(5)	Vol. 3 CA, B.9.2, Effect on aquatic organisms, Table B.9.2-1 to Table B.9.2-3:	DE: There is a typo in this table since for the study of Hoberg (1992), CGA163935/279 the endpoint is stated as 14 d EC ₅₀ 8-0.19 mg a.s./L. Please correct.	
(6)	Vol. 3 CP, B.9.3, Effect on aquatic organisms	DE: Study evaluation K-CP 10.2.1/04 Brown, R. J. & Maynard, S. J., (2003): Please correct the endpoints for <i>Lemna gibba</i> given in the RMS's conclusion. Based on frond number: (7 d ErC ₅₀ = 45 mg A8587F/L. This is the lowest endpoint. Please include this endpoint in the study evaluation and subsequent compilations referring to this study in the other documents. Based on growth rate (7 d ErC ₅₀ >100 mg A8587F/L; corresponding to >27.1 mg a.s./L) Based on biomass (7 d EbC ₅₀ = 85.2 mg	

Section 5 - Ecotoxicology

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		A8587F/L; corresponding to 23.1 mg a.s./L).	

Bees and non-target arthropods			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 (CA), B.9.3.1.1, acute toxicity to adult honeybees, page 179, table B 9.3.1.1-1	DE: According to the header of the second column in table B.9.3.1.1-1 the presented acute oral and contact LD ₅₀ values (> 200 µg a.s./bee) were taken from the EFSA Scientific Report (2005). However, these values were used for the risk assessment in the previous DAR (Netherlands, 2003) but not presented in the cited EFSA document.	
(2)	Vol. 3 (CP), B.9.6.1., Risk assessment for honeybees, page 96, Acute Risk Assessment	DE: The acute endpoints derived from the study by Jeker (2008) (oral LD ₅₀ = >83 µg a.s./bee, oral LD ₅₀ = >100 µg a.s./bee) indicate that the specific endpoints are set above 83 and 100 µg a.s./bee. This is confirmed by the results of the acute study by Barth (2000) with oral and contact LD ₅₀ values of >200 µg a.s./bee and the acute study by Schmitzer et al. (2008) with an oral LD ₅₀ of >216 µg a.s./bee and a contact LD ₅₀ of >200 µg a.s./bee. Please explain why the acute endpoints derived from the study by Jeker (2008) instead of the acute endpoints from the study by Barth (2000) or by Schmitzer et al. (2008) were used in the risk assessment.	

Comments of Germany on the assessment report on trinexapac

(17.07.17) 46/185

Section 5 - Ecotoxicology

Bees and non-target arthropods			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(3)	Vol. 3 (CP), B.9.6.1., Risk assessment for honeybees, page 97, Larval assessment	DE: It should be noted that the chronic larval study had a duration of 8 days and the actual exposure took place from day 3 (first application of the test substance) until day 8 (end of study). This sums up to a duration of 6 days, which should be considered for the calculation of the larval TER.	
(4)	LoEP, Effects on other arthropod species, Extended laboratory tests, aged residue tests	DE: Please indicate substrate used in the tests 3 rd column).	

Section 3 – Residue data

3. Residue data

Storage stability of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.1.1, Stability of residues in plants and plant products, Study 1	NO: Please include a column in Table B.7.1.1-1 for "Residue level in freezer storage stability sample (% of nominal spiking level, <u>uncorrected</u>)".	According to OECD TG 506, results should be presented in mg/kg and % of nominal spike value without being corrected by procedural recovery.
(2)	Vol. 3, B.7.1.1, Stability of residues in plants and plant products, Study 1	NO: The residue level in wheat straw samples at 24 months is 62% of nominal spiking level (uncorrected), whereas the procedural recovery for freshly spiked control samples is 92%. Therefore, residues of trinexapac acid (CGA 179500) in wheat straw are considered stable up to 12 months.	
(3)	Vol. 3, B.7.1.2, Stability of residues in animal products, Study 1	NO: The values for milk and blood samples in the column "Residue level in freezer storage stability sample (mg/kg)*" in Table B.7.1.2-1 seem incorrect.	
(4)	Vol. 3, B.7.1.2, Stability of residues in animal products, Study 1	NO: In the conclusion on Page 11, the RMS writes: <i>The average recovery is below the 70 % (67 %), the range of measurements is around 70%.</i> It is difficult to find this information in the table and we are not sure what is meant by this sentence.	
(5)	Vol. 3, B.7.1 Storage stability of residues prior to analysis, Table B.7.1.2-2	NO: Please consider to change the value for the maximum storage period for wheat straw to 18 months.	

Metabolism, distribution and expression of residues in plants

Comments of Norway on the assessment report on Trinexapac-ethyl

(18/07/17) 48/185

Section 3 – Residue data

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B.7.2.1 Plants	NO: Footnotes for Table 7.2.1.-1 seem to be missing.	

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B7.2.2.1 Poultry / LoEP, Metabolism in livestock	NO: Proposed time needed to reach a plateau concentration in eggs is 2-8 days (LoEP). However, it has been shown that a maximum concentration level was reached at different time point (3-10 days) in each animal (see Table B.7.2.2.1-6). It is therefore difficult to establish a plateau concentration from the available studies.	

Comments of coRMS on the assessment report on trinexapac dRAR

49/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Volume 4, Annex C C.1.2.3. Analytical profile of batches p.31	LV: Section not reviewed, no comments	

Physical and chemical properties of the active substance			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Physical and chemical properties of the plant protection product			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Data on application and efficacy			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Comments of coRMS on the assessment report on trinexapac dRAR

50/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		LV: Section not reviewed, no comments	

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	(LV) No comments	

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	(LV) No comments	

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3; B.6.3.2.1 Oral 90-day study in rats	(LV) Considering effects seen in cumulative body weight gain (11.1 %), kidney weight (13.2 %) and significantly increased relative pituitary weight (33.3%) at 20000 ppm, NOAEL for females should be set at 5000 ppm and 20000 ppm should be considered as LOAEL respectively.	
(2)	Vol. 3, B.6.3.2.3 Vol. 3, B.6.3.2.3	(LV): A significant reduction of absolute and relative uterus weight was seen in mid-doses and at the highest dose. HCD for the uterus weight is not available. The explanation of synchronisation of oestrus cycle stages of females in the highest dose groups due to housing conditions is not	

Comments of coRMS on the assessment report on trinexapac RAR

(18.07.2017) 52/185

Section 2 – Effects on human and animal health

Short-term toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		sufficient. It cannot be ruled out that alterations in oestrus cycle are substance related. Overall these effects should be considered as treatment related and should be taken into account for ADI setting. Overall LV is on the opinion that for this study NOAEL should be set as 40 ppm (1.4 mg/kg bw/d) based on effects seen on uterus and ovary.	

Genotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3 B6, B.6.4.1	LV: In vitro genotoxicity. In order to permit an independent review of the assessment robust data should be provided, for some in vitro studies only conclusions are reported.	

Long-term toxicity and carcinogenicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3 B6, description>>	(LV): No comments	

Comments of coRMS on the assessment report on trinexapac RAR

(18.07.2017) 53/185

Section 2 – Effects on human and animal health

Reproductive toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	(LV): No comments	

Neurotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	(LV): No comments	

Further toxicological studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol 3 CA; B.6.8.3 Studies on endocrine disruption	Agree with the RMS that further investigation is needed (at least Tox Cast data further and further investigation according OECD framework)	

Toxicological data on metabolites			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)			

Medical data and information			

Comments of coRMS on the assessment report on trinexapac RAR

(18.07.2017) 54/185

Section 2 – Effects on human and animal health

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	(LV) No comments	

Toxicological end points: ADI, ARfD, AOEL

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 1 P 2.6.11	Taking into account effects seen in the 1 yr dog study it is proposed to derive ADI from NOAEL of 40 ppm (1.4 mg/kg bw/d). Overall ADI of 0.014 mg/kg is proposed AOEL supported. Information on AAOEL is missing.	

Product exposure and risk assessment, including dermal absorption

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	(LV): No comments	

Other comments, incl comments on volume 4 (impurities, batches) and proposals for classification

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	(LV): No comments	

Section 3 – Residues data

3. Residue data

Storage stability of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comments	

Metabolism, distribution and expression of residues in plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.2.1, study by Krauss J.H. (1993), page 24	Co-RMS (LV): In the test system (25 page) there are additional stem injection and <i>in vitro</i> incubation experiments described for elucidation of the metabolic pathways. Results of these additional experiments isn't mentioned at all. Are they available?	

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comments	

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Comments of coRMS on the assessment report on trinexapac RAR

(18.07.2017) 56/185

Section 3 – Residues data

Residue definition			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B7, Residue definition for plants and processed commodities; LoEP	Co-RMS (LV): No comments	

Residue trials in plants and identification of critical GAP			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comment	

Feeding studies in poultry, ruminants, pigs and fish			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comments	

Effects of processing			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B.7.5.1, study by Scullion (2012), page 163	Co-RMS (LV): According to OECD 507 "The same labelling positions as in the available metabolism studies are preferable and should be used." This time radiolabel position was different. Could you,	

Comments of coRMS on the assessment report on trinexapac RAR

(18.07.2017) 57/185

Section 3 – Residues data

Effects of processing			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		please, explain how these divergences influence the significance of this study compared to other high temperature hydrolysis studies? Especially, because metabolite CGA224439 is identified only in this study, maybe CGA224439 could be major metabolite also in plant metabolism if used radiolabel position has been as in this study?	
(2)	Vol. 3, B.7.5.1, study by Scullion (2012), page 169	Co-RMS (LV): There's a small typo for parent concentration (mg/L) in Table B.7.5.1-5 on pH 4 (90°C) column. (0.087 mg/L instead of 0.87 mg/L)	
(3)	Vol. 3, B.7.5.3, study by Mayer T. (2010a), page 203	Co-RMS (LV): No comments	

Residues in rotational crops			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.6.1, study by Quistad G.B., Kovatchev A. (2010), page 230	CO-RMS: In results section it's stated: " <i>Total residues determined by initial combustion and sum of fractions in rotational crop RACs are given in Table A3.12-2</i> ". Table A3.12.-2 doesn't exist. In the same paragraph, fourth line, please correct "Tables B.7.6.1-3 to B.7.6.1-x" to "Tables B.7.6.1-3 to B.7.6.1-5".	

Summary of other studies

Comments of coRMS on the assessment report on trinexapac RAR

(18.07.2017) 58/185

Section 3 – Residues data

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comments	

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

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comments	

Proposed MRLs and compliance with existing MRLs

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	LoEP	Co-RMS (LV): No comments	

Proposed import tolerances and compliance with existing import tolerances

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comments	

Other comments

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of coRMS on the assessment report on trinexapac RAR

(18.07.2017) 59/185

Section 3 – Residues data

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	Co-RMS (LV): No comments	

Comments of coRMS on the assessment report on trinexapac dRAR

(18.07.2017) 60/185

Section 4 - Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		LV: Section not reviewed, no comments	

Adsorption, desorption and mobility in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		LV: Section not reviewed, no comments	

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		LV: Section not reviewed, no comments	

Fate and behaviour in air			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

PEC in soil			

Comments of coRMS on the assessment report on trinexapac dRAR

(18.07.2017) 61/185

Section 4 - Environmental fate and behaviour

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

PEC in surface water and ground water

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		LV: Section not reviewed, no comments	

PEC from airborne transport and other routes of exposure

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Definition of the residues

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Other comments incl. available monitoring data

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> LV: Section not reviewed, no comments	<u>Column 3</u> Further explanations

Comments of coRMS on the assessment report on trinexapac dRAR

(18.07.2017) 62/185

Section 4 - Environmental fate and behaviour

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> LV: Section not reviewed, no comments	<u>Column 3</u> Further explanations
(1)	Vol. #, <<data point>>, <<description>>	LV: Section not reviewed, no comments	

Section 5 - Ecotoxicology

5. Ecotoxicology

Birds and other terrestrial vertebrates			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)		LV: Section not reviewed, no comments	

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		LV: Section not reviewed, no comments	

Bees and non-target arthropods			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		LV: Section not reviewed, no comments	

Earthworms and other non-target soil macro- and mesofauna			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)		LV: Section not reviewed, no comments	

Soil nitrogen transformation			

Comments of coRMS on the assessment report on trinexapac dRAR

(18.07.2017) 64/185

Section 5 - Ecotoxicology

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		LV: Section not reviewed, no comments	

Terrestrial non-target higher plants

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		LV: Section not reviewed, no comments	

Other non-target terrestrial organisms (flora and fauna)

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		LV: Section not reviewed, no comments	

Biological methods for sewage treatment

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)		LV: Section not reviewed, no comments	

Other comments incl. available monitoring data

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		LV: Section not reviewed, no comments	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 65/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Physical and chemical properties of the active substance			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Physical and chemical properties of the plant protection product			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Data on application and efficacy			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 66/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Page 40 Conclusion on GRM020.01A	Applicant: Page 40 it is stated that the use of single transition is insufficient for full validation. This is a pre-registration method, and therefore a single transition is considered appropriate.	
(2)	Page 48 Conclusion of methods GRM020.13A and GRM020.14A	Methods are completed and have been provided. Please update text	
(3)	B3CA B.5.2.1 Methods for the determination of the active substance and/or metabolites in food/feed of plant origin	Applicant: Page 70: As matrix-matched standards were used the linearity data for each matrix should be presented to retain consistency with the earlier summaries.	
		Applicant: Page 73: As matrix-matched standards were used the linearity data for each matrix should be presented to retain consistency with the earlier summaries.	
		Applicant: On Page 76 the conclusion for the ILV of the crop method references the animal matrices. Please check this for consistency.	
(4)	B3CA B.5.2.2 Methods for the determination of the active substance and/or metabolites in food/feed of animal origin	Applicant: Page 77: As matrix-matched standards were used the linearity data for each matrix should be presented to retain consistency with the earlier summaries.	
(5)	Vol. 3 – B5 (AS), B.5.1.2.3 Methods for the determination of the active substance and/or metabolites in soil	Applicant: Page 62, the two references stated in Table B.5.1.2.3-1 are incorrect and should read: CGA300405_10025 and CGA300405_10029.	
(6)	Vol. 3 – B5 (AS),	Applicant: Page 68 questions the selection of the	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 67/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	B.5.1.2.3 Methods for the determination of the active substance and/or metabolites in soil	mass transitions, and therefore the validity of the method. This is a data generation method and therefore such justification (as for enforcement methods under SANCO/825/00 rev 8.1) is not required.	
(7)	Vol. 3 – B5 (AS), B.5.1.2.4 Methods for the determination of the active substance and/or metabolites in water	Applicant: No consideration of methods in water is included, but new studies were submitted.	
(8)	Vol. 3 – B5 (AS), B.5.2.4 Methods for the determination of the active substance and/or metabolites in water (AS)	Applicant: Page 112 and page 114 refer to the concentration range not covering 30% of the LOQ to 20% above the highest level. The Applicant has followed up on this comment with the contracted laboratory and has provided an updated version of the report to clarify the range of concentrations. The study can be found in the latest version of the Caddy supplied to the EFSA, the RMS and other MSs.	
(9)	Vol. 3 -B5.2.6 Methods for the determination of AS and or metabolites in body fluids and tissues.	Applicant: A body fluid/tissues method is now available CGA179500_11025, OECD summary CGA179500_11026	

Other comments			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 68/185

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Acute toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. B.6.3.2.2.	Applicant: Decreases in ALT are noted. These are then related to reductions in food consumption. 1) A decrease in ALT would not be indicative of an adverse response and 2) is there any evidence to link decreases in ALT to food consumption? The applicant recommend omitting reference to reductions in ALT due to a lack of toxicological relevance.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 69/185

Section 2 – Effects on human and animal health

Genotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Long-term toxicity and carcinogenicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Reproductive toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Neurotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Section 2 – Effects on human and animal health

Further toxicological studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: The applicant agree with the rapporteur's conclusion that trinexapac-ethyl does not meet the interim criteria for endocrine disruption specified in EC 1107/2009. The applicant notes that on the 4th of July 2017 The Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) voted to adopt a definition of endocrine disruption derived from the internationally recognized WHO/IPCS definition. It is considered that the interim criteria for identification of endocrine disruptors described in regulation EC 1107/2009 were a regulatory construct that do not constitute a best scientific approach to endocrine identification, and are therefore not appropriate. The applicant therefore acknowledges that the most suitable and scientifically valid approach would be for the final criteria for identification of endocrine disruptors agreed by the SCoPAFF to be used in the evaluation of trinexapac-ethyl.	
(2)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: The differences in oestrus cycle stage between treated and control animals in the 52 week dog study with trinexapac-ethyl are not the result of treatment with trinexapac but are instead reflective of a combination of methodological deficiencies in study design and normal dog reproductive biology. To provide	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 71/185

Section 2 – Effects on human and animal health

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		additional critique of the relevant data, an expert technical review of this study illustrating the deficiencies in methodology and providing a comparison with established knowledge of oestrus cyclicity in dogs has been provided to the rapporteur.	
(3)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: Whilst the applicant does not share the rapporteur's concerns around the one year dog study with trinexapac-ethyl the applicant notes that assessment of endocrine disruption should be conducted through a weight of evidence evaluation and that all studies with trinexapac-ethyl should be evaluated holistically with both positive and negative evidence considered together. The applicant does not believe that a single isolated data point that is inconsistent with all other OECD conceptual framework level 4 and 5 studies in the database should be considered to constitute evidence of endocrine disruption, particularly in the presence of a comprehensive battery of endocrine related assays indicating that trinexapac-ethyl does not have the potential to interact with components of the endocrine system. The applicant draws particular attention to the fact that no effects were seen on end-points relating to oestrogenic, androgenic and/or steroidogenic processes. A lack of effects in this set of assays provides further evidence that any inter-group differences noted in the one-year dog study oestrus cyclicity data were without	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 72/185

Section 2 – Effects on human and animal health

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		relationship to treatment with Trinexapac-ethyl and therefore incidental in nature.	
(4)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: The rapporteur noted that whilst a battery of assays designed to assess the potential for interaction with components of the endocrine system as part of the US EPA's ToxCast data had been supplied by the applicant the level of methodological information provided alongside these data was limited. The applicant has provided a review containing additional methodological information for the endocrine system related assays conducted with trinexpac-ethyl as part of the US EPA ToxCast program. Trinexapac-ethyl was negative in all of these assays, providing comprehensive evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system.  Trinexapac-ethyl ToxCast ED assays.pdf	

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. B.6.8.1.4.3	Applicant: At the time of the conduct of the rodent	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 73/185

Section 2 – Effects on human and animal health

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Genotoxicity	micronucleus study on CGA329773, proof of exposure was not a guideline requirement. None-the-less the test item was quantified in blood plasma, giving compelling evidence that the bone marrow would have been exposed. Subsequent to the RMS comments on the lack of validation of the analytical method for determining CGA329773 in plasma, the applicant extracted the study data from its archives and found a standalone toxicokinetics report for the micronucleus proof of exposure. This report (CGA329773_10002) is available. The method used is detailed within and provides more assurance that the study was conducted with suitable rigour. Paragraph 40 of the 2016 474 OECD guideline for the erythrocyte micronucleus assay points to determination of the test item in plasma as being evidence for bone marrow exposure. The RMS comments that plasma concentrations of up to 245 µg/mL two hours post exposure were not high enough to demonstrate the test item reached the bone marrow. The applicant notes that these data demonstrate that CGA329773 was readily available systemically, and as the bone marrow is a highly perfused tissue, exposure to the bone marrow can reasonably be assumed.	
(2)	Vol. B.6.8.1.4.3	Applicant: In order to clarify any genotoxic potential	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 74/185

Section 2 – Effects on human and animal health

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Genotoxicity	of CGA179500 (trinexapac acid), three <i>in vitro</i> genotoxicity studies have been conducted (bacterial reverse mutation assay/Ames, HPRT and <i>in vitro</i> micronucleus). These studies are negative and are available for the stop-clock.	

Medical data and information			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Toxicological end points: ADI, ARfD, AOEL			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Product exposure and risk assessment, including dermal absorption			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 B.6.4.1 through to B.6.6, Operator, bystander/resident and worker risk assessments	Applicant: The Applicant does not believe it is appropriate that the exposure of operators, workers, residents and bystanders is estimated using EFSA guidance applied retrospectively, for submissions made before the 1st January 2016.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 75/185

Section 2 – Effects on human and animal health

Product exposure and risk assessment, including dermal absorption			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		All risk assessments have been conducted to comply with the Council Directives that were in force at the time of submission (79/117/EEC and 91/414/EEC), and meet the criteria applied for safe exposure to aforementioned populations.	

Other comments, incl comments on volume 4 (impurities, batches) and proposals for classification			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 76/185

Section 3 – Residue data

3. Residue data

Storage stability of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Volume 1 Leve I3 3.1.4.7 Residue data	RMS: According to information from the applicant, storage stability studies for processing metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) are currently on-going. Applicant: Stability studies for processing metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) in processed commodities are completed and available. The following processing studies contain storage stability data on CGA313458 and CGA113745 (CGA313458_10011 and CGA313458_10010). Storage stability data for CPCA is in study CA876_10009. Additionally a new study investigating the storage stability of trinexapac acid in high protein crops (pulses) and high water crops is ongoing to provide data to support crops during product renewal. A one month interim report could be made available for the stop-clock.	

Metabolism, distribution and expression of residues in plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 77/185

Section 3 – Residue data

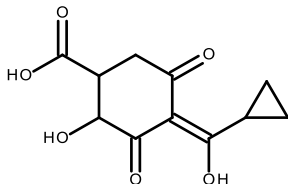
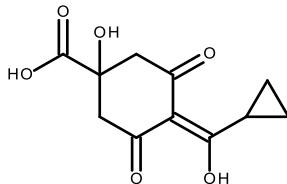
Metabolism, distribution and expression of residues in plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3CA B7, Appendix I (Page 269 section 2 metabolites)	Applicant: The position of the OH group in the hydroxylated trinexapac acid component could not be confirmed by chromatographic means as no reference standard was available, however LCMSMS analysis and chemical characterisation has enabled us to conclude on the structure of the grain metabolite, as detailed in the attached document. Position paper on identification of hyc	Exhaustive attempts have been made to synthesize all feasible hydroxylated standards, but it has not been possible to synthesize SYN548584, as detailed in the attached statement. Non-GLP work has shown that the component seen in the GLP study does not co-elute with SYN549426 or SYN549427 standards. GLP study is now complete and available (CGA163935_10838) and confirms the above. Synthesis summary for postulated hydr

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Volume 1, Level 3 Residue Definition AnnexII 3.9	RMS: Due to the lack of information on metabolite hydroxylated-CGA179500 (hydroxylated trinexapac acid) (actual amounts in residue trials	Applicant: In terms of general toxicity, hydroxylated trinexapac acid could potentially exist as a 2-hydroxy or 1-hydroxy form. It is structurally similar to trinexapac acid (CGA179500) and trinexapac-ethyl.

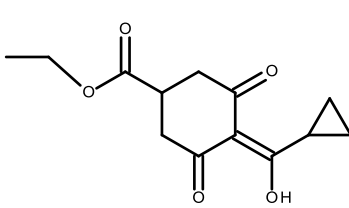
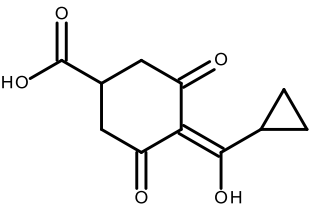
Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 78/185

Section 3 – Residue data

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	and 3.1.4.7 and 3.1.5 - Issues that could not be finalised	– as analytical standards are not yet available and general toxicity), residue definition for risk assessment could not be finalized. This metabolite is provisionally proposed for inclusion in the residue definition for risk assessment for plant matrices. and Toxicological evaluation of metabolite hydroxylated CGA179500 need to be provided for final decision making of the residue definition. RMS: In plants, residue definition for risk assessment could not be finalised due to missing information on metabolite hydroxylated CGA179500. Hydroxylated CGA179500 was detected in edible plant parts (wheat grain at 12.1 % TRR). As analytical standards are not yet available, OH-CGA179500 could not be measured in the residue trials. Although OH-CGA179500 was not observed in the rat, no alerts were identified for genotoxicity (using (Q)SAR analysis (DEREK, LHASA Ltd)). A final conclusion on the genotoxic potential cannot be drawn for this metabolite based on the information provided. Consequently, a decision on the inclusion of hydroxylated CGA179500 into the residue definition cannot be made until the applicant has provided a toxicological characterisation of	Hydroxy trinexapac acid differs from CGA179500 in the addition of a hydroxyl group on the cyclohexane ring. The addition of a hydroxyl group is unlikely to result in increased toxicity, and may make the metabolite more readily excreted (the hydroxyl group may be available for conjugation and aid rapid excretion). CGA179500 is the major rat metabolite of trinexapac-ethyl, and therefore the toxicity profile of trinexapac-ethyl effectively covers both molecules. Both hydroxy trinexapac acid potential metabolites would be expected to be of equivalent or possibly lower toxicity than trinexapac-ethyl/CGA179500. Trinexapac-ethyl is non-genotoxic, of low acute oral toxicity, and neither carcinogenic or reproductively toxic. Furthermore, new <i>in vitro</i> genotoxicity studies have been conducted and show CGA179500 to be non-genotoxic (Ames, HPRT and <i>in vitro</i> micronucleus, studies in reporting phase, see also comment Vol. B.6.8.1.4.3 Genotoxicity). Therefore the hydroxylated trinexapac acid metabolites would be expected to be of similarly low concern.  1-hydroxy trinexapac acid SYN548583  2-hydroxy trinexapac acid SYN548584

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 79/185

Section 3 – Residue data

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		hydroxylated CGA179500.	 Trinexapac-ethyl  CGA179500 Despite exhaustive attempts to isolate and/or synthesise the hydroxylated CGA179500 – identified by default as SYN548584 - it has not been possible. The molecule appears to be unstable outside the plant matrix and reverts to CGA179500. See 3CA B7 Appendix I above. As the toxicity of this molecule is likely to be equivalent to trinexapac-ethyl and of low concern and cannot be synthesised, the applicant propose that it is removed from the definition of the residue for risk assessment in plant matrices.
(2)		Applicant: DOR information is missing in dRAR (Vol 3 Annex B.7) Please see applicant dossier MCA Section 6 CA 6.7	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 80/185

Section 3 – Residue data

Residue trials in plants and identification of critical GAP			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Feeding studies in poultry, ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 3 CA B7 B7.4.3 Ruminant feeding study	Applicant: Absolute calculation of the expected residues levels in animal tissues based on the dietary burden and feeding study results should be presented for lactating ruminants. Refer to page 23 in MCA-section 6 document.	

Effects of processing			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 1 Level 3 3.1.4.7 Residue data	RMS: According to information from the applicant, magnitude of metabolite CGA113745 in processed barley and wheat commodities studies are currently on-going. Interim reports provided. Anticipated date of completion – not stated.	Applicant: These studies are completed and are available for CGA113745 and CGA313458 (CGA313458_10011 for wheat and CGA313458_10010 for barley). These studies also include storage stability data. For completeness the following processing studies are also available for CPCA (CGA224439): CA876_10003 (wheat) and CA876_10004 (barley).

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 81/185

Section 3 – Residue data

Residues in rotational crops			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Summary of other studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Estimation of the potential and actual exposure through diet and other sources			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol 3 CA B-7	Applicant: No chronic risk assessments for trinexapac-ethyl have been presented, refer to page 36 of MCA-section 6 and Appendix 2	

Proposed MRLs and compliance with existing MRLs			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 82/185

Section 3 – Residue data

Proposed import tolerances and compliance with existing import tolerances			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Section 4 - Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 1, 2.8.1 Summary of fate and behaviour in soil	Applicant: Page 117 the Applicant disagrees with the modelling soil endpoint derived by the RMS for trinexapac-ethyl. Please refer to point (3) of this table for further details.	
(2)	Vol. 1, 2.8.5 Definition of the residues in the environment requiring further assessment	Applicant: Page 122 the Applicant does not agree with the definition of residue for soil and surface water. CGA300405 should not be assessed in soil, while CGA275537 should not be assessed in soil or surface water. Please see point (10) of this table more further details. Therefore the Applicant does not believe exposure calculations should be calculated in soil for metabolites CGA300405 and CGA275537 and in surface water for CGA275537.	
(3)	LoEP, Section 4, Rate of degradation in soil (aerobic) laboratory studies active substance	Applicant: Page 36 the Applicant disagrees with the endpoint derived by the RMS for trinexapac-ethyl. The two values obtained in the Spare (1990) study originate from the same soil (Maryland) and therefore should be pre-geomeaned prior to any further averaging with the rest of the values. As a result, the final geomeatric mean DT ₅₀ value for trinexapac-ethyl should be 0.14 days . The difference in the calculations is not significant and does not impact the overall risk assessment but the value should however be updated for completeness.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 84/185

Section 4 - Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	LoEP, Residues requiring further assessment	Applicant: Page 47 the Applicant disagrees with the definition of residue for soil and surface water. CGA300405 should not be assessed in soil, while CGA275537 should not be assessed in soil or surface water. Please see point (12) of this table more further details.	
(5)	Vol. 3 – B.8 (PPP), 8 Fate and behaviour in the environment	Applicant: Page 8, the Applicant disagrees with the definition of residue for soil and surface water highlighted in Table 8-3. CGA300405 should not be assessed in soil, while CGA275537 should not be assessed in soil or surface water. Please see point (12) of this table more further details.	
(6)	Vol. 3 – B.8 (A.S), B.8, Fate and behaviour in the environment	Applicant: Page 6, Table 8-1, WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	
(7)	Vol. 3 – B.8 (A.S), B.8.1.1.1, Degradation of the active substance in aerobic soil	Applicant: Page 25 the Applicant would like to comment that even though DT ₅₀ values originating from the Hellstern (2008) study are considered unreliable due to the amount of non-extractable residues (referred in the rest of this document as NER), the study is still considered fit for purpose in assessing the route of degradation of trinexapac-ethyl.	
(8)	Vol. 3 – B.8 (A.S),	Applicant: Page 36, the Applicant would like to	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 85/185

Section 4 - Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	B.8.1.1.1, Degradation of the active substance in aerobic soil	highlight that regardless of the viability of the soils in the study, which remains to be demonstrated, levels of trinexapac-ethyl were very low while NER levels did not go above 6%. This demonstrates that the extraction methods are fit for purpose.	
(9)	Vol. 3 – B.8 (A.S), B.8.1.1.1, Degradation of the active substance in aerobic soil	Applicant: Page 37, the Applicant would like to highlight that the extraction methods are fit for purpose, but that high levels of NER were still observed in the 18 Acres and Sarpy soils. These levels could not be explained and therefore the uncertainty with regards to generating reliable DT ₅₀ for parent and metabolite CGA179500 in the 18 Acres and Sarpy soils is unacceptable. However, it is worth pointing out that the DT ₅₀ values obtained for 18 Acres and Sarpy are consistent with the reliable values obtained with other soils, which substantiates the fact that NER do not contain any trinexapac-ethyl nor CGA179500 and therefore do not play a role in determining degradation values for these two compounds.	
(10)	Vol. 3 – B.8 (A.S), B.8.1.1.1, Degradation of the active substance in aerobic soil	Applicant: Page 42-43 the Applicant would like to comment that even though DT ₅₀ values originating from the Walther (2008) study are considered unreliable due to the amount of non-extractable residues, the study is considered fit for purpose in assessing the route of degradation of trinexapac-ethyl.	

Section 4 - Environmental fate and behaviour

Route and rate of degradation in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(11)	Vol. 3 – B.8 (A.S), B.8.1.1.2, Anaerobic degradation	Applicant: Page 53 the Applicant would like to comment that the lack of reliable DT ₅₀ values originating for the Volkel (2014) study stems from the protocol of the study where there is an aerobic phase prior to the anaerobic phase, in which most of the parent must have degraded. The extraction method used is the same method that was used in the Adam photolysis study and the Adam aerobic degradation study, which is fit for purpose.	
(12)	Vol. 3 – B.8 (A.S), B.8.1.1.3.1, Overall conclusion on soil photolysis	Applicant: Page 69-70 the Applicant agrees with the RMS's comments on the microbial activity of the Gartenacker soil in the soil photolysis experiment. In dark moist conditions, degradation of metabolite CGA179500 should have been observed. Since this did not occur, it is reasonable to assume that the microbial activity was not optimal or indeed maintained during the extent of the study. It is therefore not possible to conclude that metabolite CGA179500 is formed <i>via</i> microbial degradation only. However, page 70 the Applicant does not agree that "risk assessment in soil and groundwater should be provided for both CGA275537 and CGA300405 metabolites". Since it is likely that the microbial activity is not optimal in the soil photolysis experiment, it substantiates the claim that under realistic	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 87/185

Section 4 - Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		conditions, that is to say in moist, aerobic conditions with full microbial capacity, CGA300405 and CGA275537 are unlikely to be formed over 5%, and therefore at levels of concern. The Applicant agrees that the conservative position of assessing CGA300405 and CGA275537 in groundwater might be necessary to reach a high degree of confidence that these won't indeed leach to groundwater – however, due to the very short half-life values of CGA300405 and CGA275537 (all the measured values are <0.25 day in three soils for both metabolites), it is reasonable to assume that, if ever formed under realistic conditions, their soil exposure would be negligible. As a result, CGA300405 and CGA275537 are not of concern in soil. Due to its very low half-life, CGA275537 soil exposure and therefore its surface water is negligible. Consequently, CGA275537 is not of concern in surface water. In addition, in the unlikely event that CGA275537 is ever formed under realistic conditions, the metabolite would only reach surface water via run-off or drainage as it was solely observed in the soil photolysis experiment. CGA300405 on the other hand was observed	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 88/185

Section 4 - Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		>10% AR in the direct photolysis experiment, and for that reason is assessed in surface water.	
(13)	LoEP, Section 4, Rate of degradation on soil (photolysis) laboratory active substance	Applicant: Page 40 the Applicant would like to highlight that the two indicative rates reported were obtained in a dry irradiated experiment (DT ₅₀ of 5.7 days) and a moist irradiated experiment (DT ₅₀ of 0.7days).	
(14)	Vol. 3 – B.8 (PPP), 8.1.1.1, Laboratory studies	Applicant: Page 6, the Applicant would like to highlight that even though there are high levels of NER observed in the 18 Acres and Sarpy soils for the Adam (2014) aerobic degradation study, the half-life values obtained for the two soils are consistent with the reliable values obtained with the other soils from the study, which substantiates the fact that NER do not contain any trinexapac-ethyl nor CGA179500 and therefore do not play a role in determining degradation values for these two compounds in the Adam (2014) aerobic degradation study.	
(15)	Vol. 3 – B.8 (PPP), 8.1.1.1, Laboratory studies	Applicant: Page 6 the Applicant would like to mention that a rate degradation study was carried out for metabolite CGA275537. Results confirm that, as expected and highlighted in the Applicant's dossier, the half-life of CGA275537 is very short and comparable to metabolite CGA300405 (< 0.25 day). The data, alongside a FOCUS kinetics assessment, is available and can be found in the latest version of the Caddy supplied to the EFSA, the RMS and	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 89/185

Section 4 - Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		other MSs at the end of April 2017.	
(16)	Vol. 3 – B.8 (PPP), 8.1.1.2.1, Soil dissipation studies	Applicant: Page 7 the Applicant would like to mention that a rate degradation study is available for metabolite CGA275537 and it confirms that the half-life values are well below the 60 day threshold to trigger field dissipation studies, therefore no data will be submitted under this section.	

Adsorption, desorption and mobility in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 – B.8 (PPP), 8.1.2.1, Laboratory studies	Applicant: Page 7 the Applicant would like to mention that a mobility study is available for metabolite CGA275537. As the report was only finalised in July 2017, it could not be included in the latest version of the Caddy but can be made available on request. Results confirm that, as expected and highlighted in the Applicant's dossier, the mobility of CGA275537 is high. Reliable K_{FOC} values range from 6 to 78 mL/g.	

Section 4 - Environmental fate and behaviour

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 1, 2.8.2 Summary of fate and behaviour in water and sediment	Applicant: Page 119 the Applicant would like to highlight that WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	
(2)	LoEP, Section 4, Hydrolytic degradation	Applicant: Page 43 the Applicant would like to highlight that WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	
(3)	Vol. 3 – B.8 (AS), B. 8.2.1.1 Hydrolytic degradation	Applicant: Page 134 the Applicant would like to highlight that the unknown metabolite in the Roulstone (2009) hydrolysis study was only observed >10% at 44°C and 50°C. At a relevant realistic temperature of 20°C, the levels of the unknown metabolite did not go over 6.8% AR.	
(4)	Vol. 3– B.8 (AS), B. 8.2.1.1.1 Summary Hydrolysis	Applicant: Page 135 the Applicant would like to highlight that WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	
(5)	Vol. 3 – B.8 (AS), 8.2.1.3.1, Summary Photolysis	Applicant: Page 150, the Applicant would like to highlight that the OECD Guidelines for the Testing of Chemicals, Phototransformation of Chemicals in Water- Direct and Indirect Photolysis is a draft guidance and that the guidance in place at the time of submission was the OECD Guideline number 316.	
(6)	Vol. 3 – B.8 (AS), 8.2.1.3.1, Summary Photolysis	Applicant: Page 153, the Applicant agrees that both direct and indirect photolysis could happen concomitantly. However, by definition of its	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 91/185

Section 4 - Environmental fate and behaviour

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		protocol, indirect photolysis represents a more realistic experiment than direct photolysis as aqueous sterile water, which is used as medium in aqueous direct photolysis, does not exist in the environment. Nevertheless, due to the uncertainty over the potential formation of direct photolysis metabolites CGA300405, M2 and WaterphotolysisM3, these are assessed in Document CP, Section 8.	

Fate and behaviour in air			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

PEC in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	LoEP, Section 4, PEC soil	Applicant: Page 49 The Applicant does not agree that CGA300405 and CGA275537 should be assessed in soil as under realistic field conditions, these will not form at levels of concern. Therefore, calculations of PECsoil are not necessary for these two metabolites.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 92/185

Section 4 - Environmental fate and behaviour

PEC in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		Please see point (12) of Table Route and rate of degradation in soil for further details.	
(2)	Vol. 1, 2.8.6 Summary of exposure calculations and product assessment	Applicant: Page 123 The Applicant does not agree that CGA300405 and CGA275537 should be assessed in soil as under realistic field conditions, these will not form at levels of concern. Please see point (12) of Table Route and rate of degradation in soil for further details.	
(3)	Vol. 3 – B.8 (PPP), 8.1.3, Estimation of concentration in soil	Applicant: Page 9 The Applicant does not agree that CGA300405 and CGA275537 should be assessed in soil as under realistic field conditions, these will not form at levels of concern. Please see point (12) of Table Route and rate of degradation in soil for further details.	

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.8.6 Summary of exposure calculations and product assessment	Applicant: Page 124 the Applicant does not agree that CGA275537 should be assessed in Surface Water. Please see point (12) of Table Route and rate of degradation in soil for further details.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 93/185

Section 4 - Environmental fate and behaviour

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(2)	LoEP, Section 4, PEC ground water	Applicant: Page 50 the Applicant disagrees with the modelling soil endpoint derived by the RMS for trinexapac-ethyl. Please refer to point (3) of Table Route and rate of degradation in soil for further details.	
(3)	LoEP, Section 4, PEC ground water	Applicant: Page 51-52 the Applicant does not agree with the crop interception selected by the RMS for groundwater assessment. According to the EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT₅₀ values of active substances of plant protection products and transformation products of these active substances in soil (2014), the interception for cereals at BBCH 25 should be set to 20% and not 0%, even if this doesn't impact to the outcome of the risk assessment.	
(4)	Vol. 3 – B.8 (PPP), 8.1.4, Estimation of concentration in groundwater	Applicant: Page 15-16 the Applicant would like to highlight that the correct endpoint for trinexapac-ethyl is 0.14 days. Please see point (3) of Table Route and rate of degradation in soil for further details.	
(5)	Vol. 3 – B.8 (PPP), 8.1.4, Estimation of concentration in groundwater	Applicant: Page 15-16 the Applicant agrees with the latest solubility endpoints selected by the RMS but would like to highlight that the water solubility values of parent and metabolite CGA179500 do not influence the outcome of groundwater models.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 94/185

Section 4 - Environmental fate and behaviour

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		In addition, Table 8.2 page 5 needs to be updated with these latest solubility endpoints.	
(6)	Vol. 3 – B.8 (PPP), 8.1.4, Estimation of concentration in groundwater	Applicant: Page 23 the Applicant agrees with the latest solubility endpoints selected by the RMS but would like to highlight that the water solubility values of metabolites CGA300405 and CGA275537 do not influence the outcome of groundwater models.	
(7)	Vol. 3 – B.8 (PPP), 8.1.4, Estimation of concentration in groundwater	Applicant: Page 24-25 the Applicant does not agree with the crop interception selected by the RMS for groundwater assessment. According to the EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT ₅₀ values of active substances of plant protection products and transformation products of these active substances in soil (2014), the interception for cereals at BBCH 25 should be set to 20% and not 0%, even if this doesn't impact to the outcome of the risk assessment.	
(8)	LoEP, Section 4, PEC surface water and PEC sediment	Applicant: Page 59-60 the Applicant does not agree that CGA275537 should be assessed in Surface Water. Please see point (12) of Table Route and rate of degradation in soil for further details. In addition, the Applicant would like to highlight	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 95/185

Section 4 - Environmental fate and behaviour

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		that CGA275537 was only observed in a soil photolysis study, therefore deriving surface water concentrations from parent is incorrect as any contribution from drift should not be considered for surface water calculations. Please see point (12) of this table for further details.	
(9)	Vol. 3 – B.8 (PPP), 8.2.4, Estimation of concentration in surface water	Applicant: Page 30 the Applicant would light to highlight that the correct soil DT₅₀ endpoint for use in modelling for trinexapac-ethyl is 0.14 days. Please see point (3) of Table Route and rate of degradation in soil for further details.	
(10)	Vol. 3 – B.8 (PPP), 8.2.4.1, Estimation of concentration in surface water for metabolites	Applicant: Page 33 the Applicant would light to highlight that the correct soil DT₅₀ endpoint for use in modelling for trinexapac-ethyl highlighted in Table 8.2.4.1-2 is 0.14 days, not 1 day. Please see point (3) of Table Route and rate of degradation in soil for further details.	
(11)	Vol. 3 – B.8 (PPP), 8.2.4.1, Estimation of concentration in surface water for metabolites	Applicant: Page 35 the Applicant does not agree that CGA275537 should be assessed in Surface Water. Please see point (12) of Table Route and rate of degradation in soil for further details.	
(12)	Vol. 3 – B.8 (PPP), 8.2.4.1, Estimation of	Applicant: Page 35 as highlighted in point (10) of Table Route and rate of degradation in soil,	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 96/185

Section 4 - Environmental fate and behaviour

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	concentration in surface water for metabolites	CGA275537 is not going to form at levels of concerns in soil, and therefore in surface water. In addition, the Applicant would like to highlight that CGA275537 was only observed in a soil photolysis study, therefore deriving surface water concentrations from parent is incorrect as any contribution from drift should not be considered for surface water calculations. Consequently, should the RMS, EFSA or other concerned MSs still wish to calculate concentrations for CGA275537, the Applicant suggests performing Step 1&2 using the "No drift (incorp or seed treatment)" option as the only routes of entry relevant for CGA275537, if ever formed under realistic conditions, could only be <i>via</i> run-off or drainage.	

PEC from airborne transport and other routes of exposure			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 97/185

Section 4 - Environmental fate and behaviour

Definition of the residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 – B.8 (AS), 8.4.1, CGA300405 and CGA275537 are considered to be relevant residues in soil, groundwater and surface water for the risk assessment purposes	Applicant: Page 172 the Applicant does not agree with the RMS to include metabolites CGA300405 and CGA275537 in the definition of residues in soil. In addition, the Applicant does not agree with RMS to include metabolite CGA275537 in the definition of residues in surface water. Please see point (12) of Table Route and rate of degradation in soil	

Other comments incl. available monitoring data			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Section 5 - Ecotoxicology

5. Ecotoxicology

Birds and other terrestrial vertebrates			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Aquatic organisms			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Bees and non-target arthropods			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3 – B.9 (PPP), B.9.5.1.2: New data, Kleebaum (2016)	Applicant: Since submission of the Trinexapax supplementary dossier a new chronic toxicity study to honeybee larvae with trinexapac-ethyl a.s. (Kleebaum, 2016; CGA163935_10774) was done by Syngenta for the Canadian regulatory authorities. This new study is available on request. A comparison of the reported 8-day endpoints from this 22-day repeated exposure laboratory study with honeybee larvae using trinexapac-ethyl A.I. (Kleebaum, 2016) with the reported endpoint from a previously submitted 8-d repeated exposure laboratory study with trinexapac-ethyl formulation	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 99/185

Section 5 - Ecotoxicology

Bees and non-target arthropods			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		A8587F (Kleebaum, 2014) indicated differences in the shape of the rate response, the required statistical analysis and in the endpoints. Further statistical evaluation demonstrated that the statistical method used resulted in this difference in reported endpoints. When the same statistical method is used, the endpoints from the two studies are very similar, indicating that there is no biologically significant difference between the two studies. A more detailed assessment on the statistical method is provided here:  Comments on Trinexapac Honeybe	
(2)	Vol. 3 – B.9 (PPP), B.9.6.1, Table B.9.6.1-1: Honeybee adult chronic endpoint and risk assessment.	Applicant: In Tables B.9.6.1-1 and B.9.6.1-2 the endpoints for adult chronic toxicity (Ruhland, 2014; A8587F_10096) are incorrect. The correct values are as given in the OECD summary (table B.9.5.1.2-1): Adult Chronic -10 d NOED 26.9 µg a.s./bee/day and 10d LD50 46.6 µg a.s./bee/day. These revised values should be used in risk assessment. The adult chronic NOED 26.9 µg a.i./bee/day is compared to the total exposure ETE	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 100/185

Section 5 - Ecotoxicology

Bees and non-target arthropods			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		of 0.128 µg a.i./bee/day, to give a TER of 210 indicating acceptable risk.	
(3)	Vol. 3 – B.9 (PPP), B.9.6.1: Honeybee larval risk assessment	Applicant: When referring to the honeybee larval study on the representative formulation A8587F (Kleebaum, 2014) the NOED of 83.4 µg a.s./larva in the larval risk assessment was converted to an equivalent to 11.9 µg a.s./larva/day for the EPPO risk assessment based on 7 day study duration. However the applicant believes that the conversion should be to divide by 5, based on 4 days exposure and 1 extra day for food consumption. On this basis the NOED for the risk assessment would be 16.7 µg a.s./larva/day.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 101/185

Section 5 - Ecotoxicology

Earthworms and other non-target soil macro- and mesofauna			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 – B.9 (PPP), B.9.7.1: New earthworm data for CGA300405, Luhurs (2015)	Applicant: CGA300405 - Chronic toxicity to earthworms: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC was found to be 1000 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil organisms.	
(2)	Vol. 3 – B.9 (PPP), B.9.7.1: New Collembola data for CGA300405, Luhurs (2015)	Applicant: CGA300405 - Toxicity to collembolan: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC was found to be 1000 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil organisms.	
(3)	Vol. 3 – B.9 (PPP), B.9.7.1: New Hypoaspis for CGA300405, Luhurs (2015)	Applicant: CGA300405 - Chronic toxicity to Hypoaspis: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC was found to be 1000 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil organisms.	

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 102/185

Section 5 - Ecotoxicology

Soil nitrogen transformation			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3 – B.9 (PPP), B.9.7.1: New SMO data for CGA300405, Hammesfahr (2015)	Applicant: CGA300405 – Effects on carbon and Nitrogen transformation: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC for both Carbon and Nitrogen transformation was found to be 200 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil micro-organisms.	

Terrestrial non-target higher plants			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other non-target terrestrial organisms (flora and fauna)			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Trinexapac Task Force on the assessment report on Trinexapac-ethyl (18.07.2017) 103/185

Section 5 - Ecotoxicology

Biological methods for sewage treatment			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 104/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Physical and chemical properties of the active substance			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Physical and chemical properties of the plant protection product			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Data on application and efficacy			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 105/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 106/185

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Acute toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Short-term toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Genotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 107/185

Section 2 – Effects on human and animal health

Long-term toxicity and carcinogenicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Reproductive toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Neurotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Further toxicological studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Toxicological data on metabolites			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 108/185

Section 2 – Effects on human and animal health

Medical data and information			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Toxicological end points: ADI, ARfD, AOEL			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Product exposure and risk assessment, including dermal absorption			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

Other comments, incl comments on volume 4 (impurities, batches) and proposals for classification			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 4, C.1.4.2 Assessment of the toxicological profile of impurities	Applicant Syngenta: At the request of the RMS Lithuania further work has been conducted to address the relevance and safety of impurities in the Syngenta technical specification, although it is not complete. A literature search is in progress, which will be submitted during the stop-the-clock period along	

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 109/185

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches) and proposals for classification			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		with an updated document J. This is intended to aid in fully characterising the impurities if further information is available in the scientific literature. At the suggestion of the RMS, a further QSAR tool is being used to predict the toxicological properties of the impurities. The Applicant Syngenta will submit this information during the stop-the-clock period and combine it with the DEREK predictions in an overall weight-of-evidence assessment. The Applicant Syngenta agrees with the RMS opinion that CGA158377 should be considered to be relevant based on its demonstrated skin sensitisation properties. The Applicant Syngenta proposed further testing of technical material spiked with several impurities up to the maximum level they are proposed for inclusion in the Syngenta specification. This was to address potential concerns about inclusion levels of the impurities in batches used for bacterial and mammalian gene mutation assays, and address structural alerts for skin sensitisation. These studies are in the reporting phase although the overall outcomes are available. Both bacterial reverse mutation (Ames) and HPRT mammalian gene mutation assays were negative	

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 110/185

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches) and proposals for classification			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		with this spiked batch of technical material, demonstrating that inclusion of these impurities up to their maximum level in the specification does not result in mutagenicity. The Applicant Syngenta will submit final reports for both of these studies in the stop-clock window. A local lymph node assay was conducted with spiked batch material to address skin sensitisation potential following structural alerts. This study was positive, with an EC3 value of 95.4%. An older local lymph node study with a batch of non-spiked trinexapac-ethyl Syngenta technical material is also available and was negative. The alterations in impurity profile is considered likely to be the reason for the difference in the results of these two studies. Therefore, due to potential for skin sensitisation properties (and not being able to be certain which impurity(s) is responsible), impurities CGA158377, CGA267934, CGA190042, CGA252938 and NOA42741 are considered to be potentially relevant. Given that it has already been demonstrated to be an <i>in vivo</i> skin sensitizer, it is likely that CGA158377 is responsible for the positive response with spiked Syngenta trinexapac-ethyl technical material. The weak skin sensitising potential of Syngenta trinexapac-ethyl technical material is not	

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 111/185

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches) and proposals for classification			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		considered to be of concern for human health, but Syngenta technical material should be labelled as a skin sensitiser. Trinexapac-ethyl technical (when not spiked with impurities) is not considered to be skin sensitising based on the existing studies. Due to the weak response of the Syngenta technical material in the local lymph node assay, a classification for the technical material is not considered to impact the representative formulation, A8587F as it contains trinexapac-ethyl at a lower concentration than the technical's EC3 value (i.e. less than 95.4%). A8587F contains 25% trinexapac-ethyl technical. A8587F was non-sensitising when tested previously. The applicant intends to submit final reports for both of these local lymph node studies in the stop-the-clock window.	

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 112/185

Section 3 – Residue data

3. Residue data

Storage stability of residues			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Metabolism, distribution and expression of residues in plants			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Residue definition			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 113/185

Section 3 – Residue data

Residue trials in plants and identification of critical GAP			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Feeding studies in poultry, ruminants, pigs and fish			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Effects of processing			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Residues in rotational crops			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Summary of other studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 114/185

Section 3 – Residue data

Estimation of the potential and actual exposure through diet and other sources			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Proposed MRLs and compliance with existing MRLs			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Proposed import tolerances and compliance with existing import tolerances			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 115/185

Section 4 - Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Adsorption, desorption and mobility in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Fate and behaviour in air			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 116/185

Section 4 - Environmental fate and behaviour

PEC in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

PEC in surface water and ground water			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

PEC from airborne transport and other routes of exposure			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Definition of the residues			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 117/185

Section 5 - Ecotoxicology

5. Ecotoxicology

Birds and other terrestrial vertebrates			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Aquatic organisms			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Bees and non-target arthropods			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Earthworms and other non-target soil macro- and mesofauna			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of Syngenta on the assessment report on Trinexapac-ethyl (confidential) (18.07.2017) 118/185

Section 5 - Ecotoxicology

Soil nitrogen transformation			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Terrestrial non-target higher plants			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other non-target terrestrial organisms (flora and fauna)			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Biological methods for sewage treatment			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 119/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 4 Syngenta, C.1.2.2, Manufacturing process, impurities, p.20	EFSA: small note: impurity 9 has two chiral centres	
(2)	Vol. 4 Syngenta, C.1.2.2, Manufacturing process, impurities, p.22	EFSA: small note: impurity 12 has two chiral centres	
(3)	Vol. 4 Syngenta, C.1.2.2, Manufacturing process, impurities, p.16 -21	EFSA: small note: impurities 1,2,5,6,10,11 have also one or more chirality centres	
(4)	Vol. 4 Syngenta, C.1.2.3, Specification, RMS conclusion, p. 34	EFSA agrees with the RMS on the conclusion on the proposed specification, i.e. the proposed renewal specification should be considered the reference specification. Also agrees with the conclusion on impurity 2.	
(5)	Vol. 4 Syngenta, C.1.4.2, Relevance of impurities, RMS conclusion, p. 79	EFSA: if the final decision will be that impurity 1 is considered relevant, it should be included in the specification with the proposed level.	
(6)	Vol. 4 All notifiers, C.1.2.2, Identity of impurities	EFSA: clarification is needed on the assignment of CAS numbers: 95266-40-3, 104273-73-6, 143294-89-7	
(7)	Vol. 4, Cheminova, Source 1, C.1.2.2, Identity of impurities, p. 13	EFSA: small note: Compound 3 has two chiral centres	
(8)	Vol. 4, Cheminova, Source 1, C.1.3,	EFSA: if the same ppp is used by the Task Force, at least the content of the technical material in the	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 120/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Specification of the preparation, p. 36	composition table will be dependent of the a.s. source as the min. purities are different.	
(9)	Vol. 4, Cheminova, Source 2, C.1.1.2, Method of manufacture, p. 6	EFSA: is the melting point so much influenced by the purity? It is stated that after the vacuum distillation a light yellow oil is obtained, but also that QC is done on the re-crystallized a.s. Is the final technical obtained a crystal or an oil?	
(10)	Vol. 4, Cheminova, Source 2, C.1.2.1, Specification of purity, p. 8	EFSA: is the intention of Cheminova not to have a common min. purity specification for its sources? The min. 977 g/kg proposed for the source 1 would be applicable also to source 2, based on the batch data and also QC data	
(11)	Vol. 4, Cheminova, Source 2, C.1.2.1, Specification of technical material, p. 16	EFSA: it is not clear why two individual specifications from one company are proposed and why there is not a common specification covering both manufacturing sites?	
(12)	Vol. 4, Cheminova, Source 2, C.1.3, Specification of the preparation, p. 33	EFSA: if the same ppp is used by the Task Force, at least the content of the technical material in the composition table will be dependent of the a.s. source as the min. purities are different, even for the same company.	
(13)	Vol. 4, All sources, C.1.9 Steps to form a task force, p. 74	EFSA: if a TF is formed is there the intention to propose also a common minimum purity for all TF members?	
(14)	Vol. 4, Helm, , C.1.1.2, Methods of manufacture, p. 5-11	EFSA: small note: the manufacturing plants for Cheminova and Helm seem to be the same, but it is interesting that they produce the same a.s. using slightly different procedures for the two companies.	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 121/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(15)	Vol. 4, Helm, Source 1 and 2, C.1.2.1, Specification of purity, p. 11	EFSA: it is not clear why three different min. purities are specified (977, 960 and 970 g/kg) for the a.s. originating from the same factories?	
(16)	Vol. 4, Helm, C.1.2.2.1, Identity of impurities, p. 11	EFSA: small note: on top of the <i>EZ</i> isomerisms, the substance has also two chiral centres.	
(17)	Vol. 4, Helm, C.1.2.3, Specifications, p. 29	EFSA: clarification is needed if Helm is proposing a common specification covering both sources, or individual specifications for each source	
(18)	Vol. 4, Helm, C.1.3, Specification of the preparation, p. 44	EFSA: if the same ppp is used by the Task Force, at least the content of the technical material in the composition table will be dependent of the a.s. source as the min. purities are different.	
(19)	Vol. 4, ADAMA, C.1.2.1, Specification of the purity, Source 1, p. 8	EFSA: it would have been helpful to include the min. purity and not a reference to something not part of the dossier.	
(20)	Vol. 4, ADAMA, C.1.2.2.1, Identity of impurities, Source 1, p. 9	EFSA: it would have been helpful to include the information on the identity of impurities and not a reference to something not part of the dossier. The assessment cannot be made if the information is not included.	
(21)	Vol. 4, ADAMA, C.1.2.2.1, Identity of impurities, Source 2, p. 11	EFSA: the justification for not analysing for toluene might have been accepted, if we wouldn't know that at the same factory two other companies are manufacturing the a.s. and toluene is found in the batches. It is no reason to think that toluene will not be found also in this "source" of ADAMA	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 122/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(22)	Vol. 4, ADAMA, C.1.2.3, Analytical profile of batches, Source 1, p. 13	EFSA: without the batch data this source cannot be considered for the evaluation. A reference to an equivalence document is not acceptable, if the data are not part of the dossier.	
(23)	Vol. 4, ADAMA, C.1.2.3, Analytical profile of batches, Source 2, p. 15 and p.18	EFSA: for the same batch data in this case the proposed specification for water is different than in Helm. EFSA agrees with the RMS in its conclusion on the specification for this impurity.	
(24)	Vol. 4, ADAMA, Cheminova, Helm, C.1.2.3, Specifications	EFSA: clarification is needed whether these three notifiers could agree on a common specification taking into account the common manufacturing plants used for the production?	

Physical and chemical properties of the active substance			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3CA, B.2.1/01, Melting point, p.4	EFSA: is the -36.1 a typo, or the melting point is a range of 72.7 °C? In this case not a melting point.	

Physical and chemical properties of the plant protection product			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Data on application and efficacy			

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 123/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3CA, B.5.1.2.1 Methods for risk assessment, plant matrices, p.53	EFSA: agrees with the RMS on the need for further clarification for the different names /analytes for the same results in method GRM020.015A	
(2)	Vol. 3CA, B.5.1.2.2 Methods for risk assessment, animal matrices, p.53	EFSA: agrees that the extraction efficiency was not addressed	
(3)	Vol. 3CA, B.5.1.2.3 Methods for risk assessment, soil, p.65	EFSA: the LOQ of the method Richardson M., Cashmore A. (2016) is not meeting the requirements	
(4)	Vol. 3CA, B.5.2.2. Methods for animal matrices, p.83	EFSA: the solvent bridging provided to address the extraction efficiency of method Richter S (2015a) (KCA 4.2/04) can be considered acceptable.	
(5)	Vol. 3CA, B.5.4. Methods for air, p. 127	EFSA: According to Reg. (EU) 283/2013 Part A Section 4, 4.2 Methods for post-approval control and monitoring purposes methods shall be submitted for the analysis in body fluids and	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 124/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		tissues for active substances and relevant metabolites.	

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3, B.6.1	EFSA: Although the metabolic pathway in the rat is simple it might useful to include a figure in the RAR.	
(2)	Vol.3, B.6.1 Data requirement 5.1.1: comparative <i>in vitro</i> metabolism studies	EFSA: A comparative <i>in vitro</i> metabolism study should be conducted since this is a new data requirement. EFSA considered not scientifically justified waiving the study based on the fact that there is not OECD guideline for this type of study. These types of studies are widely used for pharmaceuticals in various stages of development, from a new chemical entity characterisation to a pre-clinical safety assessment. It would be useful to include the dog since there were differences regarding the toxicological profile of trinexapac-ethyl in dogs and rats.	

Acute toxicity

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 126/185

Section 2 – Effects on human and animal health

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol.3, B.6.2 Phototoxicity	EFSA: Could the RMS/applicant confirm that the maximum absorption was observed at 290 nm?	

Short-term toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol.3, B.6.3 Page 33.	EFSA: the 7-week study in dogs should be submitted to the RMS for an independent assessment of the study.	
(2)	Vol.3, B.6.3 Krinke, 1994 Page 58	EFSA: It is not clear if a new report supporting the interpretation of dog studies was submitted during the renewal procedure.	
(3)	Vol.3, B.6.3 Krinke, 1994 Page 61	EFSA: the analysis of biological relevance of the findings described that compounds disturbing metabolism of glucose induced similar swelling of astrocytes and oligodendroglia. It is noted that according to literature on metabolites, cyclopropane carboxylic acid is considered a hypoglycemic agent (Buxton D et al, 1983) and tricarballic acid is an inhibitor of the enzyme aconitase and interferes with the Krebs cycle. The role of metabolites and interspecies differences might be further investigated to support applicant's statement on the non-relevance for humans.	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 127/185

Section 2 – Effects on human and animal health

Short-term toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		However, on the basis of current available information EFSA supported the RMS' view that in the absence of mechanistic studies and/or any human data, cerebral vacuolation observed in dogs should be considered relevant for human.	

Genotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3, B.6.4 pages 90-91	EFSA: Robust summaries reports of the <i>in vitro</i> gene mutation tests should be included in a revised RAR. Please also note the conclusion of the study by Geleick, 1993 referred to Chinese Hamster V79 cells whereas the study was performed with mouse lymphoma cells. Could the RMS/applicant indicate if colony size was measured in the mouse lymphoma assay?	
(2)	Vol.3, B.6.4 Page 101	EFSA: Please included a complete assessment of the results of the genotoxicity studies including the <i>in vivo</i> MN test submitted by Cheminova A/S in the B.6.4. Information on the active substance should not be considered confidential.	

Section 2 – Effects on human and animal health

Long-term toxicity and carcinogenicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3, B.6.5	EFSA: No comments.	

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3, B.6.6 Rat developmental toxicity study. Pages 152-153	EFSA: asymmetrically shaped sternebrae is described as anomalies. Can the RMS/applicant clarify if the anomaly should be considered malformation, variation or a grey zone anomaly according to current state of art? Based on litter incidence of asymmetrically shaped sternebrae and historical control data its biological relevance might not be excluded. Please also considered whether the incidence of asymmetrically shaped sternebrae and still absent ossification should be considered together. Could the RMS/applicant clarify if trinexapac-ethyl has been discussed by ECB or ECHA? Is there any intention to submit the CLH report to ECHA?	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 129/185

Section 2 – Effects on human and animal health

Reproductive toxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(2)	Vol.3, B.6.6 Developmental toxicity studies. Shorter administration period	EFSA: All developmental toxicity studies have been performed with a shorter administration period. EFSA noted that insults during the last trimester can cause growth retardation, developmental delay or functional disturbances. EFSA also noted that malformations of organs developing after the period of major organogenesis, e.g., the sex organs and the brain, may not be detected if the study is performed according to the prior guideline for the teratology studies. EFSA would not request to perform additional vertebrate studies; however the uncertainties regarding deviations from current OECD TG should be taken into account in the conclusions.	

Neurotoxicity			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3, B.6.7	EFSA: None.	

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.8	EFSA: According to the preliminary assessment of the applicant trinexapac-ethyl was inactive	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 130/185

Section 2 – Effects on human and animal health

Further toxicological studies			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Endocrine Disruption	regarding AR, ER, ThR receptor indicating no mode of action regarding these modalities. However EFSA supported that further detailed information on ToxCast regarding endocrine-disruption potential of trinexapac-ethyl should be submitted and assessed by the applicant within a weight of evidence approach.	

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3, B.6.8 Dietary metabolites Trinexapac ("acid")	EFSA: agreed with the assessment of trinexapac as covered by trinexapac-ethyl.	
(2)	Vol.3, B.6.8 Dietary metabolites 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid.	EFSA: an <i>in vivo</i> MN test on metabolite 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid referred as CGA329773 was conducted and it was negative. Plasma analysis was performed as recommended in the OECD guideline to demonstrate bone marrow exposure. Although there is no measurement in the bone marrow, plasma analysis indicated	

Section 2 – Effects on human and animal health

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		indirect evidence of bone marrow exposure since bone marrow is considered a well perfused tissue. Could the applicant clarify if the method of analysis was validated?	
(3)	Vol.3, B.6.8 Dietary metabolites 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid.	EFSA: Based on the results of the 28-day oral rat study metabolite 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid referred as CGA329773 might be considered less toxic than trinexapac-ethyl.	
(4)	Vol.3, B.6.8 Dietary metabolites Tricarballic acid	EFSA: According to the literature tricarballic acid is an inhibitor of the enzyme aconitase and interferes with the Krebs cycle and appears to be a well-known compound. Did the literature search include this compound? If the metabolite is a significant plant/livestock metabolite its toxicological profile should be further define in order to conduct a consumer risk assessment.	
(5)	Vol.3, B.6.8 Dietary metabolites	EFSA: Based on the structure similarities of the metabolite (i.e. hydroxylated of trinexapac) and the parent the metabolite might be considered by	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 132/185

Section 2 – Effects on human and animal health

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Hydroxylated CGA179500	trinexapac-ethyl.	
(6)	Vol.3, B.6.8 Dietary metabolites Citric acid	EFSA: citric acid is well known substance. Did the RMS consider citric acid a non-relevant metabolite of trinexapac-ethyl for dietary risk assessment?	
(7)	Vol.3, B.6.8 Dietary metabolites 3-ethoxycarbonylpentanedioic acid	EFSA: metabolite 3-ethoxycarbonylpentanedioic acid referred as CGA300405 is a potential dietary metabolite. The weight of evidence suggests CGA300405 unlikely to be genotoxic. Please address whether the metabolite could be considered of lower, equal or higher toxicity than the parent and/or specific reference values should be set in order to conduct a consumer risk assessment.	
(8)	Vol.3, B.6.8 Dietary metabolites Cyclodione acid and CGA158377	EFSA: bridging from ethyl 3,5-dioxocyclohexanecarboxylate to metabolite 3,5-dioxocyclohexanecarboxylic acid referred as Cyclodione acid is supported on the basis of chemical structure similarities. Both compounds should be considered unlikely to be genotoxic. Please address whether the metabolites could be	

Section 2 – Effects on human and animal health

Toxicological data on metabolites			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		considered of lower, equal or higher toxicity than the parent and/or specific reference values should be set in order to conduct a consumer risk assessment.	
(9)	Vol.3, B.6.8 Dietary metabolites 2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid	EFSA: CGA313458 referred as 2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid is unlikely to be genotoxic. Please address whether the metabolite could be considered of lower, equal or higher toxicity than the parent and/or specific reference values should be set in order to conduct a consumer risk assessment.	
(10)	Vol.3, B.6.8 Dietary metabolites Cyclopropane carboxylic acid	EFSA: Cyclopropane carboxylic acid is unlikely to be genotoxic on the basis of available studies. The literature search included this compound but available literature did not meet the relevance criteria according to the RMS. According to the additional search cyclopropane carboxylic acid disrupts the pyruvate metabolism (as described table 6.10-2). Please the RMS/Applicant clarifies the relevance of these mechanistic findings and clarify if further toxicological data are available on cyclopropane	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 134/185

Section 2 – Effects on human and animal health

Toxicological data on metabolites			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		carboxylic acid. If the metabolite is a significant plant/livestock metabolite its toxicological profile should be further define in order to conduct a consumer risk assessment.	

Medical data and information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol.3, B.6.9	EFSA: None.	

Toxicological end points: ADI, ARfD, AOEL, AAOEL			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol.1, 2.6 AAOEL	EFSA: Please consider whether there is a need for setting an AAOEL.	

Product exposure and risk assessment, including dermal absorption			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 135/185

Section 2 – Effects on human and animal health

Product exposure and risk assessment, including dermal absorption			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3, B.6 CP; B.6.2 Dermal absorption	EFSA: None	
(2)	Vol.3, B.6 CP; B.6.4. Exposure data	EFSA: none.	

Other comments, incl comments on volume 4 (impurities, batches)			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6. General comment Page 6	EFSA: could the RMS clarify if new toxicity studies on trinexapac-ethyl or any of its metabolites have submitted by other applicants than Syngenta? New toxicity studies (if available) should be summarised in the B.6.	
(2)	Vol. 3, B.6. General comment Scientific open literature	EFSA: articles from 1983 and 1985 were retrieved regarding the additional search. Could the RMS clarify the date span of the different literature search on the active substances and its metabolites? Could the RMS clarify the list of metabolites included in the literature search? Was the list of metabolite considered complete?	

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(3)	Vol. 4 Annex C Representativeness of the toxicological studies to the technical specification. Syngenta	EFSA: from the analysis done by the RMS EFSA would consider that at least genotoxicity studies are covered by the Syngenta technical specification. Considering other endpoints, one of the main concerns is the skin sensitisation potential of some impurities as predicted by QSAR analysis. Did trinexapac-ethyl share the same alerts as the impurities?. A read-across analysis using OECD QSAR toolbox might be useful to address this point. The impurities showing a skin sensitisation potential might be considered relevant impurities and maximum content according to classification and labelling of mixtures for skin sensitisation potential might be set from a toxicological point of view.	
(4)	Vol. 4 Annex C Representativeness of the toxicological studies to the technical specification. Syngenta	EFSA: the RMS' view to consider toluene as relevant impurity is supported. In the past, maximum content of toluene (from the toxicological point of view) was established based on classification and labelling of mixtures considering the reproductive toxicity potential of toluene. This approach might be applicable to	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017) 137/185

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
	Toluene	toluene as a relevant impurity in trinexapac-ethyl technical specification.	
(5)	Vol. 4 Annex C Representativeness of the toxicological studies to the technical specification. Task force	EFSA: The equivalence between technical materials should be reconsidered once the technical specification is agreed and supported by a complete toxicity datapackage.	

Section 3 – Residue data

3. Residue data

Storage stability of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products (Sack St, 1998)	EFSA: The validation data for the method of analysis applied should be explored in more detail. Reference to the DAR is not sufficient. The fortification level of 25X LOQ used in the study is remarkably higher than the suggested level of OECD 506 (10X LOQ) and the levels tested for the validation of the analytical method (1N and 2.5N LOQ). Applicant/RMS are invited to discuss the impact on the recovery results. Please perform a complete evaluation of the study and verify equivalent conditions to current standards were met.	
(2)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products (Sack St, 1998)	EFSA: In Table B.7.1.1-1 results (in %) for trinexapac acid presented were adjusted by procedural recovery. Recoveries should be at least reported as uncorrected values. It is expected that in straw the (uncorrected) mean drops < 70% at 24 months. Please reconsider stability period of trinexapac acid residues in straw accordingly.	
(3)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products	EFSA: Storage stability data on wheat grains and straw and on OSR seeds were not provided for the major metabolite hydroxylated trinexapac acid (SYN548584) and are in principle required if residues of this metabolite are to be determined in crops.	

Section 3 – Residue data

Storage stability of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products	EFSA: Storage stability data on the major metabolites CGA313458, CGA113745 and CGA 224439 (CPCA) in the hydrolysis studies observed are missing (reported to be ongoing). These data are essential to demonstrate the integrity of the samples analysed in processing studies.	
(5)	Vol. 3, B.7.1.2 Stability of residues in animal products (Sack St, 2000)	EFSA: it was concluded that the stability study was acceptable with no deviation from current guidance (OECD 506). Since deviations were noted (e.g. 5X LOQ spiking level for fat; initial value at 0 time point not determined) and reporting not sufficiently detailed (number of stored and freshly spiked samples per matrix and sampling time, validation data of the method of analysis), please perform a detailed evaluation of the study and verify equivalent conditions to current standards were met:-	
(6)	Vol. 3, B.7.1.2 Stability of residues in animal products (Sack St, 2000)	EFSA. Table B.7.1.2 shows that at 3 months average uncorrected residue was 67% for cattle muscle. Argumentation that recoveries at 3 months from stored and freshly spiked samples were both comparable and low is questionable since mean procedural recovery in stored commodity was corrected for a theoretical initial T=0 level before being compared. Evidence of stability of trinexapac acid in muscle matrix covering the maximum length of storage of the samples from the feeding study is missing.	

Section 3 – Residue data

Storage stability of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(7)	Vol 1, Level 2.7.1 Summary of storage stability of residues	EFSA. The argument that degradation of trinexapac acid in wheat is slow and the submitted 24-months stability study is sufficient to cover also integrity of residues from trials where samples were stored up to 25.5 months is not a valid argument. The stability of trinexapac acid on cereal grain and straw covering the maximum length of storage of the samples from the residue trials shall be demonstrated.	
(8)	Vol 1, Level 2.7.1 Summary of storage stability of residues	EFSA: trinexapac acid was reported to be stable in high oil and high starch content commodities and in straw for 24 months. Apart of the stability period actually demonstrated, it is noted that only a single commodity (wheat grain or rape seed) instead of the two required by OECD 506 for the high starch and high oil content commodity groups was presented. Data are not sufficient to conclude on stability for the two categories.	

Metabolism, distribution and expression of residues in plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.2.1 Plants (studies 1 to 5)	EFSA: The original metabolism studies in cereals/grass (wheat, rye, rice, grass) and pulses/oilseeds (OSR) were not evaluated by the	

Section 3 – Residue data

Metabolism, distribution and expression of residues in plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		RMS. The overview tables and remarks from the DAR (Netherlands, 2003) were reported in the RAR and not commented. Please perform an independent, objective and transparent assessment of these studies and a detailed analysis for compliance with current scientific and technical knowledge. Otherwise the acceptability of these studies for the renewal of a.s. could be decided on.	
(2)	Vol. 3, B.7.2.1 Plants New metabolism study in oilseeds rape (study 6)	EFSA: To cover the entire group of pulses/oilseeds which includes crop parts potentially used as feed items (e.g. rape forage and legume forage), please address the metabolic pathway of trinexapac-ethyl in OSR relevant plant parts.	
(3)	Vol. 3, B.7.2.1 Plants (studies 6 to 7)	EFSA: The code CGA275537 is assigned to tricarboxylic acid (e.g. p. 45, 47, 51) and tricarballic acid (p. 52, LoEP). RMS is invited to verify that the code is unequivocally assigned to the correct common name(s).	
(4)	Vol. 3, B.7.2.1 Plants Summary and conclusions and Vol. 1, Level 2.7.2 Metabolism in plants	EFSA: It is noted that use on grass is not authorised in EU (see MRL review). Hence, the information that metabolism study in grass was 2.8N the NEU/SEU GAP should be deleted.	
(5)	Vol. 1, Level 2.7.2 Metabolism in plants	EFSA: For sake of clearness, please add the (N) application rate at which the new metabolism study on wheat was conducted in relation to the cGAP in barley.	

Section 3 – Residue data

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.2.2.1. Poultry (study 1 and 2)	EFSA: RMS concluded that study 1/2 assessed under Directive 91/414 was acceptable with limited deviations (number of animals, duration, dosing). Missing details (e.g. on method of analysis, capability to determine free and conjugated forms of metabolites; time from collection to sample analysis; total TRR identified/characterised; poor extractability in eggs, fat and skin/fat with no apparent attempts for further extraction efforts to characterise/identify the non-extracted residues; storage stability in animal matrices) do not allow concluding on acceptability and validity. Please provide detailed evidence of equivalence to OECD 503.	
(2)	Vol. 3, B.7.2.2.2. Lactating ruminants (study 1 and 2)	EFSA: RMS concluded that study 1/2 assessed under Directive 91/414 were acceptable with limited deviations (duration, low identification rate). Missing details (e.g. time of sacrifice of animals, time from collection to sample analysis; method of analysis, efficacy of extraction, capability to determine free and conjugated forms of metabolites; total TRR identified/characterised; poor extractability in fat with no apparent attempt for further extraction efforts; information on the storage stability in animal matrices) do not allow concluding on acceptability and validity. Please provide detailed evidence to demonstrate the	

Section 3 – Residue data

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		equivalent conditions to OECD 503.	
(3)	Vol. 3, B.7.2.2.2 Lactating ruminants (study 2 and 3)	EFSA: RMS reported that plateau in milk was reached after 2 or 3 days. However, it cannot be seen from the documentation provided. A table showing the daily TRR and trinexapac levels in milk collected over the 4 days of study 2 and, additionally, study 3 shall be provided to substantiate the conclusion.	
(4)	Vol 3, B.7.2.2.4 Fish and Vol. 1, Level 2.7.2. Metabolism in animals	EFSA: Vol 3 of the RAR shall include the scientific assessment of the available experimental studies. If the applicant is of the opinion that the risk assessments can be completed without submission of data on metabolism, distribution and expression of residues in fish/feeding studies with fish, the justification supporting this opinion should be provided in Vol 1. It is noted that the argument that no agreed test method or guidance is available as reported in Vol 1 is not considered a valid justification.	
(5)	Vol 1, Level 2.7.2. Metabolism in animals	EFSA: Metabolites SYN548584, CGA275537, CGA300405 and CG351210 are major plant metabolites. The need for metabolism data in livestock dosed with a mixture of compounds reflecting the level of their exposure in feed items of the treated crops shall be addressed.	

Section 3 – Residue data

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Level 2.7.3 Definition of residues (2) trinexapac acid, free and conjugated	EFSA: In Table 2.7.3-1, the residue definition for risk assessment includes the metabolite hydroxylated-CGA179500 (SYN548584) but CFs were reported to be calculated based on the residue levels of trinexapac acid (free) and total trinexapac acid (free and conjugated) only (see footnote (e) of the table). Apart of the calculation of PFs using results from processing studies analysed for trinexapac acid only which acceptability is to be demonstrated, it is not clear how CFs for risk assessment shall be calculated, since SYN548584 was not analysed in processed products.	
(2)	Vol 1 Level 2.7.3 Definition of residues (6) hydroxylated CGA179500 (SYN548584)	EFSA: Hydroxylated trinexapac (SYN548584) represented 12% TRR (0.18 mg eq/kg) in wheat grain from the metabolism study at 1N the cGAP. Its concentrations were only theoretically calculated in cereal grains treated according to the cGAP using a CF of 1.434. Please provide information on how this value was derived.	
(3)	Vol. 1, Level 2.7.3 Definition of residues in plants	EFSA: Although the nature of residues in processed products was different than in primary crops, the residue definition (RD) for risk assessment in primary and processed products has been proposed as "sum of trinexapac acid (free and conjugated) and hydroxylated trinexapac acid, expressed as trinexapac acid" with CF of 2.5 (grain) and 5 (straw). In Table 2.7.3-1 of summary of processing studies RD is reported as	

Section 3 – Residue data

Residue definition			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		"trinexapac acid (free and conjugated)" with CF of 2 (grain) and 4 (straw). Please clarify the RD proposed for enforcement and risk assessment in processed products and address the discrepancy of RD and CFs.	
(4)	Vol 1, Level 2.7.3 Definition of residues	EFSA: The proposed residue definitions for risk assessment in plants, processed and products of animal origin need to be reconsidered pending upon further discussion and decision in Mam-Tox Section 2 on the toxicological proprieties of the metabolites observed in the plant/livestock metabolism and hydrolysis studies but not in rat metabolism.	

Residue trials in plants and identification of critical GAP			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: Evidence that the conditions of OECD 509 are met in the supervised residue field trials (only study 6 on barley and study 4 on wheat were reported to be conducted according to OECD 509) and that samples of grains and straw are covered by acceptable storage stability data shall be provided.	
(2)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: Trials with samples analysed for hydroxylated trinexapac acid (SYN548584) are missing and they may be required (see comment under Vol 1,	

Section 3 – Residue data

Residue trials in plants and identification of critical GAP			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		Level 2.7.3 Definition of residues).	
(3)	Vol. 3, B.7.3 Annex B7 (AS) Residue data, barley and wheat	EFSA: Details of the locations where each single residue trial was conducted were not reported. The information is essential to verify the independency of the residue trials on wheat and barley.	
(4)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: The calculation of theoretical concentrations of hydroxylated trinexapac acid and the CFs from enforcement to risk assessment reported in Tables B.7.3.1.-3 (barley) and B.7.3.2.-3 (wheat) were provided in Appendix I. Reference is mismatched (Appendix I of Vol 3 refers to literature review). Please help retrieving the calculations.	
(5)	Vol. 3, B.7.3 Magnitude of residue trials in plants, barley	EFSA: It is noted that trial in NC13038-02 (study TK0178795) in winter barley residues of trinexapac acid alone as well as total free and conjugated were <LOQ in grains and straw. Considering the residue levels observed in all the other trials, it shall be verified if the trial had failed to determine residues and shall be disregarded or observations are within normal agricultural practice variability.	
(6)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: EFSA: According to the proportionality principle, not only the overdosed, but also residues from trials on wheat and barley conducted at the nominal application rate ($\pm 25\%$) should be scaled (entire SEU dataset).	

Section 3 – Residue data

Residue trials in plants and identification of critical GAP			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(7)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: Since the SEU and NEU GAP on winter barley and wheat are the same, NEU and SEU (after scaling) datasets should be statistically tested if a more robust MRL/input values can be derived from combined dataset. It is advisable that if NEU/SEU data belong to similar populations (U-test, 5%), also the NEU dataset is scaled to exact application rate (entire NEU/SEU dataset).	

Feeding studies in poultry, ruminants, pigs and fish			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 3, B.7.4.1 Poultry	EFSA: Since Vol 3 of the RAR includes the scientific assessment of the available experimental studies, RMS is asked to report current situation (no feeding study available, as done for pigs and fishes). Any justification for waiver of submission of data on feeding studies with poultry should be provided in Vol 1.	
(2)	Vol 3, B.7.4.2 Ruminants (study 1)	EFSA: The feeding study on cows was conducted according to SANCO guidance 70/31/VI/95. RMS is invited to provide additional information and detailed evidence to demonstrate that equivalent conditions to OECD 505 are met. (e.g., but not exclusively: provide the dose levels as mg/bw and the body weight of the animals;	

Section 3 – Residue data

Feeding studies in poultry, ruminants, pigs and fish			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		detailed description of the validation of the analytical method; compliance of type of tissue sampled for analysis; milk data and plateau analysis; individual levels for each sample not merely the mean and average of the 3 as in Table B.7.4.2-2)	

Effects of processing			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B.7.5.3 Magnitude of residue in processed commodities	EFSA: The original processing studies (study 1-to 8, and 13) were reported not to be evaluated by the RMS. Study 9, 14, and 15 were conducted according to US-EPA guidance. Furthermore, these studies analysed trinexapac free acid only. An independent, objective and transparent assessment of these studies and a detailed analysis for compliance with current scientific and technical knowledge shall be conducted. Evidence of equivalence to OECD 508 to be provided.	
(2)	Vol. 3, B.7.5.3 Magnitude of residue in processed commodities	EFSA. None of the samples from the processing studies was analysed for hydroxylated-CGA179500 (SYN548584). The nature and magnitude in processed products need to be addressed.	
(3)	Vol. 3, B.7.5.3 Magnitude of residue in processed	EFSA: Samples of grains from 2 field trials on barley and 2 field trials on wheat were collected and split	

Section 3 – Residue data

Effects of processing			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
	commodities (study 10-12, barley; study 16-18, wheat)	each into 2 subsamples prior to undergo the different processing. It is questionable that these studies are providing 4 independent results per each processed commodity.	
(4)	Vol. 1, Level B.7.6 Summary of effects on processing	EFSA: The validity of the processing trials in wheat and barley and PFs/CFs can only be verified when clarification of questions and submission of further information as identified during the commenting of the RAR become available. For the time being review for completeness and correctness is not possible.	

Residues in rotational crops			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, B.7.6.1. Metabolism in rotational crops (study 1)	EFSA: RMS concluded that the rotational crop study assessed under Directive 91/414 was acceptable. This study was underdosed (0.75N) and conducted according to US-EPA guidance. Evidence of equivalence to current data requirements (OECD 502) should be provided.	
(2)	Vol. 3, B.7.6.2 Magnitude of residues in rotational crops and Vol.1, Level 2.7.7 Summary of residues in	EFSA: For sake of transparency, please report that the new confined rotational crop study was conducted at 1.5N (300 g/ha instead of 200 g/ha) the maximum rate of the representative crops (barley).	

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017)150/185

Section 3 – Residue data

Residues in rotational crops			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
	rotational crops		

Summary of other studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol 1; Level 2.7.8. Summary of other studies	EFSA: Although cereals are considered of low attractiveness to bees for pollen/nectar, data indicate translocation of the residues throughout the plant parts as attested by residues observed in cereals (TRR 1.4 mg eq/kg in metabolism at 1N; highest residue trinexapac (free and conjugated) 1.1 mg/kg in residue trials). Therefore, data to exclude of pollen/nectar collection by bees as required in the EFSA guidance on the risk assessment of PPP on bees need to be addressed. The argument that not agreed test method or guidance is available is not considered a valid justification.	

Estimation of the potential and actual exposure through diet and other sources			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 1, Level 2.7.9 Estimation of potential and actual exposure throughout the diet and	EFSA: The consumer risk assessment for trinexapac acid is pending clarification of questions and submission of further information as identified during the commenting of the RAR, in particular	

Section 3 – Residue data

Estimation of the potential and actual exposure through diet and other sources			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	other concerns	with regards to the levels and toxicological relevance of metabolites observed in plants, livestock and processed products.	
(2)	Vol. 1, Level 2.7.9 Estimation of potential and actual exposure throughout the diet and other concerns	EFSA: For acute/chronic risk assessment of the processing metabolite CPCA, the TTC concept comparing predicted dietary exposure levels through processed products from cereals treated according to representative uses with a threshold (Cramer II, 1.5 µ/kg bw) is not acceptable. There is currently not implemented guidance on the subject tool and the metabolites is common to other a.s.	

Proposed MRLs and compliance with existing MRLs			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Level 2.7.10	EFSA: The proposed MRL values and residue definitions in cereals can be verified when a confirmation of a complete set of valid and independent trials with samples analysed according to the residue definition for enforcement and risk assessment is available and meets currently applicable guidance for AIRIII.	

Section 3 – Residue data

Proposed import tolerances and compliance with existing import tolerances			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	NA		

Other comments			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	LoEP. Section 3 Residue pattern in processed commodities	EFSA: it is reported that metabolite CGA224439, included in the table summing up results of the hydrolysis study (see p. 21) was not included in "standard reference compound lists". The remark is not clear. Nevertheless, in principle the lists should include all cited compounds.	
(2)	LoEP Section 3 Stability of residues (p. 24)	EFSA: LoEP to be amended by including the matrix "eggs" as per template LoEP (SANCO/12483/2014 rev. 3)	
(3)	Vol. 3, B.7.8 Reference relied on. Literature search and Appendix I Literature data	RMS is asked to confirm that the open literature found by the applicant during the rapid assessment has been screened and none was of potentially relevant or unclear for relevance (no details reported also in the literature search available on the "K"-drive).	
(4)	Vol. 3, B.7.8 Reference relied on. Literature search and Appendix I Literature data	Literature search on major metabolites identified in plants such as hydroxylated trinexapac acid (SYN548584) and CGA 275537 was not conducted. It seems that the search was done combining a.s. with the metabolites plus main categories (e.g. METABOL? OR RESIDUE). Thus, limiting the records	

Section 3 – Residue data

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		found. Please provide clarification regarding the exclusion criteria and strategy applied in the literature search.	

Section 4 – Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.8 (CA), 8.1.1.1 Degradation of the active substance in aerobic soil, Spare 1992a, p 17	EFSA: Soil bacterial biomass was determined pre-dosing to be $>3 \cdot 10^8$ CFU/g (first aerobic incubation) and after 90 days of aerobic incubation soil bacterial biomass was $>3.0 \cdot 10^8$ CFU/g. It seems strange that after 90 day the bacterial biomass did not change. Please, check the values.	
(2)	Vol. 3, B.8 (CA), 8.1.1.1 Degradation of the active substance in aerobic soil, Hellstern 2008, p 19 List of endpoints, Route of degradation (aerobic) in soil, p 35	EFSA: High percentage of non-extractable residues was found in the study by Hellstern 2008. For extraction it was used the same method as in Mamouni 2000, which was questioned already in the first evaluation. Therefore, more clarifications on the extraction method used should be provided.	
(3)	Vol. 3, B.8 (CA), 8.1.1.1 Degradation of the active substance in aerobic soil, Adam 2014, p 25 List of endpoints, Route of degradation (aerobic) in soil, p 35	EFSA: In the comment concerning the study by Adam (2014) it was reported that not validated extraction methods were used. High percentage of non-extractable fraction was detected at first sampling point for 18 Acres and Sarpy soils. It was explained that current extraction procedure was improved, however more clarifications on the improvement should be provided. It is not clear to which selected samples the last extraction method was applied.	
(4)	Vol. 3, B.8 (CA), 8.1.1.1	EFSA: High percentage of non-extractable fraction	

Section 4 – Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Degradation of the active substance in aerobic soil, Walther 2008, p 37 List of endpoints, Route of degradation (aerobic) in soil, p 35	detected at early sampling points. Extraction method similar to Mamouni (2001) was used, which was questioned during previous evaluation. More clarification on the extraction method used should be provided.	
(5)	List of endpoints, Rate of degradation in soil (aerobic) laboratory studies active substance, p 36	EFSA: the pH values reported for Loam (Gartenacker) and Sandy Clay Loam (18 Acres) soils from the study by Adam (2014) are not the same as the ones reported in Vol. 3, B.8 (CA) (Table 8.1.1.1-21, p 26). The correct values should be 7.2 and 6.47 respectively. Please, correct the LoEP.	
(6)	Vol. 3, B.8 (CA), 8.1.2.1.1 Aerobic degradation of the active substance, Terry 2015, p 76	EFSA: In the figure showing the graphs of the different kinetic models applied for deriving persistence endpoints to the Gartenacker (Adam 2014) soil, the y axis for FOMC seems to have an order of magnitude different from the order graphs.	
(7)	Vol. 3, B.8 (CA), 8.1.2.1.1 Aerobic degradation of the active substance, Terry 2015, p 76	EFSA: it is not clear why a persistence endpoint was not derived for metabolite trinexapac acid in the Gartenacker (Adam 2014) soil.	
(8)	Vol. 3, B.8 (CA), 8.1.1 Route and rate of degradation in soil	EFSA: The molecular structures of trinexapac-ethyl and trinexapac acid could lead to the formation of isomers. Information on whether the different isomers of trinexapac-ethyl and trinexapac acid	

Section 4 – Environmental fate and behaviour

Route and rate of degradation in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		are degraded in soil at different rates is missing. Clarification on this point needs to be provided.	
(9)	List of endpoints, Rate of degradation in soil (aerobic) laboratory studies active substance and transformation products, p 36-38	EFSA: Where the rate of degradation endpoints result from a biphasic fit, the alpha, beta, k1, k2 and g values should be reported in the list of endpoints.	

Adsorption, desorption and mobility in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(10)	Vol. 3, B.8 (CA), 8.1.3.1.1 Adsorption and desorption of the active substance	EFSA: the study by Spare (1990) on the adsorption/desorption of trinexapac acid is reported under the paragraph concerning the active substance. However, trinexapac acid is a metabolites, and then it should be moved under paragraph 8.1.3.1.2 concerning the adsorption/desorption of metabolites.	

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(11)	Vol. 3, B.8 (CA), 8.2.4	EFSA: Article 4 (approval criteria for active	

Section 4 – Environmental fate and behaviour

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	Impact on water treatment processes, p 167 Vol. 1, 2.14 Effect of water treatment processes on the nature of residues present in surface water, p 154	substances) 3. (b) of Regulation (EC) No 1107/2009 requires that 'it shall have no immediate or delayed harmful effects on human health, including that of vulnerable groups, or on animal health,.....through drinking water (taking into account substances resulting from water treatment)'. Information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water has not been presented or discussed in the RAR.	
(12)	Vol. 3, B.8 (CA), 8.2.1.1 Hydrolytic degradation, Adam 2008, p 129	EFSA: it is reported that the hydrolysis of pure [¹⁴ C]-Trinexapac was studied in Adam (2008). However, the reported IUPAC name is: 4-cyclopropyl(hydroxyl)methylene-3,5-dioxo[3,5-14 C]cyclohexane[¹⁴ C]carboxylate which seems to be trinexapac-ethyl. Could the RMS clarify which was the tested substance?	
(13)	Vol. 3, B.8 (CA), 8.2.1 Route and rate of degradation in aquatic system	EFSA: The molecular structures of trinexapac-ethyl and trinexapac acid could lead to the formation of isomers. Information on whether the different isomers of trinexapac-ethyl and trinexapac acid are degraded in aquatic systems at different rates is missing. Clarification on this point needs to be provided.	

Fate and behaviour in air

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017)158/185

Section 4 – Environmental fate and behaviour

No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	none		

PEC in soil			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(14)	Vol. 3, B.8 (CP), 8.1.3 Estimation of concentrations in soil, p 9 List of endpoints, PEC soil, p 48	EFSA: in Table 8.1.3-1 the DT50 vales used in the determination of PECsoil for trinexapac-ethyl and trinexapac acid were 1.2 and 40 days, respectively. However, it is not clear the origin of these values. Furthermore, the worst case endpoint derived in dry conditions at 20°C should be used when calculating the PECsoil.	

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(15)	Vol. 3, B.8 (CP), 8.1.3 Estimation of concentrations in groundwater	EFSA: It is not clear why relative application dates (25 days after emergence) were used when modelling with PEARL in Gabsi (2015) and Bramley (2016).	
(16)	Vol. 3, B.8 (CP), 8.1.3 Estimation of concentrations in groundwater List of endpoints, PEC	EFSA: in Bramley (2016) the application date in Jokioinemi scenario was set in October because it reflects more the agricultural practices in the scenario for cereals. However, the same approach was not followed in the study by Gabsi (2015a). Clarifications for using different approaches	

Section 4 – Environmental fate and behaviour

PEC in surface water and ground water			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	groundwater	should be provided.	
(17)	Vol. 3, B.8 (CP), 8.1.4 Estimation of concentrations in groundwater, p 20	EFSA: in Table 8.1.4-11 the calculation for CGA179500 in spring cereals does not seem to be correct. The correct number should be 82 instead of 65.6.	
(18)	Vol. 3, B.8 (CP), 8.1.4 Estimation of concentrations in groundwater List of endpoints, PEC groundwater	EFSA: for metabolite CGA275537 degradation and adsorption endpoints are not available and then endpoints derived for metabolite CGA300405 were used. However, more scientifically based justifications for using values from metabolite CGA300405 as surrogate for metabolite CGA275537 should be provided. Otherwise, worst case or laboratory values should be used.	
(19)	Vol. 3, B.8 (CP), 8.2.4.1 Estimation of concentrations in surface water for metabolite, p 33	EFSA: in Table 8.2.4.1- 2 the DT50 in soil reported for trinexapac-ethyl is 1 d. Could the RMS clarify the origin of this value?	

PEC from airborne transport and other routes of exposure			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	none		

Definition of the residues

Comments of EFSA on the assessment report on trinexapac-ethyl

(18.07.2017)160/185

Section 4 – Environmental fate and behaviour

No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(20)	Vol. 1, 2.8.5 Definition of the residues in the environment requiring further assessment, p 122	EFSA: the sediment compartment is missing in the table reporting the residues requiring further assessment.	
(21)	List of endpoints, Residues requiring further assessment, p 47	EFSA: in surface water and sediment metabolite CGA275537 is missing.	

Other comments incl. available monitoring data			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(22)	Vol. 3, B.8 (CA), 8.6.1 Literature review, p 173	EFSA: Regulation (EC) No 1107/2009 requires a search of the scientific peer-reviewed open literature. The APPL submitted the search, however the terms used for the search do not consider all the metabolites (possible systematic names, CAS No. etc.) identified in the RAR at levels that trigger assessment (as CGA179500, CGA275537, WaterM3Hydrolysis and M2). Therefore, data or justifications for not providing those data are required. Furthermore, could be confirmed that the EFSA guidance (2011) on open literature search was followed?	
(23)	Name of metabolite CGA179500	EFSA: the correct name for metabolite 'trinexapac acid' should be 'trinexapac'. Therefore, the name should be changed to 'trinexapac' or the code CGA179500 should be used in the whole RAR and	

Section 4 – Environmental fate and behaviour

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		LoEP.	

Section 5 - Ecotoxicology

5. Ecotoxicology

Birds and other terrestrial vertebrates			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3, (AS) B.9.1.1.3-Sub chronic toxicity and reproduction to birds-Hakin 1991a	EFSA: It is unclear why the reduction in eggs production at 600 ppm was not considered as biologically significant.	
(2)	Vol. 3, (AS) B.9.1.4 Other data on effects on terrestrial vertebrate wildlife.	EFSA: It is not sufficient to provide the LC50 for the available amphibian test, a summary of this study should be included in the RAR and the study report should be provided in the dossier.	
(3)	Vol. 3, (PPP) B.9.2.1 Risk assessment for birds-Secondary poisoning	EFSA: A risk assessment for secondary poisoning is needed for the surface water metabolites, for fish-eating birds and mammals, and for the soil metabolites for earthworm-eating birds and mammals unless the LogKow is lower than 3.	
(4)	Vol. 3, (PPP) B.9.2.1 Risk assessment for birds-Metabolites	EFSA: The extrapolation of the toxicity from mammals to birds is questionable. Further consideration is needed also for metabolites CGA 275537, CGA300405, CGA313458 and CGA 329773. Could a list of plant metabolites relevant for the assessment, possibly in a tabular format be provided?	
(5)	Vol. 3, (PPP) B.9.2.2 Risk assessment for mammals-Metabolites	Please could it be clarified if CGA 113745 is a relevant plant metabolite, it is not mentioned as such when relevant plants metabolites are listed e.g. for birds. It is unclear why the metabolite CGA275537 was	

Section 5 - Ecotoxicology

Birds and other terrestrial vertebrates			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		considered of low toxicological concern since it is acutely more toxic than the parent compound. Further consideration is needed also for metabolites CGA300405. Could a list of plant metabolites relevant for the assessment, possibly in a tabular format be provided?	
(6)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP e.g. acute toxicity study with bobwhite quail.	
(7)	List of endpoints	EFSA: Could the available toxicity data on metabolites for mammals be included in the LoEP.	

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 (AS) B9.2; Vol. 3 (PPP) B9.3. Effects on aquatic organisms	EFSA: Please could the results of the analytical verifications of the tested concentrations be included in all the study summaries of the aquatic toxicity studies? In various cases only the overall recovery percentage is reported. Also, it should be specified were relevant whether trinexapac ethyl or trinexapac acid (or both) were measured in the tests with the trinexapac-ethyl technical. In addition, EC10 and EC20, or a justification for not providing those, should be provided for all the available chronic toxicity studies, this was not done for Putt 1991 (reproductive toxicity study for	

Section 5 - Ecotoxicology

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		<i>Daphnia magna</i>).	
(2)	Vol. 3 (AS) B9.2.1- ELS study- Sousa 1991	EFSA: Please include the valid EC10 and EC20 for this study in the LoEP.	
(3)	Vol. 3 (AS) B9.2.2- Bioconcentration in fish- Fackler (1990)	EFSA: Please include an assessment of the validity criteria for this study. In addition, could it be clarified whether the bioconcentration factors as a function of lipid content of the fish was determined?	
(4)	Vol. 3 (AS) B9.2.2- Bioconcentration in fish- Fackler (1991)	EFSA: Please include an assessment of the validity criteria for this study.	
(5)	Vol. 3 (AS) B9.2.4- Acute toxicity to aquatic invertebrates- Smith 1990	EFSA: The mean measured tested concentrations are reported only for 3 concentrations out of 5, where the analytical measurements limited to those three concentrations?	
(6)	Vol. 3 (AS) B9.2.4- Acute toxicity to aquatic invertebrates- Mysids- Sousa 1991	EFSA: Could it be indicated whether the drop in the oxygen was observed in all treatments and control?	
(7)	Vol. 3 (AS) B9.2.5.3- Sediment dwelling organisms	EFSA: Further information is needed to address the risk to sediment organisms for CGA179500 (trinexapac acid).	
(8)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Taylor and Pickering 2015b,d,e, f	EFSA: The study from Hoberg (1991a), Hoberg (1991b), Hoberg (1991c) were not considered valid; the EC10 and EC20 estimates are not needed and should not be considered valid.	
(9)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Hoberg	EFSA: Please could it be further described why the studies from Hoberg (1991a), Hoberg (1991b),	

Section 5 - Ecotoxicology

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	(1991a), Hoberg (1991b), and Hoberg (1991c)	and Hoberg (1991c) were considered not reliable? The level of details in the study summaries is not sufficient for an independent assessment of these studies.	
(10)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Maetzler 2001	EFSA: Please include additional details of the biological finding (biomass/yield/growth rate in the control and in the treatments) of this study possibly in a tabular format. The endpoints from this study were not included in the LoEP. It is additionally noted that for this study EC10 were not available.	
(11)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Grade 2001a,b; 1995b	EFSA: It is not agreed that the validity criteria of OECD 201 does not apply to <i>Anabaena flos-aquae/Navicula pelliculosa</i> since this species is listed between the test species in the same test guideline. Please clarify.	
(12)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Grade 1995c	EFSA: The validity criteria in line with OECD 201 (most recent version) are not met. It is, however, noted that this species is not listed between the test species in the guideline. In consideration of the above, it is unclear whether this study should be considered as valid. Please include further details on the results i.e. biological finding (biomass/yield/growth rate in the control and in the treatments).	
(13)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Seeland-Fremer & Emnet 2015a	EFSA: Please include further details on the EC10 and EC20 derivation.	
(14)	Vol. 3 (AS) B9.2.7- Effects	EFSA: The studies from Hoberg (1991), Hoberg	

Section 5 - Ecotoxicology

Aquatic organisms			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	on aquatic Macrophytes-Hoberg (1991), Hoberg (1992),	(1992) were not considered valid; the EC10 and EC20 estimates are not needed and should not be considered valid.	
(15)	Vol. 3 (AS) B9.2.7- Effects on aquatic Macrophytes-Grade (2001)- trinexapac ethyl study	EFSA: The test item concentrations were not maintained within 20% with respect to the nominal concentration; therefore the endpoints cannot be expressed in term of nominal concentrations. Please include the details of the biological findings in a tabular format and an assessment of the validity criteria.	
(16)	Vol. 3 (AS) B9.2.7- Effects on aquatic Macrophytes-Kirkwood (2015)	EFSA: EC10 and EC20 estimates were not provided for this study.	
(17)	Vol. 3 (AS) B9.2.7- Effects on aquatic Macrophytes-Grade (2001)- trinexapac acid study	EFSA: Please include additional details of the biological finding of this study possibly in a tabular format.	
(18)	Vol. 3 (PPP) B9.3.1- Effects on aquatic Macrophytes- Brown and Maynard 2003	EFSA: Since the concentrations were not maintained within 20% of the nominal the endpoints from this study should be expressed in term of mean measured concentrations.	
(19)	Vol. 3 (PPP) B9.3.3- Aquatic risk assessment	EFSA: The endpoint expressed in term of growth rate should be used in the aquatic risk assessment for algae.	
(20)	Vol. 3 (PPP) B9.3.3- Aquatic risk assessment-metabolites	EFSA: From the available acute toxicity data for trinexapac-ethyl <i>Mysidopsis bahia</i> seems to be the most sensitive species. However, a chronic	

Section 5 - Ecotoxicology

Aquatic organisms			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		toxicity test is not available for this species. In addition, a test on this species is not available for trinexapac acid.	
(21)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP. It seems that only the lowest endpoints were included whilst all valid endpoints should be included.	
(22)	List of endpoints	EFSA: Please double check the acute endpoint for Daphnia magna for trinexapac acid it should be >100 m a.s./L (ref. study from Grade (1995)).	

Bees and non-target arthropods			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3(AS) B.9.3.1 Effects on bees- Hoxter 1990	EFSA: Please clarify why this study was considered not acceptable. The presented summary does not include enough details for an independent assessment.	
(2)	Vol. 3 (PPP) B.9.5.1 Effects on bees- Bocksch (2004)	EFSA: Please include a summary table of the biological observations for this study.	
(3)	Vol. 3 (PPP) B.9.5.1 Effects on bees- Ruhland 2014	EFSA: Was the mortality assessed at daily interval in this study? It is additionally noted that an assessment of the sublethal effects e.g. effects on the HPG was not performed. Please clarify how the endpoint is expressed in the results; it is not consistently reported see section B.9.6 and the	

Section 5 - Ecotoxicology

Bees and non-target arthropods			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		list of endpoints.	
(4)	Vol. 3 (PPP) B.9.5.1 Effects on bees- Kleebaum (2014)	EFSA: The available larvae test foresee a single dosage and it is therefore not a repeated exposure study, as it is recommended in the EFSA bee guidance.	
(5)	Vol. 3 (PPP) B.9.6- Risk assessment for honeybees	EFSA: A risk assessment according to the EFSA Bee Guidance Document was included in the RAR. However, this does not include an assessment via all the relevant exposure routes; an assessment of the exposure via contaminated water is missing. Although it is acknowledged that the EFSA Bee Guidance Document is yet to be implemented, it was recently agreed at the Pesticides Peer Review Expert Meeting 133 (September, 2015) that it should be used (at least the first tier scheme and the general principles for the higher tier). The previous risk assessment schemes are not able to consider various aspects which are now considered to be important in the risk assessment for bees (e.g. chronic, larvae, additional exposure scenarios). Furthermore, it is now necessary to provide chronic adult and larvae data according to regulation 283/2011. Therefore, in the absence of an alternative risk assessment scheme which is able to address these points, it was agreed that the EFSA Bee Guidance should be used.	
(6)	Vol. 3 (PPP) Risk assessment for	EFSA: In addressing the risk assessment for bees according to the EFSA guidance document	

Section 5 - Ecotoxicology

Bees and non-target arthropods			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
	honeybees	information/assessment is needed of the potential for accumulative effects.	
(7)	Vol. 3 (PPP) Risk assessment for honeybees	EFSA: In accordance with Regulation (EU) 283/2013, a consideration of the risk to bees from metabolites is needed. It is suggested that the methodology in the EFSA (2013) Bee guidance is followed to identify which plant metabolites should be assessed.	
(8)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP. It seems that only the part of the endpoints was included whilst all valid endpoints should be included.	
(9)	List of endpoints	EFSA: The risk assessment for bees in line with EFSA (2013) should be included in the LoEP.	

Earthworms and other non-target soil macro- and mesofauna			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 3 (AS) B.9.4 Earthworms and other non-target soil macro- and mesofauna	EFSA: No chronic studies performed with the active substance are available for earthworms and other non-target soil macro- and mesofauna.	
(2)	Vol. 3 (PPP) B.9.7 Effects on on-target soil meso- and macrofauna- Friedrich 2015	EFSA: The NOEC for reproduction was set at 309 mg test item /kg soil dw, however, at that level a reduction in the number of juveniles with respect to the control was observed. Please clarify why	

Section 5 - Ecotoxicology

Earthworms and other non-target soil macro- and mesofauna			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		this effect was not considered as biologically significant.	

Soil nitrogen transformation			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 (AS) B.9.5 Effects on soil nitrogen transformation	EFSA: Further information may be needed to address the risk to soil microorganisms for trinexapac acid.	

Terrestrial non-target higher plants			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3 (CP) B.9.7 Effects on other terrestrial organisms	EFSA: It is reported that in the study Chetram 1991 an inverse dose response in the radicle elongation was observed. Could additional details on these findings be included?	
(2)	List of endpoints	EFSA: For completeness it should be indicated that the studies from Wardle (2003) were neither performed under GLP nor according nor were guideline studies. This makes it difficult to assess their validity.	

Section 5 - Ecotoxicology

Other comments incl. available monitoring data			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 4 Batches used in the ecotoxicological test	EFSA: The equivalence between technical materials should be reconsidered once the technical specification is agreed. Pending on the above, it should be also assessed whether the batches used in the ecotoxicological testing are compliant with the technical specifications of the first approval.	
(2)	Vol. 3 (CA) B.911 Literature review	EFSA: Please include additional details on how the literature search was performed e.g. identifiers used in the search for the active substance and the metabolites. In addition the criteria for assessing the reliability and relevance of the studies should be included. Could be confirmed that the EFSA guidance (2011) on open literature search was followed?	
(3)	Classification and labelling	EFSA: It is noted that the classification and labelling is included in the harmonised C&L section, please move it in the Peer Review proposal section. The C&L of trinexapac-ethyl was not yet harmonised.	
(4)	Endocrine disruption	EFSA: The ecotoxicity data available for trinexapac-ethyl may not be sufficient to conclude on endocrine disruption in non-target organisms.	
(5)	Formulations tested	EFSA: It is noted in the ecotoxicological section a different formulation that the representative one was tested. It should be ensured that the additional formulation tested is comparable to the representative one.	
(6)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP.	

Section 5 - Ecotoxicology

Other comments incl. available monitoring data			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		It seems that only the part of the endpoints was included whilst all valid endpoints should be included.	

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 173/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Physical and chemical properties of the active substance			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Physical and chemical properties of the plant protection product			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Data on application and efficacy			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 174/185

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Further information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Methods of analysis			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	Vol. 1, 2.5.2, Methods for post control and monitoring purposes	EURLs: multi-residue methods for enforcement of the residue definition 'trinexapac (sum of trinexapac (acid) and its salts, expressed as trinexapac)' as well as for trinexapac-ethyl are available, with LOQs of 0.01 mg/kg being achievable for both compounds in high water content, high acid content, high fat content and dry commodities. The EURLs have so far not developed any methods for any of the metabolites of trinexapac	

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 175/185

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Acute toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Short-term toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Genotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Long-term toxicity and carcinogenicity			

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 176/185

Section 2 – Effects on human and animal health

Reproductive toxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Neurotoxicity			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Further toxicological studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Toxicological data on metabolites			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Medical data and information			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 177/185

Section 2 – Effects on human and animal health

Toxicological end points: ADI, ARfD, AOEL			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Product exposure and risk assessment, including dermal absorption			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments, incl comments on volume 4 (impurities, batches) and proposals for classification			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 178/185

Section 3 – Residue data

3. Residue data

Storage stability of residues			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Metabolism, distribution and expression of residues in plants			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Residue definition			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Residue trials in plants and identification of critical GAP			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 179/185

Section 3 – Residue data

Residue trials in plants and identification of critical GAP			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Feeding studies in poultry, ruminants, pigs and fish			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Effects of processing			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Residues in rotational crops			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Summary of other studies			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 180/185

Section 3 – Residue data

Estimation of the potential and actual exposure through diet and other sources			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Proposed MRLs and compliance with existing MRLs			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Proposed import tolerances and compliance with existing import tolerances			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 181/185

Section 4 - Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Adsorption, desorption and mobility in soil			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Fate and behaviour in air			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

PEC in soil			

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 182/185

Section 4 - Environmental fate and behaviour

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

PEC in surface water and ground water

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

PEC from airborne transport and other routes of exposure

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Definition of the residues

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments incl. available monitoring data

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Section 5 - Ecotoxicology

5. Ecotoxicology

Birds and other terrestrial vertebrates			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Aquatic organisms			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Bees and non-target arthropods			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Earthworms and other non-target soil macro- and mesofauna			
No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Soil nitrogen transformation			

Comments of EURLs on the assessment report on Trinexapac-ethyl

(18.07.17) 184/185

Section 5 - Ecotoxicology

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Terrestrial non-target higher plants

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other non-target terrestrial organisms (flora and fauna)

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Biological methods for sewage treatment

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Other comments incl. available monitoring data

No.	<u>Column 1</u> Reference to assessment report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

TABLE OF CONTENTS

	Document
00	Cover page
01	Comments on the assessment report
02	Reporting table
03	Pesticides peer review meeting reports
04	Evaluation table
05	Comments on the additional information assessment
06	Comments on the draft EFSA conclusion

section 0 – General comments

0. General

General				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
No comments				

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(1)	-Vol.1	NL: No comments		
1(2)	Vol.4 C.1.1.1-C.1.2.4-2, Cheminova, source 1	Cheminova comments (9)	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(3)	Vol.4 C.1.1.1-C.1.2.4-1, Cheminova, source 2	Cheminova comments (6)	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(4)	Vol4 C.1.1.2 (Cheminova; Helm; ADAMA)	FR comment	please refer to separate Reporting tables, Confidential (Cheminova, Adama, Helm)	please refer to separate Reporting tables, Confidential (Cheminova, Adama, Helm)
1(5)	Vol.4, Cheminova, source 2, C.1.1.2	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(6)	Vol.4, Helm, C.1.1.2	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(7)	Vol.4, Cheminova, source 2, C.1.2.1	EFSA comments	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(8)	Vol. 4, Helm, Source 1 and 2, C.1.2.1	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(9)	Vol. 4, ADAMA, C.1.2.1	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(10)	Vol. 4 All notifiers, C.1.2.2, Identity of impurities	EFSA comment	please refer to the separate confidential Reporting tables	please refer to the separate confidential Reporting tables
1(11)	Vol.4, Syngenta,C.1.2.2	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(12)	Vol.4, Cheminova, source 1, C.1.2.2	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(13)	Vol.4, Helm, C.1.2.2.1	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(14)	Vol.4, ADAMA, C.1.2.2.1	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(15)	Vol.4, ADAMA, C.1.2.2.1	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(16)	Vol. 4, Adama, Information on the source 1 (general)	NL comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(17)	Vol 4 C.1.2.2, Syngenta	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(18)	Vol4 C.1.2.2 Helm, Adama	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(19)	Vol. 4, C.1.2.2.2-C.1.2.3.2 Adama, source 2	Adama comments (5)	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(20)	Vol.4, Syngenta, C.1.2.3	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(21)	Volume 4, Annex C C.1.2.3, p.31	LV: Section not reviewed, no comments	-	-
1(22)	Vol.4, ADAMA, C.1.2.3, source 1	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(23)	Vol.4, ADAMA, C.1.2.3, source 2	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(24)	Vol.4, C.1.2.3.1, Helm, source 1	Helm comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(25)	Vol.4, C.1.2.3.2, Helm, source 2	Helm comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(26)	Vol.4, Helm, C.1.2.3	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(27)	Vol.4, ADAMA, Cheminova Helm, C.1.2.3	EFSA comment	please refer to the separate confidential Reporting tables	please refer to the separate confidential Reporting tables
1(28)	Vol. 4, Table C.1.2.3, Syngenta	NL comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(29)	Vol.4 C.1.2.3.1, Helm	NL comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(30)	Vol. 4 C.1.2.3.1, Cheminova	NL comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(31)	Vol4 C.1.2.4.2, Cheminova	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(32)	Vol4 C.1.2.1.1, Helm	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(33)	Vol4 C.1.2.2, Helm, Adama	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(34)	Vol4 C.1.2.4.1, Helm	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(35)	Vol.4 C.1.2.4.1, Helm	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(36)	Vol.4, Syngenta, C.1.4.2	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(37)	Vol4 C.1.2.4.2, Helm	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(38)	Vol4 C.1.2.4.2, Adama	NL comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(39)	Vol4 C.1.2.4.3, Helm p44	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(40)	Vol4 C.1.1.1, Adama	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(41)	Vol4 C.1, Adama	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(42)	Vol4 C.1.2.3.1, Adama	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(43)	Vol4 C.1.2.3.2, Adama, p14	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(44)	Vol4 C.1.2.4.2.2, Adama	FR comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(45)	Vol.4, Cheminova, source 1, C.1.3	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(46)	Vol.4, Cheminova, source 2, C.1.3	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(47)	Vol.4, Helm, C.1.3	EFSA comment	please refer to the separate confidential Reporting table	please refer to the separate confidential Reporting table
1(48)	Vol. 4, All sources, C.1.9 Steps to form a task force, p. 74	EFSA: if a TF is formed is there the intention to propose also a common minimum purity for all TF members?	please refer to the separate confidential Reporting tables	please refer to the separate confidential Reporting tables

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(49)	Vol. 3CA, B.2.1/01, Melting point, p.4	EFSA: is the -36.1 a typo, or the melting point is a range of 72.7 °C? In this case not a melting point.	RMS (August 2017): Noted. This is a typo and will be corrected in the revised RAR. Melting point was determined to be from +36.1°C to +36.6°C (= 309.3 K to 309.8 K). (Addressed) Applicant (August 2017): The applicant confirms that the melting point range has been determined to be between 36.1°C and 36.6°C.	Addressed.
1(50)	Vol3 CA B2.1.10 P6 Spectra for active substance in 3 solutions	FR: pH of acidic solution and basic solution used should be indicated FR characteristics of other spectra should be provided: IR, MS and H-NMR spectra	RMS (August 2017): Noted. For the UV spectra pH values were not available in the study report. The information was given on concentration and solvent used: <i>Neutral:</i> 13.65 mg. in 1000 mL methanol; <i>Acidic:</i> 13.65 mg. in 1000 mL methanol / 1N HCl 1N HCl (90+10) <i>Basic:</i> 13.65 mg. in 1000 mL methanol / 1N HCl 1N NaOH (90+10) Applicant clarification below. Regarding the other spectra information on chemical structure and shifts (1H-NMR),	Open point: RMS to update Vol.3 CA B.2.1.10 with the information in col.3 of the RT

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			absorptions – wavelengths and assigned structures (IR) and m/z and fragment ions from the study report will be included in the revised RAR. (Open point: RMS to provide information in the revised Vol.3 CA B.2.1.10) Applicant (August 2017): UV-VIS spectra of the active substance has been determined adequately using the correct OECD method guideline 101. The neutral solution is prepared in pure methanol and therefore, no pH measurement is possible (100% in organic solvent). In regards of the acidic and basic conditions, they are identical as stated in the OECD Guideline 101. The guideline also states the pH's when the described procedure has to be followed, less than 2 (acidic) and at least 10 when 10 % by volume of HCl or NaOH in aqueous solution are added (page 4). The solvent composition is given in Syngenta report; CGA163935_0504 (CA B2.1.10) The RMS should provide an update dRAR. Applicant: The RMS should provide an update dRAR.	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(51)	Solubility in organic solvents (p7)	FR: A method CIPAC MT 181 should be used, instead of method CIPAC MT 157.3	MS (August 2017): The study on technical grade trinexapac-ethyl was performed in 1998. The study report states <i>'As there is no general method available for the determination of the solubility in organic solvents, a procedure similar to that described in CIPAC method MT 157.3 (Water solubility) was used for the determination of the solubility.'</i> The method CIPAC MT 181 (Solubility in organic solvents) has been available since 2003 (CIPAC Handbook K, 2003) which states that <i>'The method is not suitable for the determination of solubilities below 10 g/l. To determine lower solubilities or when precision higher than the predefined ranges described is required, MT 157 (Water solubility) may be adapted.'</i> The solubility of trinexapac-ethyl is not below 10 g/L in the solvents tested. However the new study on trinexapac-ethyl solubility in organic solvents according to CIPAC MT 181 has not been available in the dossier of 2015 submitted for the renewal. Clarification by the applicant on the methods applicability is given below.	Addressed.

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			(Data requirement: clarification on method CIPAC 181 applicability for trinexapac-ethyl solubility. Open point: to update Vol.3 CA B2 accordingly). Applicant (August 2017): The applicant would like to indicate to FR that CIPAC MT 157.3 is still valid for the determination of organic and water solubility of the active ingredients and still accepted by authorities in Europe. Currently, there is no justification to repeat these organic solubilities using CIPAC MT 181. Moreover, trinexapac-ethyl is readily soluble in organic solvents.	
1(52)	Vol 3CA B2.9-01b flammability	FR: The applicant should determine auto- flammability according to CLP regulation.	RMS (August 2017): Noted. This is correct. This is the requirement of the CLP Regulation 1272/2008 enforced as quoted below: <i>Test N.1: test method for readily combustible solids (UN RTDG Manual of Tests and Criteria ST/SG/ AC.10/11/Rev. 5 – Part III, section 33.2.1.4) ref. is applicable.</i> Test N.1: <i>"If the substance does not ignite and propagate combustion either by burning with flame or smouldering along 200 mm of the powder train within the 2 minute test period ,</i>	Addressed: At the PRAS 150 it was noted that the legislation for data requirement is not fully aligned with CLP legislation with regard to physical and chemical properties. The meeting agreed that a full set of data for classification and labelling with regard to physical and chemical properties should be included in an amendment of the data requirements Regulation in alignment with CLP Regulation.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			<i>then the substance should not be classified as a flammable solid and no further testing is required."</i> Results of preliminary test (EEC A10) performed by the applicant (<i>ref. Jackson, 2014</i>) on trinexapac-ethyl flammability showed that the test substance (trinexapac-ethyl, 96.8 % w/w) did not propagate combustion and the burning time over 200 mm could not be determined for technical grade trinexapac ethyl. Therefore, full test series were not required since the substance could not be classified as flammable According to the CLP Regulation [EC]No. 1272/2008, Point 2.7.2.1, a substance is classified if in the burning rate test they exhibit a burning time <45 s or burning rate >2.2 mm/s. Trinexapac-ethyl is not classified based on its flash point which is above 55°C (156 ±8°C) or burning characteristics of the test substance: Trinexapac-ethyl did not exhibit a burning time above this cut-off criteria. The test substance melted and did not propagate the flame. (Data requirement: Applicant to address the	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			flammability according to CPL Regulation. Open point: RMS to evaluate the new information in the revised Vol 3CA B2.9-01b) Applicant (August 2017): The applicant will address this property by an adequate statement during the stop-the-clock period.	
1(53)	Vol 3CA B2.11/01 p11	FR: Explosive properties should be performed UN RTDG method, in accordance with CLP regulation.	RMS (August 2017): Noted. For the compliance to the CPL the United Nations Recommendations on the Transport of Dangerous Goods (UN RTDG) Manual of Tests and Criteria ST/SG/AC.10/11/ Rev. 5 – Part I (Test series), section 11 could have been considered within the dossier (KCA 2.9). Comparison of the available information to the CLP criteria: Based on the CLP Regulation [EC]No. 1272/2008, Point 2.1.4.3 a substance is not classified as explosive if there are no chemical groups associated with explosive properties present in the molecule. Trinexapac-ethyl is not expected to be explosive. An examination of the chemical structure of trinexapac-ethyl concluded that it does not contain any of the bond groupings known to confer explosive properties. This assessment is considered relevant for classification and labeling for explosive	Addressed: See comment 1(52)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			properties. Trinexapac-ethyl (96.8 %) was also examined for explosive properties following the procedures specified in test method EEC A.14 (<i>ref. Jackson, 2014</i>) and was found to be not explosive. In this case the test A 14 could have been justified as an alternative test and therefore to be used for classification purposes of tested trinexapac-ethyl. (Data requirement: Applicant to address the flammability according to CPL Regulation. Open point: RMS to evaluate the new information in the revised Vol 3CA B2.11/01) Applicant (August 2017): The applicant will address this property by an adequate statement during the stop-the-clock period	
1(54)	Vol 3CA B.2.13/01b	FR: Oxidising properties should be performed UN RTDG method, in accordance with CLP regulation.	RMS (August 2017): Noted. The United Nations Recommendations on the Transport of Dangerous Goods (UN RTDG) Manual of Tests and Criteria ST/SG/AC.10/11/Rev. 4 – Part I (Test series) should have been considered and the UN RTDG method performed. The tests Test O.1: Test for oxidizing solids (UN RTDG	Addressed: See comment 1(52)

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Manual of Tests and Criteria ST/SG/AC.10/11/Rev. 5 – Part III, section 34.4.1) Test O.2: Test for oxidizing liquids (UN RTDG Manual of Tests and Criteria ST/SG/AC.10/11/Rev. 5 – Part III, section 34.4.2) would have been applicable dependent on purity of trinexapac-ethyl (O₂ in particular). In the same time according to the CLP Regulation [EC]No. 1272/2008, point 2.14.4.1, a substance is not classified if it contains oxygen, fluorine or chlorine and these elements are chemically bounded only to carbon or hydrogen. The structure of trinexapac ethyl meets this criteria, and trinexapac-ethyl is therefore not considered an oxidising substance. This was supported by the results of the oxidising properties testing following EC method A.21. The test sample of technical grade (96.8% w/w) trinexapac-ethyl (which is solidified melt at room temperature) was liquefied in a hot water bath for testing. Test sample mixture of trinexapac-ethyl was found to have a mean pressure rise time much longer (timed out (90s)) than that	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the active substance				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			observed for the nitric acid reference mixture. Therefore trinexapac-ethyl is not classified as an oxidising substance. (Data requirement: Applicant to address the flammability according to CPL Regulation. Open point: RMS to assess the new information for accordingly revised Vol 3CA B2.13/01b) Applicant (August 2017): The applicant will address this property by an adequate statement during the stop-the-clock period.	
1(55)	Vol. 3 CA, Physical and chemical properties of the active substance, p. 4-12, general comment.	NL: Please state if the provided studies were accepted or not accepted by the reviewer, this is however no always clear.	RMS (August 2017): noted. This will be added in the revised DAR. (Open point: RMS to revise Vol.3 CA where relevant) Applicant (August 2017): These points should be clarified by the RMS.	Open point: RMS to update Vol.3CA B.2 with the comments on acceptability of studies, where relevant, in an updated RAR.
1(56)		LV: Section not reviewed, no comments	RMS (August 2017): noted.	Addressed.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the plant protection product				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(57)	Vol. 3 CP B.2.2/01	FR: Explosive properties should be performed UN RTDG method, in accordance with CLP regulation	RMS (August 2017): Agreed. For the compliance to the CPL the United Nations Recommendations on the Transport of Dangerous Goods (UN RTDG) Manual of Tests and Criteria ST/SG/AC.10/11/ Rev. 5 – Part I (Test series), section 11 should have been considered for the test on explosive properties of the new representative formulation. Based on the CLP Regulation [EC]No. 1272/2008, Point 2.1.4.3 a mixture is not classified as explosive if there are no chemical groups associated with explosive properties present in the molecule. An examination of the chemical structure of trinexapac-ethyl formulation A 8587F should have been provided provided by the applicant in addition to the test on explosive properties performed (EEC A 14) to verify that the formulation does not contain any of the bond groupings known to confer explosive properties. Instead of the UN RTDG method applicable for explosivity testing the formulation was examined following the procedures specified in method EEC A.14 and was found to be not explosive (<i>ref. Jackson, 2003</i>). The liquid formulation A8587F did not give a positive result in tests used to determine its sensitivity	See comment 1(52)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the plant protection product				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			to shock or heating under confinement and was found to be not explosive in accordance to the criteria of test EEC A 14. Therefore, given the additional clarification based on the composition of formulation and comparability of EEC A14 test to that recommended by the UN, the test EEC A 14 could likely be considered as an alternative test for the classification of the new representative formulation. (Data requirement: Applicant to address the explosive properties according to the CPL Regulation. Open point: RMS to assess the new information to revise Vol 3CP B2.2/01) Applicant (August 2017): The applicant will address this property by an adequate statement during the stop-the-clock period.	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the plant protection product				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(58)	Vol. 3 CP B.2.3/01	FR: The applicant should determine flash point with UN RTDG method, according to CLP regulation.	RMS (August 2017): Agreed. Considering the CPL regulation, test methods according to table 2.6.3 of Annex I, Part 2 of Regulation (EC) No 1272/2008 (5) (liquids) have been applicable. The flash point ($44\pm 2^{\circ}\text{C}$) of the formulation A8587F was determined by the method EEC A9 (<i>Jackson, 2003</i>); Pensky -Martens closed cup method applied (EN ISO 2719), using ASTM D93-02a. The Pensky Martens closed cup method (ISO 2719 as amended) is referenced in the table 2.6.3 mentioned above and regarded as method applicable for flash point determination according to CLP regulation. The formulation A8787F was found to be classified as flammable in terms of its flash point (flash point $\geq 23^{\circ}\text{C}$ and $\leq 60^{\circ}\text{C}$). (Data requirement: Applicant to address the flash point according to the CPL Regulation. Open point: RMS to assess the new information to revise Vol 3CP B2.3/01). Applicant (August 2017): The applicant will address this property by an adequate statement during the stop-the-clock period.	See comment 1(52)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the plant protection product				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(59)	Vol3 B.2.7 storage stability	FR agrees with RMS, concentrations tested of 0.75% and 0.1% are acceptable for use concentrations at 0.125% to 0.8%.	RMS (August 2017): Noted. (Addressed) Applicant (August 2017): The applicant agrees with FR that the concentrations tested of 0.75% and 0.1% are acceptable.	Addressed.
1(60)	Vol. 3 CP, Shelf life following storage at ambient temperature B.2.7/03, p.10.	NL: If the decrease of the active substance after storage > 5% (compared to the initial content), information on degradation products (or a sufficient justification by the applicant) should be provided. It is not sufficient to compare the after storage results with a different stored sample.	RMS (August 2017): Noted. The active substance concentration decrease was found to be 5.08 % w/w when compared to the content of trinexapac-ethyl in the initial sample of the formulation A8587F (batch SEZ3EP001). On the other hand, the content of trinexapac ethyl decrease was found to be 4.71 % w/w compared to the deep frozen reference sample of the formulation A 8587F (batch SEZEP001), i.e. the formulation sample stored for 2 years at -10°C. The content of active substance in the initial (not frozen) sample was 256 g/L while the content of active substance in the deep frozen sample was 255 g/L. Therefore the decrease of the active substance content 4.71 % can be considered as acceptable since this is less than 5 % decrease. (Open point: RMS to revise Vol 3CP B2.7/03	Addressed.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Physical and chemical properties of the plant protection product				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			accordingly) Applicant (August 2017): The applicant confirms that no degradation after storage, greater than 5% was observed. A non-significant loss of 4.7% was found based on the content on currently analysed reference sample. Therefore no information on degradation product is necessary.	
1(61)		LV: Section not reviewed, no comments	RMS (August 2017): noted.	Addressed.

Data on application and efficacy				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(62)		FR: No comment	RMS (August 2017): noted.	Addressed.
1(63)		LV: Section not reviewed, no comments	RMS (August 2017): noted.	Addressed.

Further information				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(64)		FR: No comments	RMS (August 2017): noted.	Addressed.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Further information				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(65)		NL: No comments	RMS (August 2017): noted.	Addressed.
1(66)		LV: Section not reviewed, no comments	RMS (August 2017): noted.	Addressed.

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(67)	Vol. 1, 2.5.2, Methods for post control and monitoring purposes	EURLs: multi-residue methods for enforcement of the residue definition 'trinexapac (sum of trinexapac (acid) and its salts, expressed as trinexapac)' as well as for trinexapac-ethyl are available, with LOQs of 0.01 mg/kg being achievable for both compounds in high water content, high acid content, high fat content and dry commodities. The EURLs have so far not developed any methods for any of the metabolites of trinexapac	MS (August 2017): the comment is appreciated as it confirms practical acceptability of the multi-residue methods developed by the applicant for the enforcement. (Addressed)	Addressed.
1(68)	Vol. 1, 5.2.5, Vol. 1, 2.13.2 and list of endpoints, residue definition for monitoring purposes	DE: In different parts of the RAR different residue definitions for monitoring in air are given. In Vol. 1, 2.13.2 trinexapac acid is also included whereas in the list of endpoints the parent compound is mentioned only. Please check and	RMS (August 2017): Agreed. (Open point: RMS will correct the residue definition in the Vol.1, 2.13.2. (trinexapac-ethyl in air) and revise RAR accordingly).	Open point: RMS to harmonise the residue definition in air in a revised RAR.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		harmonise the residue definition.	Applicant (August 2017): The Applicant would like to highlight that the definition of residue for monitoring usually includes parent only. As trinexapac-ethyl very rapidly degrades to CGA179500 in the soil and in the water compartments, the two compounds have been reported in the definition of residue for monitoring in various documents (Vol 1., 2.13.2; LoEP - Analytical methods for residues (Regulation (EU) N° 283/2013, Annex Part A, point 4.2 & point 7.4.2); Vol 3., 8.4.2). This is however incorrect for the air compartment. Indeed, as concluded in the EFSA Scientific Report (2005) 57, 1– 70, Conclusion on the peer review of trinexapac, Appendix 1 – list of endpoints, there is no need to report a monitoring method for CGA179500. Whereas trinexapac-ethyl readily degrades in the soil and the water compartments, the active substance is not only stable in air but also non-volatile. Therefore, trinexapac-ethyl is the sole residue to be considered for monitoring in air. This conclusion should be reflected in the rest of the documents as suggested by the Member State DE.	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(69)	Vol. 3 CA, B.5.1.1 Methods for the analysis of the relevant impurities as manufactured, p.5.	NL: No section for the analytical methods for the determination of the relevant impurities in trinexapac-ethyl technical, or information on the absence of these analytical methods or reference to the confidential part Vol. 4. have been provided. Please include this information under B.5.1.1.	RMS (August 2017): noted. As long as the specification of the active substance have not been clarified it would not seem reasonable to have impurity methods in the DRAR CA_B5_B.5.1.1 (2). Provided the relevance of impurities is confirmed, the DRAR CA_BV5_B.5.1 is revised. Co-RMS point of view in regards to the relevance of the trinexapac-ethyl impurities is important. At the time of assessment the relevance of the impurities could not be confirmed and therefore the methods of relevant impurities could not be considered (please refer to the dRAR Vol.4). (Data requirement: RMS will revise Vol.3 B.5 by the methods of relevant impurities determination from the confidential part Vol.4 as soon as the relevance of impurities confirmed).	Addressed.
1(70)	Vol. 3 CA, B.5.1.2.1 KCA 4.1.2/03a-b, KCA 4.12/04a, KCA 4.1.2/05a- b, KCA 4.1.2/06a-c, p.23- 34.	NL: Please specify in the conclusion by the reviewer the guidance document to which the analytical methods are fully validated, SANCO/3029/99 rev. 4 and/or SANCO/825/00 rev. 8.1.	RMS (August 2017): noted. (Open point: Acceptability of methods validation considering full set of methods available included their amended revisions will further be reconsidered in the revised Vol.3 CA B.5.1.2.1).	Open point: RMS to include the information on the guidance document according to the analytical methods are fully validated in a revised RAR.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(71)	Vol. 3 CA, B.5.1.2.1 KCA 4.1.2/07-08, p.36-40.	NL: The criteria of SANCO/3029/99 rev.4 are not met, however it is unclear if the reviewer accept or does not accept the analytical methods, please clarify.	RMS (August 2017): noted. (Open point: will be clarified in the revised Vol.3 B.5 CA).	Open point: RMS to include the information on the acceptability of the methods in a revised RAR. See also comments 1(75), 1(80), 1(83)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(72)	Vol. 3 CA, B.5.1.2.1 KCA 4.1.2/091-10, p.40-44	NL: Please indicate if the analytical methods are complaint with SANCO/3029/99 rev. 4 and/or SANCO/825/00 erv. 8.1 and are accepted or not accepted by the reviewer, based on the provided information.	RMS (August 2017): noted. (Open point: the outcome of compliance to all the basic validation criteria of methods for data generation will be considered in the revised Vol.3 B.5 CA).	See open points 1(70) and 1(71)
1(73)	Vol. 3 CA, B.5.1.2.1 Page 40, Conclusion on GRM020.01A	Applicant ¹ : Page 40 it is stated that the use of single transition is insufficient for full validation. This is a pre-registration method, and therefore a single transition is considered appropriate.	RMS (August 2017): noted. The guidance document applicable for generating and reporting methods of analysis in support of pre-registration data SANCO/3029/99 rev. 4. 3.2 <i>Confirmation of analyte identification</i> indicates that <i>Where mass spectrophotometric confirmatory analysis is carried out, a minimum 3 ions (ideally with an m/z ratio of >100) should be used for identification /quantification. These ions should be reported and justified.</i> “ The method GRM020.01A validation report indicates one m/z transition used for quantification (m/z 223→135) which has not been considered as fully sufficient to meet the criteria of SANCO/3029/99 rev.4.	Data requirement: Additional validation data for the method GRM020.01A for confirmation of the analyte

¹ Applicant - Task Force here and in the text bellow

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(74)	Vol.3 CA, B.5.1.2.1 Page 48 Conclusion of methods GRM020.13A and GRM020.14A	Applicant: Methods are completed and have been provided. Please update text	RMS (August 2017): the methods GRM20.13A and GRM020.14A were only submitted additionally at the end of the dossier assessment (2017) and therefore could not be timely assessed in the first version of the Vol.3 B.5.1.2.1. (Open point: the information on methods GRM020.13A and GRM020.14 will be provided in the revised Vol.3 B.5).	Data requirement: Applicant to submit methods GRM20.13A and GRM020.14A to be evaluated in a revised RAR.
1(75)	Vol. 3 CA, B.5.1.2.1 KCA 4.1.2/13-14, p.49-54	NL: Please indicate if the analytical methods are accepted or not accepted by the reviewer and are complaint with SANCO/3029/99 rev. 4 and/or SANCO/825/00 erv. 8.1.	RMS (August 2017): noted. (Open point: the acceptability of method GRM020.15A) validation will further be clarified in the revised Vol.3 B.5.1.2.1).	See open point 1(71)
1(76)	Vol. 3CA, B.5.1.2.1 Methods for risk assessment, plant matrices, p.53	EFSA: agrees with the RMS on the need for further clarification for the different names /analytes for the same results in method GRM020.015A	RMS (August 2017): noted. (Data requirement: applicant to clarify the information. Open point: RMS to revise Vol.3 CA B.5.1.2.1 accordingly). Applicant (August 2017): Agreed. Typographical error in Table 4 (page 31) of GRM020.15A. p31 CGA224489 should read CGA224439. Method to be updated and re- issued as version B.	Open point: RMS to correct the error in Table 4 concerning the right codes.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(77)	Vol. 3CA, B.5.1.2.2 Methods for risk assessment, animal matrices, p.53	EFSA: agrees that the extraction efficiency was not addressed	RMS (August 2017): noted. (Data requirement: to address extraction efficiency issue in animal matrices. Open point: RMS to include information on extraction efficiency consideration in the revised Vol.3 B.5.1.2.2. It would be important to consider that the recoveries from spiked matrices would often show good results compared to the results with the incurred pesticide residues). Applicant (August 2017): Water/methanol mixtures are used for extraction of residues of CGA179500 from commodities of animal origin. This is comparable in polarity to the acetonitrile/water mixtures used for extraction in the goat metabolism study. Extraction is likely to be similar for both solvent mixtures. No further animal metabolism studies have been conducted to allow further ¹⁴C radiovalidation of extractability and no samples from residue feeding studies are available for cross-validation therefore it is not possible to confirm this assumption. Recoveries from spiked matrices indicate acceptable	Open point: RMS to include the information from col.3 of the RT concerning the solvent bridging in a revised RAR.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			extractability under the conditions described in the method.	
1(78)	Vol. 3 CA B.5.1.2.3 Methods for the determination of the active substance and/or metabolites in soil	Applicant: Page 62, the two references stated in Table B.5.1.2.3-1 are incorrect and should read: CGA300405_10025 and CGA300405_10029.	RMS (August 2017): Agreed. The typo in references have been corrected in the revision of Vol.3 B.5 CA, Table B.5.1.2.3-1 (p.62). (Addressed)	Addressed.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(79)	Vol. 3CA, B.5.1.2.3 Methods for risk assessment, soil, p.65	EFSA: the LOQ of the method Richardson M., Cashmore A. (2016) is not meeting the requirements	RMS (August 2017): Agreed. As indicated in the conclusion of the method, the LOQ (0.15 mg/kg) is three times higher than LOQ proposed in SANCO/3029/99 rev.4 applicable to this methods for soil. Therefore the cross reference to relevance of final conclusion on acceptability of overall fate study was made to Vol.3 B.8 CA. Applicant (August 2017): The Applicant would like to highlight that even if the method Richardson M., Cashmore A. (2016) does not meet the LOQ requirement from SANCO/3029/99 rev. 4, 11/7/00, it is still appropriate for the purpose of defining degradation rates for CGA300405. As reported in Document M-CA Section 7, CGA300405 was applied in the study at a rate of 3mg/kg. The LOQ, 0.15mg/kg, represents 5% of the applied amount. This means that the method gives reliable measurements down to 95% of the degradation of CGA300405. Combined with robust standard deviation values, this gives confidence that the Richardson M., Cashmore A. (2016) method is fit for purpose for the intended purpose of a kinetic evaluation.	Open point: RMS to include the information from the col.3 of the RT in a revised Vol.3 CA B.8., method Richardson M., Cashmore A. (2016)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(80)	Vol. 3 CA, B.5.1.2 KCA 7.1.2.1/01, p.63-65	NL: Please indicate if the analytical method was accepted and is validated in compliance with SANCO/3029/99 rev. 4 or fit for the intended purpose, this is not clear from the comments/conclusions made by the reviewer.	RMS (August 2017): noted. (Open point: the outcome of compliance to all the essential criteria of methods validation for data generation will be clarified in the revised Vol.3 B.5 CA) Applicant (August 2017): Please see point 1(79) above.	See open point 1(71)
1(81)	Vol. 3 CA B.5.1.2.3 Methods for the determination of the active substance and/or metabolites in soil	Applicant: Page 68 questions the selection of the mass transitions, and therefore the validity of the method. This is a data generation method and therefore such justification (as for enforcement methods under SANCO/825/00 rev 8.1) is not required.	RMS (August 2017): noted. The RMS see the point of data generation methods as indicated by the applicant and this their comment have already been cited in the draft Vol.3 CA B.5.1.2.3. Nevertheless, the guidance document SANCO/3029/99 rev.4 applicable to the methods for data generation indicates the importance of mass transitions and says that the ions used should be reported and justified. Despite that the method could not be considered as acceptably validated in terms of criteria of SANCO/3029/99 rev.4, there might have probably been a possibility to consider it as fit for purpose for the fate and behaviour study assessment and therefore the reference was made to Vol.3 CA B.8.	Addressed.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(82)	Vol. 3 – B5 (AS), B.5.1.2.4 Methods for the determination of the active substance and/or metabolites in water	Applicant: No consideration of methods in water is included, but new studies were submitted.	RMS (August 2017): The new methods provided by the applicant for the residue determination in water had been were located in the dossier part of <i>Methods for post approval control and monitoring purposes</i> KCA.4.2/12-KCA.4.2.17 rather than in the part KCA.4.1.2 of the <i>Methods for risk assessment</i> . This allocation of methods to CA.4.2 <i>Methods for post approval and monitoring purposes</i> was also in the summary document prepared by the applicant <i>MCA Section 4, Analytical methods</i> and its supplement, i.e. document <i>MCA section 4</i> revised 2016.03.24. Therefore the new methods have been considered as methods for the enforcement and assessed in the relevant part of the Vol. 3 CA B.5.2.4.	Addressed.
1(83)	Vol. 3 CA, B.5.1.2 KCA 4.2/19, p.124-126	NL: Please indicate if the analytical method was fully validated according SANCO/825/00 rev. 8.1 and or SANCO/3029/99 rev. 4.	RMS (August 2017): noted. The information on the method for the air needed some further clarification. KCA 4.2/19 is the GLP validation study report of the <i>draft</i> analytical method GRM 020.12A for trinexapac-ethyl determination in air. It was not fully clear why the study report <i>Ford K and Wiltshire K. 2015</i> was referenced in the GLP study report of method validation (<i>KCA. 4.2/19, Wiltshire K., 2015 Syngenta File No. CGA163935_10647</i>). The draft method has	See open point 1(71)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			not been available while the procedure of it was indicated to have been followed. The information on the equipment used and sorbent tubes was missing in the GLP study report as well as validation part did not include chromatograms at ambient temperature and RH, equations for linearity graphs. The other report with the description of method GRM020.12A has been available (<i>Wiltshire K., 2015, Syngenta File No. CGA163935_10647</i>) that was developed for use on an Applied Biosystems API 4000, however it indicated that <i>'Other instrumentation can also be used, though optimisation may be required to achieve the desired separation and sensitivity'</i> The study report (<i>Wiltshire K., 2015, Syngenta File No. CGA163935_10647</i>) has not been referenced in the GLP validation study report therefore the procedural part needed further clarification. (Data requirement: Applicant to provide information missing on the method GRM020.12A (<i>Ford K. and Wiltshire K., 2015</i>) performed in the GLP validation study (<i>Wiltshire K., 2015, Syngenta File No.</i>	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			CGA163935_10648) for trinexapac-ethyl determination in air. Open point: RMS to revise Vol.3 B5 accordingly).	
1(84)	Vol3CA B5.1.2	FR: Extraction efficiency should be determined for each method in pre- registration.	RMS (August 2017): Agreed. (Data requirement: applicant to provide information on the extraction efficiency for the methods of pre-registration for plant and animal matrices in consideration to available metabolism studies performed. Open point: RMS to revise Vol.3 CA B.5.1.2 accordingly).	Data requirement: Applicant to provide information on the extraction efficiency for the methods of pre-registration for plant and animal matrices in consideration to available metabolism studies performed.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(85)	Vol. 3, B.5.2, extraction efficiency of monitoring method in plants	DE: The statements on extraction efficiency in plant material are a little bit too general. The extraction procedure of QuEChERS method (homogenisation with acetonitrile/water (1/1, v/v) containing 1 % acetic acid) seems to be not completely comparable to the different extraction procedure used in metabolism studies. It should be at least stated, which amount of trinexapac is extracted after initial extraction. We would also appreciate a justification for adding acetic acid to the extraction solvent.	RMS (August 2017): noted. The RMS agree with the comment that the statement is rather general and more information is necessary on the extraction efficiency in the revised Vol.3 CA B.5.2 (Data requirement: Applicant to provide more detailed information on extraction efficiency considering QuEChERS method for plants in relation to procedures in metabolism studies; justification for addition of acetic acid to the extraction would be very important. Open point: RMS to assess the information clarifying the issue of extraction efficiency based on criteria of the guidance document as requested for the revised Vol.3 B.5.2)	Data requirement: Applicant to provide information on the extraction efficiency for the monitoring methods for plant matrices in consideration to available metabolism studies performed.
1(86)	Vol3CA B.5.2.1 Extraction efficiency in method for trinexapac ethyl residues in plant.	FR: In analytical method of Richter S (2015), the validation data of extraction efficiency should be reported in detail (study No 20120098 and study no 20120173). Please report in this part B5 details for the validation of the extraction efficient (in % TRR) from (study No 20120098 and study no 20120173, provided in metabolism studies.) In study 20120173 (Piskorski R. (2015) (B.7) :	RMS (August 2017): noted. The issues raised will be further detailed in the revised Vol.3 B.5.2.1 with the reference to the residue part of assessment, Vol.3 CA B.7.2.1 which is [¹⁴ C] –Trinexapac ethyl metabolism in plants two studies of Piskorski R., 2015 (oilseed rape and wheat) 1) Study (2012173): Extraction procedure (p.22):seed sample `was extracted at room temperature four times: a)twice	See data requirement 1(85)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		Please clarify the composition of solvent used, ratio of acetonitrile and water with hexane should be detailed. There is 67.4% of extractable radioactive residues (with 21.8% of trinexapac acid), please specify if trinexapac acid is in unextracted fraction for the validation of extraction efficiency. In study 20120098 (Piskorski R. (2015a) : Please clarify the composition of solvent used, ratio of acetonitrile and water should be detailed. There is 64.8% of extractable radioactive residues (with 21.8% of trinexapac acid) in grain or straw, please specify if trinexapac acid is in unextracted fraction for the validation of extraction efficiency.	<i>with two parts acetotitrile:water (80:20) to one part hexane, followed by (b) twice with acetonitrile water (50:50).'</i> Unextracted radioactivity fraction was further analysed with no evidence to trinexapac acid (p.32, 5; p.14 1.2 below): <i>In further characterisation of the unextracted radioactive residues with SDS, only 5.8% TRR (0.023 mg/kg) was rendered soluble indicating only a small proportion of the residue was associated with proteinaceous material. No chromatographic analysis was undertaken due to low residue levels released and the high levels of endogenous coextractives present.</i> <i>Following extraction of the unextractable radioactive residues with 1 M HCl at 60 °C and 6 M HCl at 140 °C (reflux), a further 4.0% TRR (0.016 mg/kg) and 15.2% TRR (0.060 mg/kg) was rendered water soluble respectively. No chromatographic analysis was undertaken on 1M HCl extract due to low residue levels released and the high levels of endogenous coextractives present. The HCl reflux extract was subjected to treatment with dabsyl chloride to derivatise amino acids present in the sample followed by TLC co-chromatography with (i) dabsyl derivative of glutamate; and (ii) [14C]glucose. It was not possible to conclude on the presence of natural incorporation into amino acids however there was some evidence of natural incorporation of 14C into glucose. A further 16.2 % TRR (0.064 mg/kg) remained as unextractable residues, however based on the</i>	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			<i>harsh extraction conditions employed any residue present would not be bioavailable. Also, evidence of extensive natural incorporation into oil seed indicates that the residue is due to further incorporation into natural components.'</i> (Data requirement: To be further clarified by the applicant.) 2) Study No.20120098 (spring wheat). Composition of solvent used: ref.p.26, 3.7.1: sub-samples <i>were extracted with solvents at a sample weight to volume ration of approximately 10:1 to 5:1. As a standard procedure, samples were extracted at room temperature three times with acetonitrile / water (4:1, v/v) and once with acetonitrile / water (1:1, v/v)</i> The lowest extractable radioactivity was in straw (64.8% TRR) where 35.2% TRR (0.481 mg/kg) remained unextracted in a debris fraction. Non extractable radioactive residues were subject to a fractionation procedure (Moens, 2000) which characterised radioactivity to be associated with lignin, hemicellulose and cellulose. The RMS understanding is that trinexapac acid could not be found in unextractable debris.	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(87)	Vol3 CA B.5.2.1 Methods for the determination of the active substance and/or metabolites in food/feed of plant origin	Applicant: Page 70: As matrix-matched standards were used the linearity data for each matrix should be presented to retain consistency with the earlier summaries. Applicant: Page 73: As matrix-matched standards were used the linearity data for each matrix should be presented to retain consistency with the earlier summaries. Applicant: On Page 76 the conclusion for the ILV of the crop method references the animal matrices. Please check this for consistency.	RMS (August 2017): the applicants comments in regards to presenting linearity data had been noted and therefore the information for each matrix to retain earlier summaries was already presented in the Vol.3 CA B.5.2.1 of 31 March 2017. This is correct. The Vol.3 CA B.5.2.1 was corrected by the commodities analysed in the conclusion of the ILV assessment (31 March 2017). (Addressed).	Addressed.
1(88)	Vol3CA B.5.2.2 Method for trinexapac residues in animal matrices	FR: in study KCA 4.2/04 Richter S., 2015a, extraction efficient should be provided.	RMS (August 2017): noted. This is the validation study report of the QuEChERS method for the residues determination in animal matrices. <i>Testing of extraction efficiency as mentioned in the guidance document SANCO/825/00 rev.8.1 was not done as part of this study (p.13).</i> Nevertheless, the statement of extraction efficiency for the multi-residue method in comparison to metabolism studies was provided by the applicant in the doc. M CA making references to the metabolism study (ref.GLP reports assessed in the DAR) to verify acceptability of the extraction – KIIA 6.2.2: Mueller, 1993 (5/93); Ray, 2002 (624-00) and Mueller, 1993 (6/93).	Open point: RMS to correct in the revised Vol.3 CA B.5 the text as indicated in the col.3 of the RT See also comment 1(90)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			The applicants statement is cited below: <i>'The extraction procedures using 80:20 acetonitrile:water used in the QuEChERS method for animals is the similar to the one used in the metabolism studies (Reports 624-00 (CGA163935/0944), 5/93 (CGA163935/0305), 6/93(CGA163935/0306)). The Quechers method for the determination of trinexapac acid in fat samples is performed so that the fat is melted and partitioned between 80/20 v/v acetonitrile/water to extract trinexapac acid residues into the acetonitrile/water mixture which is immiscible with the melted fat. The sample is frozen to solidify the fat and leave trinexapac acid in the 80/20 v/v acetonitrile/water. This procedure is based on similar principles and uses similar polarity solvents to that used in 14C metabolism studies (5/93 (poultry goat) and 6/93 (goat-poultry)) where the fat was dissolved in 80/20 chloroform/methanol which is then partitioned with aqueous buffer to extract the trinexapac acid residues.'</i> Acetonitrile/water (4:1 v/v) was indicated in the Report 624-00 (CGA163935_0944) for liver, kidney and muscle. (Open point: to correct in the revised Vol.3 CA B.5 the text as indicated above and to	

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			add information on the relevant metabolism studies assessment with reference to the Vol.3 CA B.7.2.2.2.) See also comment 1 (91).	
1(89)		FR: title of table "Method for products of plants" is not in accordance with point B.5.2.2, about method for products of animals matrices.	RMS (August 2017): Noted. The the word <i>plant</i> was incorrectly indicated instead of word <i>animal</i> which will be corrected in the revised Vol.3 CA B.5.2.2. (Addressed). Applicant (August 2017): Agreed. Typographical error. The Table should refer to animals not plants.	Open point: RMS to correct the typo in the title of table in Vol.3 CA B.5.2.2.
1(90)	Vol. 3CA, B.5.2.2. Methods for animal matrices, p.83	EFSA: the solvent bridging provided to address the extraction efficiency of method Richter S (2015a) (KCA 4.2/04) can be considered acceptable.	RMS (August 2017): Agreed. The study reports of metabolism in lactating ruminants (goats) and laying hen that had been assessed in the DAR provide information on the extraction procedures with acetonitrile/water (80/20 v/v). The extraction procedures are similar to those in the QuEChERS method and its ILV. (Addressed)	Addressed: See also comment 1(88)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(91)	Vol3CA B.5.2.2 Methods for the determination of the active substance and/or metabolites in food/feed of animal origin	Applicant: Page 77: As matrix-matched standards were used the linearity data for each matrix should be presented to retain consistency with the earlier summaries.	RMS (August 2017): the applicants comments in regards to presenting linearity data had been noted and therefore the information for each matrix to retain earlier summaries was presented in the Vol.3 CA B.5.2.2 of 31 March 2017. (Addressed)	Addressed.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(92)	Vol3CA B.5.2.3 Method for the determination of residues in soil	FR: The residue definition proposed in Trinexapac ethyl and trinexapac (acid) only for monitoring in soil, i.e without esters and its salts. The analytical method GRM020.04A is not in accordance with residue definition of Trinexapac in soil. Samples are heated at reflux in ultra-pure water, there is a hydrolyse step. Sum of trinexapac acid, ester and its salts are determined with this method, expressed as trinexapac acid. It should be precised that this method would overestimate the content of trinexapac	RMS (August 2017): noted and agreed. (Open point: to further consider the strong hydrolysis in the method GRM020.04A and therefore possible overestimation of trinexapac acid content due to trinexapac acid, its salts and trinexapac ester determined as trinexapac acid. (Data requirement: applicant to further clarify the issue of CGA179500, its salts and trinexapac-ethyl determination in soil). Applicant (August 2017): GRM020.04A will measure and quantify residues of CGA179500 and any salt of CGA179500 as the salts of CGA179500 in aqueous solution are indistinguishable from free CGA179500. The majority of trinexapac-ethyl is likely to be hydrolysed to CGA179500 under the extraction conditions used and will also be determined as CGA179500. Any residues of CGA179500 determined using method GRM020.04A will therefore be a sum of free CGA179500, any salts of CGA179500 and trinexapac-ethyl hydrolysed to CGA179500. The method will be updated to reflect the above statement and will be provided during the stop-the –clock period. Residues of trinexapac-ethyl may be determined separately using the methodology described in GRM020.03A.	Open point: RMS to include the information from the col.3 of the RT in a revised Vol.3CA B.5 concerning the method for residues in soil.
Rapporteur: Lithuania				

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(93)	Vol.3 CA, B.5.2.4 Methods for the determination of the active substance and/or metabolites in water (AS)	Applicant: Page 112 and page 114 refer to the concentration range not covering 30% of the LOQ to 20% above the highest level. The Applicant has followed up on this comment with the contracted laboratory and has provided an updated version of the report to clarify the range of concentrations. The study can be found in the latest version of the Caddy supplied to the EFSA, the RMS and other MSs.	RMS (August 2017): noted. (Open point: to further assess the updated version of the document indicated by the applicant as a part of the latest version of Caddy and to provide the assessment in the revised Vol.3 B.5.2.4)	Open point: RMS to update the RAR Vol.3 CA, B.5.2.4 Methods for the determination of the active substance and/or metabolites in water based on the updated version of the report.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(94)	Vol3CA B.5.3.2 Methods for the determination of residues in water	FR: The residue definition proposed in Trinexapac ethyl and trinexapac (acid) only for monitoring in water, i.e without esters and its salts. The analytical method GRM020.02A and its ILV for the determination of trinexapac ethyl and trinexapac (acid) in water, is not specific to trinexapac acid only, it is not in accordance with residue definition of trinexapac ethyl in water. A step of hydrolyse is performed with HCl for analyse trinexapac (acid). This method quantifies trinexapac, its esters and its salts. Please specify that the method determines sum of trinexapac acid, its ester and its salt, expressed as trinexapac (acid). It should be precised that this method would overestimate the content of trinexapac For the determination of trinexapac ethyl, no hydrolyse is performed, the method is specific to trinexapac ethyl	RMS (August 2017): noted. (Open point: to clarify the extent hydrolysis (due to HCl addition) under the method conditions for trinexapac acid determination in water to ensure the method determines trinexapac acid and its salts expressed as trinexapac acid but not the ester (trinexapac-ethyl) and therefore does not overestimate the content of residues of concern.) Applicant (August 2017): GRM020.02A will measure and quantify residues of CGA179500 and any salts of CGA179500 present as the salts of CGA179500 in aqueous solution are indistinguishable from free CGA179500. However, trinexapac-ethyl will not be hydrolysed to CGA179500 under the mild acidic conditions required to retain CGA179500 on the SPE cartridge. Residues of Trinexapac-ethyl are determined separately in the same method	Open point: RMS to include the information from the col.3 of the RT in a revised Vol.3CA B.5 concerning the method for the determination of residues in water

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(95)	Vol3 CA B.5.2.5 Methods for the determination of residues in air	FR: Trinexapac (acid) is included in residue definition of trinexapac ethyl in air for monitoring, an analytical method should be provided for the determination of trinexapac acid in air.	RMS (August 2017): noted. The understanding of the RMS is that trinexapac-ethyl, parent, has been included in the residue definition in air for the enforcement and the residue definition has not changed since Annex I inclusion. Provided the residue definition of trinexapac- ethyl in future is changed, the issue will further be reconsidered. (Addressed). Applicant (August 2017): Please see point 1(68) for more clarification on the need for a monitoring method for metabolite CGA179500 in air.	Addressed: See also comment 1(68)

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(96)	Vol. 3CA, B.5.4. Methods for body fluids and tissues, p. 127	EFSA: According to Reg. (EU) 283/2013 Part A Section 4, 4.2 Methods for post-approval control and monitoring purposes methods shall be submitted for the analysis in body fluids and tissues for active substances and relevant metabolites.	RMS (August 2017): Agreed. This has been indicated by the RMS in the draft RAR B.5.2.6 (p.125). (Data requirement: to provide as a part of trinexapac-ethyl renewal dossier the study report of validated method for the analysis in body fluids and tissues and its summary evaluation. Open point: RMS to assess the method in the revised Vol.3 CA B.5.4). Applicant (August 2017): See 1(98)	See data requirement 1(98)
1(97)	Vol3 CA B.5.4	FR: An analytical method should be provided for the renewal of the active substance for the determination of Trinexapac ethyl residues in body fluid and tissues, according to Reg (EU) 283/2013.	RMS (August 2017): agreed see 1 (96) above.	See data requirement 1(98)
1(98)	Vol. 3 -B5.2.6 Methods for the determination of AS and or metabolites in body fluids and tissues.	Applicant: A body fluid/tissues method is now available CGA179500_11025, OECD summary CGA179500_11026	RMS (August 2017): please see the comment 1 (96) above.	Data requirement: Applicant to submit the method for body fluid/tissues: CGA179500_11025 and OECD summary CGA179500_11026
1(99)		LV: Section not reviewed, no comments	RMS (August 2017): noted.	Addressed.
1(100)	Point included after commenting phase.	RMS: EFSA could clarify the ambiguity regarding one issue which was not included in the Reporting table. Therefore,		Data requirement Applicant to further address the

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Methods of analysis				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	dRAR Vol 1 (3.1.8, 168 pp.)	the RMS LT would like to clear ambiguity regarding specific area where expert consultation was considered necessary based on the dRAR Vol 1 (3.1.8, 168 pp.) submitted on 31-03-2017: 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 The conclusion whether the analytical methods for diet analysis of trinexapac-ethyl and for diet/plasma analysis of metabolite CGA329773 used in 10 studies (Oral 90-day study in rats and dogs, 1 year dog study, Carcinogenicity study in rats and mice, Two-Generation Reproduction toxicity study in rats, Subchronic neurotoxicity studies in rats, 28-day dietary immunotoxicity study in mice, 28-day study in rats on metabolite CGA 329773, in vivo micronucleus test in rats on metabolite CGA 329773) fit-for-purpose and support the toxicological studies could not be reached.		concerns raised by the RMS regarding the analytical methods for diet analysis of trinexapac-ethyl and for diet/plasma analysis of metabolite CGA329773 used in 10 studies (Oral 90-day study in rats and dogs, 1 year dog study, Carcinogenicity study in rats and mice, Two-Generation Reproduction toxicity study in rats, Subchronic neurotoxicity studies in rats, 28-day dietary immunotoxicity study in mice, 28-day study in rats on metabolite CGA 329773, in vivo micronucleus test in rats on metabolite CGA 329773) since a conclusion on whether they fit-for-purpose and support the toxicological studies could not be reached.

Section 1 – Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of analysis

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(101)		FR: No comment	RMS (August 2017): noted.	Addressed.
1(102)		NL: No comments	RMS (August 2017): noted.	Addressed.
1(103)		LV: Section not reviewed, no comments	RMS (August 2017): noted.	Addressed.

Section 2 – Effects on human and animal health

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(1)		LV: No comments	RMS (August 2017): Noted Addressed	Addressed.
2(2)	Vol. 3 CA, B.6.1., in vitro metabolism	NL: we agree with the data requirement set in Volume 1 level 3 for an <i>in vitro</i> metabolism study.	Applicant: the applicant notes this comment. An <i>in vitro</i> metabolism study has been conducted and the report will be available during the Stop-the-clock period. RMS (August 2017): Noted. Please see comment 2(5) Data requirement	See data requirement in 2(5).
2(3)	Vol. 3, B.6.1.1, p. 5	DE: Data gap: The <i>in vitro</i> metabolism study has not been conducted.	Applicant: see 2(2). RMS (August 2017): The RMS agrees with DE comment. Please see comment 2(5) Data requirement	See data requirement in 2(5).
2(4)	Vol.3, B.6.1	EFSA: Although the metabolic pathway in the rat is simple it might useful to include a figure in the RAR.	RMS (August 2017): The RMS agrees with comment.	Data requirement Applicant to provide a figure illustrating the metabolic pathway of trinexapac in

Section 2 – Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Data requirement: Applicant to provide a figure regarding the metabolic pathway in the rat. Open point	the rat.
2(5)	Vol.3, B.6.1 Data requirement 5.1.1: comparative <i>in vitro</i> metabolism studies	EFSA: A comparative <i>in vitro</i> metabolism study should be conducted since this is a new data requirement. EFSA considered not scientifically justified waiving the study based on the fact that there is not OECD guideline for this type of study. These types of studies are widely used for pharmaceuticals in various stages of development, from a new chemical entity characterisation to a pre-clinical safety assessment. It would be useful to include the dog since there were differences regarding the toxicological profile of trinexapac-ethyl in dogs and rats.	Applicant: see 2(2). The study has already been conducted, but only compares rat and human metabolism. RMS (August 2017): The RMS agrees with EFSA comments. This issue was also indicated by the RMS as a data gap in Vol 1, 3.1.4.6. Additionally, the inclusion of the dog in a comparative <i>in vitro</i> metabolism study would have been valuable due to observed differences of toxicological profile of trinexapac-ethyl between dogs and rats and therefore it is supported by the RMS. This justification was provided by the Applicant, however it was not presented in the RAR: "At the time of submission of the supplementary dossier, there are no guidelines describing the conduct of an <i>in vitro</i> metabolism study comparing key	Data requirement Applicant to provide a comparative <i>in vitro</i> metabolism study for trinexapac, including an assessment of the metabolism in key animal test species (including dog) and possible identification of specific human metabolites. See also comments 2(2), 2(3).

Section 2 – Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			<i>animal test species and humans or describing how to evaluate the data. Therefore, in accordance with the guidance document, SANCO/10181/2013-rev 2.1, no study has been provided at this stage."</i> Data requirement: A comparative <i>in vitro</i> metabolism study should be submitted by the Applicant.	

Acute toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(6)		LV: No comments	RMS (August 2017): Noted Addressed	Addressed.
2(7)	Vol. 3 CA, B.6.2.4, skin irritation	NL: we agree with the RMS that no further studies are needed on skin irritation. This is line with the current data requirements which state that when no skin irritation was observed in the acute dermal toxicity at the limit dose of 2000 mg/kg bw than	Applicant: Agreed. RMS (August 2017): Noted Addressed	Addressed.

Section 2 – Effects on human and animal health

Acute toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		this shall be used to waive the need for any dermal irritation study.		
2(8)	Vol.3, B.6.2 Phototoxicity	EFSA: Could the RMS/applicant confirm that the maximum absorption was observed at 290 nm?	Applicant: The maximum absorption was observed at 290 nm. The report detailing this will be available during the stop-the- clock period. RMS (August 2017): Data to confirm that the maximum absorption was observed at 290 nm should be provided by the Applicant. Data requirement: Applicant to provide data to confirm that the maximum absorption was observed at 290 nm. Open point	Addressed. It is confirmed in section B.2.4 that in neutral, basic or acidic solution, the maximum absorption is observed between 270 and 280 nm (and is > 10 L/mol.cm). Above 340 nm, absorption can be expected to be negligible.

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(9)	Vol. 3, B.6.3.1.1, p. 27 Oral 28-day study in rats	DE: Exposure to all tested doses of trinexapac-ethyl resulted in a statistically significant dose-related effect on liver	Applicant: The diet treated and control animals were fed was the same, but due to logistical reasons the female control	Addressed.

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		weight (up to 75 %). It is stated that this effect is due to higher glycogen content in the livers in response to differences in feeding conditions between the control and treated groups. Could you please give more detail what are the differences in the diet?	animals were killed one day before the female treated animals. This was despite all animals being fasted concurrently for the haematology and clinical chemistry sample collection. Animals were then reintroduced to diet prior to termination. Therefore the treated animals had twenty-hours longer to recover from the fasting period than the controls. It would appear that the differential glycogen effect is an artefact of a flaw in the study design. RMS (August 2017): The most important deviation from the guideline OECD 407 (1981) was listed in the study design: <i>"At the time of sacrifice, the control females were fasted overnight and the treated females were fed. In addition, all treated female groups were killed one day later than the controls and at a different time of the day."</i> As the exposed females were not properly fasted before sacrifice, it was difficult to assess which effects were treatment-related, and thus not possible to set a NOAEL for females.	

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Point addressed.	
2(10)	Vol. 3, B.6.3.2.1, p. 30 Oral 90-day study in rats	DE: The cumulative body weight gain in females was decreased (11.1 %) at the highest dose (20000 ppm). At this dose also a significant increase in the relative pituitary weight (33.3 %) and kidney weight (13.2 %) was detected. Furthermore a strong increase in neutrophils could be observed for females in the two highest dose groups (93 % and 66.9 %); is there any explanation for these haematologic findings? Due to the observed effects on organ weights, 20000 ppm should be regarded as LOAEL rather than NOAEL in females.	Applicant: The applicant agrees that 20000 ppm is a LOAEL rather than a NOAEL. RMS (August 2017): The RMS acknowledges that this NOAEL value (20000 ppm) for females written in the text of Vol 3, B.6.3.2.1 was typo. However, it should be noted that NOAEL value 395 mg/kg bw/d in the text is correct and this correct value also indicated in Vol 1, 2.6.3. The correct NOAEL for females should be 5000 ppm, equal to 395 mg/kg bw/d, based on a decrease in cumulative mean body weight gain and in food consumption for females. Relative kidney weights were statistical significantly increased in 20000 ppm females. However, these changes were less than 15% of the control values and no histological effects were seen in the kidney at any group of females. Therefore, these findings were considered not to be adverse. The statistically significant increases (33.3%) in relative pituitary weight among female groups at dose levels of 500 and	Addressed. RMS to correct in an amended RAR, this action is needed according to SANCO/10180/2013-rev.1. See also comment 2(11).

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			20000 ppm were not dose related and no histological effects were reported. Therefore, these findings were considered not to be adverse. Statistically significant alterations noted in the females for mean percent neutrophils (increase in 93% and 66.9%, respectively) and lymphocytes (decrease in 14% and 11%, respectively) at 5000 and 20000 ppm doses had the lack of a definitive dose-response relationship and lack of a similar response in the opposite sex. Furthermore, these changes in the number of lymphocytes and neutrophils were unaccompanied by changes in total number of white blood cells (WBC) and therefore were not considered to be of toxicological significance. Open point: RMS to correct NOAEL value (ppm) for females in the text of the revised RAR.	
2(11)	Vol. 3; B.6.3.2.1 Oral 90-day study in rats	LV: Considering effects seen in cumulative body weight gain (11.1 %), kidney weight (13.2 %) and significantly increased relative pituitary weight (33.3%) at 20000 ppm, NOAEL for females should be set at 5000 ppm and 20000 ppm should be considered as LOAEL respectively.	Applicant: The applicant agrees that 20000 ppm is a LOAEL rather than a NOAEL. RMS (August 2017): Unfortunately, there were no comments to this study in timely response (on 13.01.2017) of the co-	See comment 2(10).

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			RMS LV. Please see comment 2(10)	
2(12)	Vol. 3, B.6.3.2.2.	Applicant: Decreases in ALT are noted. These are then related to reductions in food consumption. 1) A decrease in ALT would not be indicative of an adverse response and 2) is there any evidence to link decreases in ALT to food consumption? The applicant recommends omitting reference to reductions in ALT due to a lack of toxicological relevance.	RMS (August 2017):): Comment acknowledged partly. 1) As noted on Volume 3, B.6.3.2.2. Conclusion "...Decrease in alanine aminotransferase (ALT) activity in the 15000 & 30000 ppm females was considered to be a secondary effect to the reductions in food consumption. Therefore, all these findings were considered not to be adverse." 2) A treatment-related, statistically significant decrease (34.5%) in ALT activity was observed in the 15000 & 30000 ppm females. A treatment-related, statistically significant decrease in mean food consumption was observed throughout the study in the 30000 ppm females on days 14-42 and 70-91 (32-41%). Food consumption averages approximately 65% of control for females. Statistical reductions in mean percent body weight gain occurred in the 30000 ppm females on days 7 – 42 and 56 – 91. The body weight reductions were attributed to a decrease in feed intake. Actually, there was an apparent tendency	Addressed. RMS to correct in an amended RAR, this action is needed according to SANCO/10180/2013-rev.1.

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			for decrease in mean food consumption (up to 20%) and in mean percent body weight gain (up to 20%) in the 15000 ppm females; however none of the differences obtained statistical significance. In case it is considered necessary by EFSA the statement could be changed in the following way: <i>"...Decrease in alanine aminotransferase (ALT) activity in the 30000 ppm females was considered to be a secondary effect to the reductions in food consumption and body weight gain. Therefore, all these findings were considered not to be adverse."</i> This statement follows <i>WHO, Guidance document for WHO monographers and reviewers (2015)</i>. In addition, this statement is in line with PSD Guidance document <i>Toxicological significance of reduced levels of serum ALT and/or AST in animal studies (May 2007)</i>. Open point	
2(13)	Vol.3, B.6.3 Page 33.	EFSA: the 7-week study in dogs should be submitted to the RMS for an independent assessment of the study.	Applicant: The applicant will supply this study and a study summary in the stop-the-clock period.	Data requirement Applicant to provide the pilot 7-week

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			RMS (August 2017): The RMS agrees with EFSA. The 7-week study with Beagle dogs (<i>Spoede S et al, 1989</i>) was only shortly mentioned in the RAR, however this study is relevant for some endpoints (e.g. the cerebral vacuolation and thymic atrophy in dogs). Furthermore, the non-guideline 7-week study with dogs was evaluated in JMPR Monograph (<i>Pesticide residues in food – 2013 evaluations. Part II. Toxicological. World Health Organization, 2013.</i>) Data requirement: Applicant to submit the 7-week study with Beagle dogs (<i>Spoede S et al, 1989</i>) and the detailed summary in word format. Open point: RMS to update Vol. 3 B.6.3 including the assessment of the additional data provided.	oral feeding study in dogs (<i>Spoede S et al, 1989</i>) and robust summary report. See also expert consultation in 2(14).
2(14)	Vol. 3, B.6.3.2.3, p. 46 ff Oral 1-year study in dogs	DE: A significant reduction of absolute and relative uterus weight was observed at 1000, 10000 and 20000 ppm. Concurrently it could be observed that in these dose	Applicant: Dogs are monoestrous ovulators and the majority of a female dog's life is spent in anoestrus. As described in the evaluation of this one year	Expert consultation: Experts to discuss the toxicological endpoints in the dog studies,

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		groups more or all females were in the middle/late metoestrus cycle. Historical control data for the uterus weight was not available. The explanation of synchronisation of oestrus cycle stages of females in the highest dose groups due to housing conditions is not sufficient as this should also affect the control group. Even though the data on oestrus cycle might explain the alterations in uterus weight, it cannot be excluded that the alterations in oestrus cycle are substance related. In addition a significant decrease of testes weight could be observed at dose levels 1000, 10000 and 20000 ppm and the weight of ovary was also reduced at these dose levels. Altogether these effects are considered as adverse. Due to the effects seen in on the uterus, ovary and testes weight as well as on the oestrus cycle DE is of the opinion that the dose of 31.6 mg/kg bw/d should be regarded as a LOAEL and the dose of 1.4 mg/kg bw/d as NOAEL This should be taken into account for the establishment of the ADI.	dog study provided to the rapporteur (Scollon and Charlton, 2017) laboratory dogs spend approximately 50% of their life in anoestrus, approximately 25% of their life in dioestrus/metoestrus, and only 15% of their life in pro-oestrus or oestrus. The animals in the one year dog study with trinexapac-ethyl were not distributed along these lines, but were predominantly in or around metoestrus/dioestrus at the point of necropsy. The applicants' comments around oestrus cycle synchronisation are intended to address the high degree of similarity in oestrus cycle staging rather than to explain any inter-group variabilities. The one year dog study with trinexapac-ethyl suffers from a number of methodological deficiencies that make it unsuitable for the accurate determination of oestrus cyclicity. The minor differences in oestrus cycle stage between treated and control animals in this study are not the result of treatment with trinexapac but are instead reflective of a combination of these deficiencies in study design and normal dog reproductive biology. A critique of the relevant data illustrating the deficiencies in	including changes in brain and reproductive organs. See also data requirement in 2(13). See also comments 2(15), 2(16) and 2(17).

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			methodology and providing a comparison with established knowledge of oestrus cyclicity in dogs has been provided to the rapporteur (Scollon and Charlton, 2017). Variations to ovarian weight observed in this study are related to oestrus cycle stage and as such are similarly unrelated to treatment with trinexapac-ethyl (Scollon and Charlton, 2017). Whilst statistically significantly lower absolute testis weights were observed in dogs administered doses ≥ 1000 ppm, testis weights adjusted for body or brain weights were not statistically significant at any dose level. Furthermore, no evidence of testicular histopathological changes was observed in any animal. In the absence of a statistically significant change in testis weight after correction for body weight or brain weight, and in the absence of corroborating histological findings, the change in absolute testis weight is considered incidental to treatment. The applicant notes that any potential effects on endocrine organs have been reviewed in the appropriate context in the	

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			review for endocrine disruption submitted by the applicants (Green, 2015). This review also contains a large quantity of endocrine specific <i>in vitro</i> assay data indicating a total lack of interaction between trinexapac-ethyl and components of the endocrine system. This provides further evidence that variations in uterine, ovarian and testis weight, and in oestrus cycle stage are unrelated to treatment with trinexapac-ethyl as any such effects would lack a mechanistic basis. As these effects are not treatment related they do not provide an appropriate basis for the establishment of any risk assessment reference value. RMS (August 2017): The RMS disagrees with DE comments that due to the effects on the uterus, ovary and testes weight as well as on the oestrus cycle the dose of 31.6 mg/kg bw/d should be regarded as a LOAEL. The RMS considerations regarding this issue are included in the study report Vol 3, B.6.3.2.3. (46-48 pp.). Since no histopathological effects were seen in the uterus, ovary and testes at any dose in this study it was difficult to assess the	

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			toxicological relevance of the weight changes of these organs. Therefore, organ absolute and relative weights data were interpreted in an integrated fashion with other findings (data on the oestrus cycle) and parameters (control group range values, inter-individual variations and dose-response relationship and statistical significance). - <i>Uterus</i>. Absolute and relative uterus weight changes (statistically significant) were clearly consistent with the physiological changes of uterus at the two highest doses (10000 and 20000 ppm) only: all females were in the middle/late oestrus cycle stage, whereas fewer females at 1000 ppm were in this oestrus cycle stage. - <i>Ovary</i>. A clear dose-response relationship was seen with respect to reduction in absolute ovary weight; however neither absolute nor relative mean values did attain statistical significance. Furthermore, compilation of individual pathology and physiology data on the ovaries was not submitted. Therefore, the decrease in ovary weight was not considered toxicologically relevant. - <i>Testes</i>. The change in absolute	

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			testes weights was not considered toxicologically relevant, as neither statistically significant changes in relative weight nor histopathological changes were observed at any dose in this study, nor in other dog or rodent studies. Furthermore, an effect on uterus weight was considered toxicologically relevant at 10000 ppm (357.1 mg/kg bw/d for female) due to possible adverse effect of trinexapac-ethyl on the oestrus cycle via a hormonally mediated mechanism. Hence, the RMS proposes to remain NOEL at 1000 ppm (31.6 mg/kg bw/day) based on adverse effect on uterus weight the next higher dose group. Final conclusion regarding toxicological relevance will depend on further detailed information on ToxCast regarding endocrine-disrupting potential. Expert consultation: Experts to discuss the relevance of the uterus, ovary and testes weight changes in a 52-wk oral toxicity study in dogs in relation with further detailed information on ToxCast regarding endocrine-disrupting potential.	

Section 2 – Effects on human and animal health

Short-term toxicity				
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2(15)	Vol. 3, B.6.3.2.3	LV: A significant reduction of absolute and relative uterus weight was seen in mid-doses and at the highest dose. HCD for the uterus weight is not available. The explanation of synchronisation of oestrus cycle stages of females in the highest dose groups due to housing conditions is not sufficient. It cannot be ruled out that alterations in oestrus cycle are substance related. Overall these effects should be considered as treatment related and should be taken into account for ADI setting. Overall LV is on the opinion that for this study NOAEL should be set as 40 ppm (1.4 mg/kg bw/d) based on effects seen on uterus and ovary.	RMS (August 2017): Unfortunately, there were no disagreements with the assessment regarding this critical issue in timely response (on 13.01.2017) of the co-RMS LV. Please see comment 2(14)	See expert consultation in 2(14).
2(16)	Vol.3, B.6.3 Krinke, 1994 Page 58	EFSA: It is not clear if a new report supporting the interpretation of dog studies was submitted during the renewal procedure.	Applicant: The RMS to clarify. RMS (August 2017): Three supplementary reports were submitted (on 28th October 2015) for the purpose of renewal to support interpretation of dog studies/study: • Persohn E, 1999 (points Vol 3,	See expert consultation in 2(14).

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			<i>B.6.3.2.3.1.);</i> <i>Krinke G and Mahrous A, 1999 (points Vol 3, B.6.3.2.3.2.);</i> <i>Krinke G, 1994 (points Vol 3, B.6.3.2.3.3.).</i> <i>As stated in Vol.3 Version History Box "changes to the original text and reconsideration of old studies of the original DAR, new studies or information submitted in the framework of the application for renewal of a.s. approval are highlighted by yellow shading".</i> <i>Additionally, it is stated above every report: "A new report submitted to support interpretation of Dog studies/1-year dog study".</i> <i>It is also stated in Vol 3, B.6.11 References relied on.</i> Addressed	
2(17)	Vol.3, B.6.3 Krinke, 1994 Page 61	EFSA: the analysis of biological relevance of the findings described that compounds disturbing metabolism of glucose induced similar swelling of astrocytes and oligodendroglia. It is noted that according to literature on	Applicant: The applicant notes the hypothesis proposed by EFSA, but notes that neither cyclopropane carboxylic acid nor tricarballic acid were identified in the rat ADME studies, and dog ADME data are not available. It would seem unlikely therefore that either of these metabolites	See expert consultation in 2(14).

Section 2 – Effects on human and animal health

Short-term toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		metabolites, cyclopropane carboxylic acid is considered a hypoglycemic agent (Buxton D et al, 1983) and tricarballic acid is an inhibitor of the enzyme aconitase and interferes with the Krebs cycle. The role of metabolites and interspecies differences might be further investigated to support applicant's statement on the non-relevance for humans. However, on the basis of current available information EFSA supported the RMS' view that in the absence of mechanistic studies and/or any human data, cerebral vacuolation observed in dogs should be considered relevant for human.	are generated <i>in vivo</i>, and are subsequently responsible for cerebral vacuolation in the dog. RMS (August 2017): Noted Addressed	

Genotoxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(18)	Vol.3, B.6.4 pages 90-91	EFSA: Robust summaries reports of the <i>in vitro</i> gene mutation tests should be included in a revised RAR.	Applicant: The applicant will prepare summary results tables for the genotoxicity studies during the stop-the-clock period. The applicant notes that the typographical	Data requirement Applicant to provide detailed summary reports for <i>in vitro</i> genotoxicity studies: - Deparade E. (1988), study report No.

Section 2 – Effects on human and animal health

Genotoxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		Please also note the conclusion of the study by Geleick, 1993 referred to Chinese Hamster V79 cells whereas the study was performed with mouse lymphoma cells. Could the RMS/applicant indicate if colony size was measured in the mouse lymphoma assay?	error with the Geleick was also made in the original draft assessment report (2005). Colony sizing was not performed on the 1993 Geleick study as there was no indication of a positive response with the total number of colonies. RMS (August 2017): Comment acknowledged. Applicant to provide robust/detailed summaries reports in word format for five <i>in vitro</i> genotoxicity studies (<i>Deparade E. (1988)</i>; <i>Deparade E. (2001a)</i>; <i>Dollenmeier P. (1988)</i>; <i>Geleick D. (1993)</i>; <i>Ogorek B. (2001)</i>). The submitted summaries will be included in the revised RAR. Data requirement: Applicant to provide detailed summaries reports (<i>Deparade E. (1988)</i>; <i>Deparade E. (2001a)</i>; <i>Dollenmeier P. (1988)</i>; <i>Geleick D. (1993)</i>; <i>Ogorek B. (2001)</i>) in word format. Open point: RMS to include the detailed summaries of results in a revised RAR (<i>Deparade E. (1988)</i>; <i>Deparade E.</i>	871414 - Deparade E. (2001a), study report No. 20001169 - Dollenmeier P. (1988), study report No. 871415 - Geleick D. (1993), study report No. 931004 - Hertner (1988), study report No. 871411 - Meyer (1988), study report No. 871413 RMS to provide update and also correction in an amended RAR, this action is needed according to SANCO/10180/2013-rev.1. Expert consultation Experts to discuss the amended results of the genotoxicity studies with trinexapac-ethyl. See data requirements in 2(18) and 2(69). See also open point in 2(22).

Section 2 – Effects on human and animal health

Genotoxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			(2001a); Dollenmeier P. (1988); Geleick D. (1993); Ogorek B. (2001)). Regarding the study by Geleick, 1993 Point noted. The conclusion of the study by <i>Geleick, 1993</i> will be amended accordingly in a revised RAR. Addressed	
2(19)	Vol. 3 CA, B.6.4.1	NL: it would be informative to have detailed results table on the results from the <i>in vitro</i> genotoxicity studies in the RAR.	Applicant: The applicant will prepare summary results tables for the genotoxicity studies during the stop-the-clock period. RMS (August 2017): Comment acknowledged. Please see comment 2(18).	See data requirement in 2(18).
2(20)	Vol. 3 B6, B.6.4.1	LV: <i>In vitro</i> genotoxicity. In order to permit an independent review of the assessment robust data should be provided, for some <i>in vitro</i> studies only conclusions are reported.	Applicant: The applicant will prepare summary results tables for the genotoxicity studies during the stop-the-clock period. RMS (August 2017): Comment acknowledged. Please see comment 2(18)	See data requirement in 2(18).
2(21)	Vol 3 CA, B.6.4.2	NL: Although it has not been definitively shown that the bone marrow was reached	Applicant: Agreed. RMS (August 2017): Noted	Addressed.

Section 2 – Effects on human and animal health

Genotoxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		we agree with the RMS that based on the ADME studies it is likely that bone marrow was reached.	Addressed	
2(22)	Vol.3, B.6.4 Page 101	EFSA: Please include a complete assessment of the results of the genotoxicity studies including the <i>in vivo</i> MN test submitted by Cheminova A/S in the B.6.4. Information on the active substance should not be considered confidential.	Applicant: The <i>in vivo</i> micronucleus study conducted by Cheminova A/S and the study summary will be made available during the stop-the-clock period to allow complete assessment of the genotoxicity data. RMS (August 2017): A complete assessment of the results of five genotoxicity studies on the active substance submitted by Cheminova A/S (Ames tests, Williams, L. (2009) & Donath, C. (2011); Chromosome Aberration Test <i>in vitro</i>, Lloyd, M. (2010); Gene Mutation Test <i>in vitro</i>, Stone, V. (2009); <i>in vivo</i> MN; Whitwell J. (2010),) will be included in the revised RAR Vol 3, B.6.4. from the confidential Vol 4 Cheminova and will not be considered as confidential any more. Additionally, the results from these five genotoxicity studies will be summarised in the revised RAR Vol 1, 2.6.4 and the list of references (Vol 2, A.6) as well as List of Endpoints (Section 2) will be updated. Open point: RMS to update Vol 3 B.6.4.	Open point RMS to provide an updated non-confidential RAR with the genotoxicity studies provided by Cheminova A/S. See also expert consultation in 2(18).

Section 2 – Effects on human and animal health

Genotoxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Vol 1 2.6.4 and Vol 2 A.6 as well as List of Endpoints including five genotoxicity studies of Cheminova A/S.	

Long-term toxicity and carcinogenicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(23)		LV: No comments	RMS (August 2017): Noted Addressed	Addressed.
2(24)	Vol.3, B.6.5	EFSA: No comments.	RMS (August 2017): Noted Addressed	Addressed.
2(25)	Vol. 3 CA, B.6.5.1, combined chronic toxicity and carcinogenicity in rats	NL: Regarding the squamous cell carcinoma we do not agree with the argument that this finding has little if any biological relevance to humans. The CLP guidance states that while humans do not have forestomach, they do have comparable squamous epithelial tissue in the oral cavity and the upper two-thirds of the oesophagus and that it cannot be ruled out that the substance could cause similar	Applicant: The applicant agrees the squamous cell carcinomas are incidental. The CLP guidance also suggests that tumours observed only in this tissue, with no other observed tumours, are unlikely to lead to classification. RMS (August 2017): Noted The statement that this finding has <i>little if</i>	Addressed.

Section 2 – Effects on human and animal health

Long-term toxicity and carcinogenicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		tumours of comparable cell/tissue origin. However, considering the low incidence and the lack of related non-neoplastic findings we do agree that the squamous cell carcinoma can be regarded as incidental.	<i>any biological relevance to humans</i> was used by the Applicant in the Addendum (January 2005) to the DAR (2003) and was given for the renewal of approval of the active substance (21 September 2015). New careful re-evaluation of this study has been performed by the RMS LT: comments and conclusions were presented below the study. The RMS comment that "<i>the relevance of this tumour to humans is probably low</i>" refers to <i>OECD Guidance Notes for Analysis and Evaluation of Chronic Toxicity and Carcinogenicity Studies, 2002</i>. Addressed	

Reproductive toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(26)		LV: No comments	RMS (August 2017): Noted Addressed	Addressed.
2(27)	Vol.3, B.6.6	EFSA: asymmetrically shaped sternebrae is	Applicant: The applicant finds the	Data requirement

Section 2 – Effects on human and animal health

Reproductive toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Rat developmental toxicity study. Pages 152-153	described as anomalies. Can the RMS/applicant clarify if the anomaly should be considered malformation, variation or a grey zone anomaly according to current state of art? Based on litter incidence of asymmetrically shaped sternebrae and historical control data its biological relevance might not be excluded. Please also considered whether the incidence of asymmetrically shaped sternebrae and still absent ossification should be considered together. Could the RMS/applicant clarify if trinexapac-ethyl has been discussed by ECB or ECHA? Is there any intention to submit the CLH report to ECHA?	historical control data as reported to have deficiencies – means plus standard deviation have been reported, with no range. The applicant has compiled an historical control data analysis using data from studies conducted at the same laboratory, covering several years before and after this study. The asymmetrically shaped sternebrae are within this control range and therefore this finding is considered not related to treatment. This historical control analysis will be available during the stop-the-clock period. RMS (August 2017): Asymmetric sternebra in rats as well as in others species is neither malformation nor variation, it should be considered a grey zone anomaly according to current state of art, i.e. the updated harmonized nomenclature for developmental toxicology, based on the revised IFTS terminology (Makris et al. 2009), (last update October 2012). Regarding litter incidence of asymmetrically shaped sternebrae and historical control data the Applicant should	Applicant to provide more detailed historical control data for the rat developmental toxicity study. Expert consultation Experts to discuss the developmental toxicity studies with trinexapac-ethyl. See also comment 2(28).

Section 2 – Effects on human and animal health

Reproductive toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			submit the detailed historical control analysis. <i>Vertebra cervical centrum incomplete ossification</i> should be considered a variation according to the harmonized nomenclature for developmental toxicology mentioned above. Hence, asymmetrically shaped sternbrae and still absent ossification should not be considered together as these anomalies are classified differently. Trinexapac-ethyl (ISO) does not yet benefit from a harmonised classification and is not listed in Annex VI to Regulation (EC) No 1272/2008. Only the classifications provided by companies to ECHA in <i>CLP notifications</i> are available. Expected date of submission by the RMS LT a harmonised classification proposal to the European Chemicals Agency in accordance with Article 37(1) of Regulation (EC) No 1272/2008 is 31/10/2017 and notification date is 23/01/2017. Data requirement: Applicant to submit the detailed historical control analysis	

Section 2 – Effects on human and animal health

Reproductive toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			regarding asymmetrically shaped sternebrae anomaly. Open point	
2(28)	Vol.3, B.6.6 Developmental toxicity studies. Shorter administration period	EFSA: All developmental toxicity studies have been performed with a shorter administration period. EFSA noted that insults during the last trimester can cause growth retardation, developmental delay or functional disturbances. EFSA also noted that malformations of organs developing after the period of major organogenesis, e.g., the sex organs and the brain, may not be detected if the study is performed according to the prior guideline for the teratology studies. EFSA would not request to perform additional vertebrate studies; however the uncertainties regarding deviations from current OECD TG should be taken into account in the conclusions.	Applicant: Studies in the rat and rabbit were conducted to the contemporary guidelines at the time i.e. OECD 414 (1981): EPA Guideline Reference number 83-3 which were prior to the introduction of OECD 414 (2001), OPPTS 870.3700 (1998) and 2004/73/EC B.31 (2004). The major differences between the more recent guideline requirements and the trinexapac rat and rabbit studies are: The length of treatment (only through organogenesis vs. the full length of gestation). Treatment encompassed the period of major organogenesis, hence malformations and most variations would have been detected. Double staining of the skeletons - despite the lack of cartilage staining in these studies the detail of the observations in the reports suggests that if there were significant changes they would have been detected. Examination of the skeleton	See expert consultation in 2(27).

Section 2 – Effects on human and animal health

Reproductive toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			identified the ghost outline of most of the cartilage that had yet to convert to bone, enabling the diagnosis of any treatment-related effects. In accordance with Article 8(d) of regulation (EC) 1107/2009 and the ANNEX Point 5 (Tests on vertebrate animals) of regulation (EC) 843/2013 Syngenta believes that the developmental studies conducted with trinexapac in the rat and rabbit provide sufficient data to conclude on the potential for developmental toxicity of trinexapac and further studies are not justified. RMS (August 2017): Indeed, two developmental toxicity studies have been performed with a shorter administration period: solely the period of major organogenesis (i.e. days 6-15 in the rat and days 7-19 in the rabbit) was examined. The studies reports were checked for compliance with OECD TG 414 (Prenatal Developmental Toxicity Study) (adopted 22nd January 2001)), however, this deficiency was not noted by the RMS LT among other differences between the modern guideline requirements and the old	

Section 2 – Effects on human and animal health

Reproductive toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			studies. Anyhow, it was concluded that the studies do not appear to comply with the updated OECD guideline. The RMS agrees that worthy of notice in Vol 1, 2.6.6 <i>"that these old studies do not appear to comply with the updated OECD TG 414 (2001) as main differences were identified: solely the period of major organogenesis (i.e. days 6-15 in the rat and days 7-19 in the rabbit) was examined, groups were with fewer than 16 animals with implantation sites at necropsy (rabbit study) and instead of recommended two- to four-fold intervals other intervals of doses were used."</i> Additionally, this deficiency should be noted in the comments and conclusions of two studies in Vol 3, B.6.6.2. The RMS LT would like to note that developmental toxicity studies with shorter study duration are probably the case for many old substances. On the other hand, it should be acknowledged that some malformation of organs mentioned by EFSA would be expected to be seen in two-generation reproduction toxicity study in rat which has longer exposure periods. However, none of	

Section 2 – Effects on human and animal health

Reproductive toxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			the effects were seen in that study. Open point: RMS to include additional difference between the modern guideline requirements and the old studies in the conclusions in a revised RAR.	

Neurotoxicity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(29)		LV: No comments	RMS (August 2017): Noted Addressed	Addressed.
2(30)	Vol.3, B.6.7	EFSA: None.	RMS (August 2017): Noted Addressed	Addressed.

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(31)	Vol. 3, B.6.8 Endocrine Disruption	EFSA: According to the preliminary assessment of the applicant trinexapac-ethyl was inactive regarding AR, ER, ThR receptor indicating no mode of action regarding these modalities. However EFSA supported that further detailed information on ToxCast regarding endocrine-disruption potential of trinexapac-ethyl should be submitted and assessed by the applicant within a weight of evidence approach.	Applicant: The applicants agree with EFSA that available mechanistic data demonstrate that there is no evidence of endocrine modalities for trinexapac-ethyl. Trinexapac-ethyl has been evaluated in a battery of assays designed to assess the potential for interaction with components of the endocrine system as part of the US EPA's ToxCast program. Whilst this data has been presented by the applicants the rapporteur requested further methodological information about these data. The applicants have provided a review containing additional methodological information for the endocrine system related assays conducted with trinexapac-ethyl as part of the US EPA ToxCast program. Trinexapac-ethyl was negative in all of these assays, providing comprehensive evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system. This review is present in this commenting table in row number 2(39).	Data requirement: Applicant to submit further detailed information on ToxCast results regarding endocrine-disruption potential of trinexapac-ethyl. Expert consultation: Potential for endocrine disruption of trinexapac-ethyl to be discussed by the experts. See data requirements in 2(31) and 2(33). See also comments 2(32), 2(34), 2(35), 2(36), 2(37), 2(38) and 2(39).

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Available ToxCast data has already been evaluated in the weight of evidence review for endocrine disruption presented in the trinexapac-ethyl DAR (Green, 2015). This review demonstrated that, on a weight of evidence basis, trinexapac-ethyl does not meet the WHO/IPCS definition of an endocrine disruptor. RMS (August 2017): The RMS agrees with EFSA. A data gap was indicated by the RMS in Vol 1, 3.1.4.6: "<i>Possible adverse effect of trinexapac-ethyl on the oestrus cycle in 1-year dog study needs to be further addressed and further clarification of the ED potential using mechanistic data is requested.</i>" Regarding ToxCast data presented in the review for endocrine disruption (Green, 2015), only Table with summarised <i>in vitro</i> assays as well as negative results of all assays were provided. Further detailed information on ToxCast regarding endocrine-disruption potential of trinexapac-ethyl should be submitted in	

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			word format and assessed by the applicant within a weight of evidence approach. Data requirement: Applicant to submit in word format and assess further detailed information on ToxCast regarding endocrine-disruption potential of trinexapac-ethyl.	
2(32)	Vol. 1, 2.6.8.3, p. 51	DE: DE supports the opinion of the RMS that in the absence of further data on the effect of trinexapac-ethyl on the oestrus cycle and weight of reproductive organs an endocrine disrupting potential cannot be excluded. Further data are needed (e.g. suitable studies from the OECD Endocrine Disruptor Screening Program).	Applicant: Trinexapac-ethyl has been evaluated in a battery of assays designed to assess the potential for interaction with components of the endocrine system as part of the US EPA's ToxCast program. Whilst this data has been presented by the applicants the rapporteur requested further methodological information about these data. The applicants have provided a review containing additional methodological information for the endocrine system related assays conducted with trinexapac-ethyl as part of the US EPA ToxCast program. Trinexapac-ethyl was negative in all of these assays, providing comprehensive evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system.	See expert consultation in 2(31).

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			This review is present in this commenting table in row number 2(39). RMS (August 2017): Noted. Please see comment 2(31).	
2(33)	Vol 3 CA, B.6.8.3 Studies on endocrine disruption	NL: Could the RMS provide a more detailed summary of the Böhmler et al. 2006 study.	Applicant: The applicant has drafted a detailed summary of this paper and it will be available during the stop-the-clock period. RMS (August 2017): A more extended summary in word format should be provided by the Applicant. Data requirement: Applicant to provide a more extended summary of the study (Böhmler G. et al., 2006) in word format. Open point: RMS to update the presentation of the study in the revised RAR.	Data requirement: Applicant to provide a more detailed summary of the study by Böhmler G. et al., 2006. See also expert consultation in 2(31).
2(34)	Vol 3 CA, B.6.8.3 Studies on endocrine disruption	NL: Based on the available information it does seem likely that the effects on uterus	Applicant: The applicants agree that it is unlikely that any differences in oestrus cycle stage in this study are the result of	See data requirement and expert consultation in 2(31).

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		weight in the 1-year dog study are due to differences in oestrus cycle stage between the dose groups and not by a specific endocrine effect. However, the ToxCast data should be submitted to support this. We therefore agree with the RMS that further clarification is needed.	treatment with trinexapac-ethyl. Trinexapac-ethyl has been evaluated in a battery of assays designed to assess the potential for interaction with components of the endocrine system as part of the US EPA's ToxCast program. Whilst this data has been presented by the applicants the rapporteur requested further methodological information about these data. The applicants have provided a review containing additional methodological information for the endocrine system related assays conducted with trinexapac-ethyl as part of the US EPA ToxCast program. Trinexapac-ethyl was negative in all of these assays, providing comprehensive evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system. This review is present in this commenting table in row number 2(39). RMS (August 2017): Noted. Please see comment 2(31).	

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(35)	Vol 3 CA; B.6.8.3 Studies on endocrine disruption	LV: Agree with the RMS that further investigation is needed (at least Tox Cast data further and further investigation according OECD framework)	Applicant: Trinexapac-ethyl has been evaluated in a battery of assays designed to assess the potential for interaction with components of the endocrine system as part of the US EPA's ToxCast program. Whilst this data has been presented by the applicants the rapporteur requested further methodological information about these data. The applicants have provided a review containing additional methodological information for the endocrine system related assays conducted with trinexapac-ethyl as part of the US EPA ToxCast program. Trinexapac-ethyl was negative in all of these assays, providing comprehensive evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system. This review is present in this commenting table in row number 2(39). RMS (August 2017): Noted Please see comment 2(31).	See data requirement and expert consultation in 2(31).
2(36)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: The applicant agrees with the rapporteur's conclusion that trinexapac-	RMS (August 2017): Noted.	See expert consultation in 2(31).

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		ethyl does not meet the interim criteria for endocrine disruption specified in EC 1107/2009. The applicant notes that on the 4th of July 2017 The Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) voted to adopt a definition of endocrine disruption derived from the internationally recognized WHO/IPCS definition. It is considered that the interim criteria for identification of endocrine disruptors described in regulation EC 1107/2009 were a regulatory construct that do not constitute a best scientific approach to endocrine identification, and are therefore not appropriate. The applicant therefore acknowledges that the most suitable and scientifically valid approach would be for the final criteria for identification of endocrine disruptors agreed by the SCoPAFF to be used in the evaluation of trinexapac-ethyl.	Please see comment 2(31).	
2(37)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: The differences in oestrus cycle stage between treated and control animals in the 52 week dog study with trinexapac-ethyl are not the result of treatment with trinexapac but are instead reflective of a	RMS (August 2017): Noted. It should be noted that there were differences between the Applicant and the RMS in the interpretations of some	See expert consultation in 2(31).

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		combination of methodological deficiencies in study design and normal dog reproductive biology. To provide additional critique of the relevant data, an expert technical review of this study illustrating the deficiencies in methodology and providing a comparison with established knowledge of oestrus cyclicity in dogs has been provided to the rapporteur.	findings. The concern for endocrine disrupting potential was raised from the supplementary report with additional information regarding the trinexapac-ethyl 1 year dog study. However, due to a number of deficiencies in 1 year dog study and the supplementary report it was difficult to assess the biological relevance of the results. Therefore, an adverse effect of trinexapac-ethyl on the oestrus cycle via a hormonally mediated mechanism cannot be ruled out. Please see comment 2(31).	
2(38)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: Whilst the applicant does not share the rapporteur's concerns around the one year dog study with trinexapac-ethyl the applicant notes that assessment of endocrine disruption should be conducted through a weight of evidence evaluation and that all studies with trinexapac-ethyl should be evaluated holistically with both positive and negative evidence considered together. The applicant does not believe that a single isolated data point that is inconsistent with all other OECD conceptual framework level 4 and 5 studies in the database should be	RMS (August 2017): The RMS agrees that the most studies available do not give any clear indications of an endocrine potential of trinexapac-ethyl. The concern for endocrine disrupting potential was raised from the supplementary report with additional information regarding the trinexapac-ethyl 1 year dog study and an adverse effect of trinexapac-ethyl on the oestrus cycle via a hormonally mediated mechanism could not be ruled out. Extensive consideration of the RMS in this context is given in RAR Vol 1, 2.6.8.3.	See expert consultation in 2(31).

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		considered to constitute evidence of endocrine disruption, particularly in the presence of a comprehensive battery of endocrine related assays indicating that trinexapac-ethyl does not have the potential to interact with components of the endocrine system. The applicant draws particular attention to the fact that no effects were seen on end-points relating to oestrogenic, androgenic and/or steroidogenic processes. A lack of effects in this set of assays provides further evidence that any inter-group differences noted in the one-year dog study oestrus cyclicity data were without relationship to treatment with Trinexapac-ethyl and therefore incidental in nature.	Please see comment 2(31).	
2(39)	Vol. 3, B.6.8.3, Studies on endocrine disruption	Applicant: The rapporteur noted that whilst a battery of assays designed to assess the potential for interaction with components of the endocrine system as part of the US EPA's ToxCast data had been supplied by the applicant the level of methodological information provided alongside these data was limited. The applicant has provided a review containing additional methodological information for the endocrine system related assays conducted with trinexapac-ethyl as part of	RMS (August 2017): Noted. Please see comment 2(31).	See data requirement and expert consultation in 2(31).

Section 2 – Effects on human and animal health

Further toxicological studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		the US EPA ToxCast program. Trinexapac-ethyl was negative in all of these assays, providing comprehensive evidence that trinexapac-ethyl does not interact with isolated components of the endocrine system.  Trinexapac-ethyl ToxCast ED assays.pdf		

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(40)	Vol.3, B.6.8 Dietary metabolites Citric acid	EFSA: citric acid is well known substance. Did the RMS consider citric acid a non-relevant metabolite of trinexapac-ethyl for dietary risk assessment?	Applicant: RMS stated citric acid is non-relevant in dRAR Volume 1, page 63. RMS (August 2017): In view of the fact that citric acid was not identified by the Applicant as so-called dietary metabolite, or potential dietary metabolite and no information was provided on this metabolite to section 2, it	Open point RMS to add the detailed assessment of the toxicological profile of citric acid in a revised RAR. See experts' consultation at 2(53).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			was not evaluated from toxicological point of view. According to residue section (RAR Vol 1, 2.7.3 (7) & Vol 3, B.7.2.1) Citric acid is minor plant metabolite found in wheat straw only (0.027 mg/kg, 2.0 % TRR). No exposure assessment of citric acid was provided by the Applicant. The RMS considers citric acid a toxicologically non-relevant metabolite based on rationale given below (references <i>Evaluation of active substances, Regulation (EU) No 528/2012, Assessment report, Citric Acid as Product-type 2, March 2016; Toxicological evaluation of certain food additives with a review of general principles and of specifications, Seventeenth Report of the Joint FAO/WHO JECFA, 1974; EFSA Scientific opinion, EFSA Journal 2015, 13(2):4010</i>). Citric acid occurs in all living organisms as an intermediate in the tricarboxylic acid or Krebs cycle. It is a natural component of fruit, vegetables and plants (roots and leaves). Citric acid is currently listed in the European Union Register of Feed Additives as a technological additive (functional	

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			group: preservative) for use in fee for all animal species without restrictions. Citric acid (E330) is approved as a food additive for general use in foodstuffs following the <i>quantum satis</i> principle (limits set for some food products, i.e. juices, infant foods). There is set a lowest dietary limit by EFSA for inclusion into fruit and vegetable juices of 100 mg/kg bw/d considering the limiting factor of irritation in the gastro-intestinal tract. It has a long history of use as an additive in food, cosmetics, pharmaceuticals (human and veterinary), plant protection products, biocides and household cleaning products. Citric acid has been assessed by the Joint FAO/WHO JECFA (1974). The Committee allocated an acceptable daily intake (ADI) of 'not limited' for citric acid. This position was retained by the Scientific Committee on Food (SCF) (EC, 1991). An ADI without an explicit indication of the upper limit of intake is assigned to substances of very low toxicity, especially those that are food constituents or that may be considered as foods or normal metabolites in man. There is a Maximum Recommended Therapeutic Dose (MRTD) in US Food and	

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			Drug Administration (FDA) list of 100 mg/kg bw/d, this quantity is added to the background level exposure from the diet, without inducing adverse effect. In case it is considered necessary this statement could be included in the revised RAR Vol 1, 2.6.9.1. Open point	
2(41)	Vol.3, B.6.8 Dietary metabolites Trinexapac ("acid")	EFSA: agreed with the assessment of trinexapac as covered by trinexapac-ethyl.	RMS (August 2017): Noted This comment refers to Point B.6.8.1.2: The toxicity of the trinexapac acid (CGA179500) is considered covered by the parent trinexapac-ethyl (CGA163935). However, it should be noted that the evaluated data in Vol 3CA B-6 belong to the trinexapc-ethyl (CAS No 95266-40-3) which is equated to name "Trinexapac" (please refer to Table B.6.8.1-1). Therefore, a general clarification is needed on assignment of name "Trinexapac". Furthermore, CAS No 143294-89-7 is associated with the IUPAC name 'Trinexapac' according to ECHA database. In addition, clarification regarding on the	Addressed. The name trinexapac should be attributed to CGA179500. See experts' consultation at 2(53).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			assignment of CAS numbers (95266-40-3, 104273-73-6, 143294-89-7) and specific keto/enol isomers of trinexapac-ethyl / trinexapac acid please see comment 1(7) in <i>Reporting table Confidential Helm</i>. Open point	
2(42)	Vol.3, B.6.8 Dietary metabolites Tricarballic acid	EFSA: According to the literature tricarballic acid is an inhibitor of the enzyme aconitase and interferes with the Krebs cycle and appears to be a well-known compound. Did the literature search include this compound? If the metabolite is a significant plant/livestock metabolite its toxicological profile should be further define in order to conduct a consumer risk assessment.	Applicant: The literature search did not include tricarballic acid. In dRAR Volume 1, page 60, a full explanation of why tricarballic acid is not a significant metabolite is given, on the basis that it is a naturally occurring compound in grass. For this reason it was not included in the literature search originally, however the applicant will provide a literature search on tricarballic acid during the stop-the-clock window. RMS (August 2017): Based on limited data/information submitted to section 2 it was concluded that this metabolite was of higher acute	Data requirement Applicant to provide a literature search (covering the last ten years) for the toxicological properties of the tricarballic acid metabolite, 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid (CGA329773) and CPCA (CGA224439). Based on currently available information further data would be needed to conclude on genotoxicity (<i>in vitro</i> chromosome aberration test) and general toxicity (repeated toxicity study) for metabolite tricarballic acid. See also comment 2(70). See also comments 2(43), 2(50),

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			oral toxicity than the parent substance whereas a final conclusion on the genotoxic potential was not drawn as only Ames test (negative) and QSAR prediction for genotoxicity (negative) were provided. The literature search provided to section 2 did not include this compound. In addition, according to the classification provided by companies to ECHA in CLP notifications this substance causes serious eye irritation, causes skin irritation and may cause respiratory irritation. CGA275537 (Tricarballic acid) is a postulated metabolite in the crops (wheat, rape, grass, rice) and is considered to be dietary metabolite, or potential dietary metabolite. According to residue section (RAR Vol 1, 2.7.3 (4) & Vol 3, B.7.2.1) Tricarballic acid is observed in significant amounts in wheat forage, hay and straw (7.8 to 10.3% TRR) and to a lesser extent in wheat grain (2% TRR, 0.03 mg/kg) and oilseed rape seeds (1% TRR, 0.004 mg/kg). Tricarballic acid occurs naturally in animal feed and regarding exposure of tricarballic acid and the applicant refers	2(51), 2(52) and 2(53). See experts' consultation at 2(53).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			to assessment report of a.s. prohexadione calcium, which is another plant growth regulator approved in Europe (<i>RMS FR, DAR, Addendum to the Additional report to Volume 3 Annex B.7 revised in August 2009, Linked to Evaluation Table Open points, October 2009; B.7.3.1.4., 46-47 pp.</i>). However, five references presented in the above mentioned report were not provided to the RMS LT by the Applicant. The contribution to the animal intakes from trinexapac-ethyl was considered insignificant based on this non-comprehensive information provided in residue section and thus no further consideration of its toxicity was required. Hence, based on the information mentioned above might be considered that Tricarballic acid is a toxicologically non-relevant metabolite, however more comprehensive information should be provided. Data requirement: Applicant to provide a literature search on tricarballic acid (CGA275537). Open point: RMS to update Vol 3, B.6.10 including the assessment of the additional information provided.	

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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2(43)	Vol.3, B.6.8 Dietary metabolites 4- (cyclopropanecarbonyl)- 3,5-dihydroxy-benzoic acid.	EFSA: Based on the results of the 28-day oral rat study metabolite 4- (cyclopropanecarbonyl)-3,5-dihydroxy- benzoic acid referred as CGA329773 might be considered less toxic than trinexapac- ethyl.	Applicant: Agreed. RMS (August 2017): Consideration of the RMS in this context is given in RAR Vol 1, 2.6.9.1 <i>Toxicological evaluation of metabolite CGA329773</i> (63 p.): "Metabolite CGA 329773 has also been tested in a repeated dose 28-day oral toxicity study in rats and NOAEL was set ≥ 1021 mg/kg bw/day (highest dose tested). The available data on general toxicity – acute oral toxicity and short-term toxicity study in rats - clearly demonstrated that the compound is of comparable or low toxicity and thus comparable toxic than the parent substance." Actually, based on the results of the 28- day oral rat study (Bachmann, 1997) metabolite CGA 329773 might be considered less toxic than trinexapac-ethyl. In a 28-days rat oral study (Basler W., 1988) on parent trinexapac-ethyl the NOAEL for males was set at 100 mg/kg bw/d, based on increased water consumption, increased in absolute and relative liver and kidney weight as well as	See experts' consultation at 2(53).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			liver and kidney pathology: hepatocellular hypertrophy in centrilobular regions of the liver and PAS-positive droplets in the epithelia of the collecting ducts of the kidneys at 1000/2000 mg/kg bw /d (LOAEL). In the 28-day oral rat study (Bachmann, 1997) on metabolite CGA 329773 the NOAEL was set $\geq$ 1021 mg/kg bw/d for both sexes (highest dose tested) as no adverse effects were observed. It should be noted that the literature search provided to section 2 did not include this metabolite. Point noted. RMS will update the final conclusion on metabolite CGA329773 in more accurate manner in a revised <i>RAR Vol 1, 2.6.9.1 Toxicological evaluation of metabolite CGA329773</i>: „The available data on general toxicity – short-term toxicity study in rats - clearly demonstrated that the compound might be considered less toxic than parent trinexapac-ethyl.“ Addressed	
2(44)	Vol. 3 CA, B.6.8.1.4.3	NL: Pending the outcome of validation of the	Applicant: Agreed.	Addressed.

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	study 4, <i>in vivo</i> micronucleus	analytic method used, relatively high values of metabolite CGA329773 were found in the plasma (172-245 µg/ml). Considering that bone marrow is highly perfused we do consider it likely that the bone marrow was reached.	RMS (August 2017): Please see comment 2(45)	
2(45)	Vol.3, B.6.8 Dietary metabolites 4- (cyclopropanecarbonyl)- 3,5-dihydroxy-benzoic acid.	EFSA: an <i>in vivo</i> MN test on metabolite 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid referred as CGA329773 was conducted and it was negative. Plasma analysis was performed as recommended in the OECD guideline to demonstrate bone marrow exposure. Although there is no measurement in the bone marrow, plasma analysis indicated indirect evidence of bone marrow exposure since bone marrow is considered a well perfused tissue. Could the applicant clarify if the method of analysis was validated?	Applicant: Please see 2(46). The report for this validation is available for the stop-the-clock period. RMS (August 2017): The test substance CGA329773 in the study (<i>Clay P, 2004</i>) was shown to reach the plasma: the concentrations ranged from 172 µg/mL to 245 µg/mL approximately 2 hours after rats received an oral dose of 2000 mg/kg. However, the RMS considered that the data did not definitively demonstrate that plasma concentrations of CGA329773 were high enough to reach the bone marrow as concentration of CGA329773 present in bone marrow was not determined. On the other hand, the RMS LT could assume that the CGA329773 administered reached the bone marrow because: - Plasma levels of metabolite CGA329773 (172-245 µg/ml) found 2 hours after oral dose of 2000 mg/kg are	Data requirement: Applicant to provide validation of the analytical method used to quantitate plasma CGA329773 levels (to be assessed under B.5) or additional evidence of bone marrow exposure in the micronucleus test with CGA329773. See also comments 2(44) and 2(46). See experts' consultation at 2(53).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			comparable with mean plasma level (339.0 µg/mL) of trinexapac acid 4 hours post dose administration of Trinexapac-ethyl (1400 mg/kg/day) in the <i>in vivo</i> MN rat study (<i>Whitwell J., 2010</i>). It was considered that the trinexapac-ethyl administered reached the bone marrow in the latest study. - The findings from the ADME studies on the trinexapac-ethyl in the rats detected distribution of trinexapac-ethyl in bones, blood and plasma, after single oral low (1 mg/kg bw) and high (~200 mg/kg bw) dose administration (<i>Bissig R., 1995, Study Report No. 015AM01 & 015AM02</i>). In addition, bone showed the longest slow phase half-life (T_{1/2}), after low and high dose administration: 3.2 h and 12 h, respectively. - Bone marrow is considered a well perfused tissue. However, validation of the analytical method used to quantitate plasma CGA329773 levels should be provided and considered in the RAR Volume 3, chapter B.5.1.2. Data requirement: Applicant to provide	

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			validation of the analytical method used to quantitate plasma CGA329773 levels. Open point: The final conclusion on indirect evidence of bone marrow exposure of metabolite CGA329773 will be amended accordingly in a revised RAR.	
2(46)	Vol. 3, B.6.8.1.4.3 Genotoxicity	Applicant: At the time of the conduct of the rodent micronucleus study on CGA329773, proof of exposure was not a guideline requirement. None-the-less the test item was quantified in blood plasma, giving compelling evidence that the bone marrow would have been exposed. Subsequent to the RMS comments on the lack of validation of the analytical method for determining CGA329773 in plasma, the applicant extracted the study data from its archives and found a standalone toxicokinetics report for the micronucleus proof of exposure. This report (CGA329773_10002) is available. The method used is detailed within and provides more assurance that the study was conducted with suitable rigour. Paragraph 40 of the 2016 474 OECD	RMS (August 2017): The RMS LT could assume that the CGA329773 administered reached the bone marrow and additional considerations are given: please see comment 2(45). However, it should be noted that limited information of analytical method was provided on request (2017-02-03). However, the summary of the method in word format was not provided and therefore was not considered in the RAR Vol 3, B.5.1.2. The conclusion whether the method fits-for-purpose and supports the toxicological study was not reached in the RAR. Data requirement Please see comment 2(45)	See data requirement in 2(45).

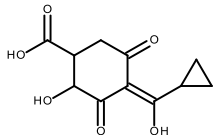
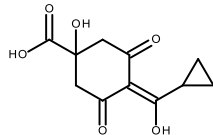
Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		guideline for the erythrocyte micronucleus assay points to determination of the test item in plasma as being evidence for bone marrow exposure. The RMS comments that plasma concentrations of up to 245 µg/mL two hours post exposure were not high enough to demonstrate the test item reached the bone marrow. The applicant notes that these data demonstrate that CGA329773 was readily available systemically, and as the bone marrow is a highly perfused tissue, exposure to the bone marrow can reasonably be assumed.		
2(47)	Vol. B.6.8.1.4.3 Genotoxicity	Applicant: In order to clarify any genotoxic potential of CGA179500 (trinexapac acid), three <i>in vitro</i> genotoxicity studies have been conducted (bacterial reverse mutation assay/Ames, HPRT and <i>in vitro</i> micronucleus). These studies are negative and are available for the stop-clock.	RMS (August 2017): The toxicity of the trinexapac acid (CGA179500) is considered covered by the parent trinexapac-ethyl (CGA163935). Addressed	Data requirement In vitro genotoxicity studies already performed for the metabolite CGA179500 (trinexapac acid) to be provided to the RMS for their inclusion in the revised RAR. See experts' consultation at 2(53).
2(48)	Vol. 3 CA, B.6.8.1.5 Hydroxylated CGA179500	NL: CGA179500 was considered to be covered by the parent based on the rat metabolism study. Could a similar	Applicant: The applicant agrees, see point 3(48) for the applicant's assessment.	See comment 2(49).

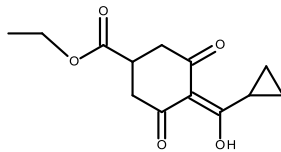
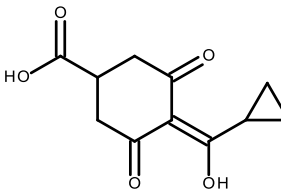
Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		conclusion be drawn for hydroxylated- CGA179500 based on structural similarity to CGA179500.	RMS (August 2017): Please see comment 2(49)	
2(49)	Vol.3, B.6.8 Dietary metabolites Hydroxylated CGA179500	EFSA: Based on the structure similarities of the metabolite (i.e. hydroxylated of trinexapac) and the parent the metabolite might be considered by trinexapac-ethyl.	Applicant: Agreed – Please see 3(48) for the applicant's assessment. RMS (August 2017): Based on limited data/information submitted (no alerts for genotoxicity using Derek Nexus v 4.1.0) to section 2 no conclusion on the genotoxic potential and the general toxicity was drawn regarding this metabolite. However, the following supplementary information was provided by the Applicant to residue section on 31.01.2017: <i>In terms of general toxicity, hydroxylated trinexapac acid could potentially exist as a 2-hydroxy or 1-hydroxy form. It is structurally similar to trinexapac acid (CGA179500), and trinexapac-ethyl.</i> <i>Hydroxy trinexapac acid differs from CGA179500 in the addition of a hydroxyl group on the cyclohexane ring. The addition of a hydroxyl group is unlikely to</i>	Based on the available information, it can be assumed that the toxicity of the hydroxylated CGA179500 is covered by the trinexapac acid (CGA179500) as well as by the parent trinexapac-ethyl (CGA163935).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			result in increased toxicity, and may make the metabolite more readily excreted (the hydroxyl group may be available for conjugation and aid rapid excretion). CGA179500 is the major rat metabolite of trinexapac-ethyl, and therefore the toxicity profile of trinexapac-ethyl effectively covers both molecules. Both hydroxy trinexapac acid potential metabolites would be expected to be of equivalent or possibly lower toxicity than trinexapac-ethyl/CGA179500. Trinexapac-ethyl is non-genotoxic, of low acute oral toxicity, and neither carcinogenic or reproductively toxic. Therefore the hydroxylated trinexapac acid metabolites would be expected to be of similarly low concern.  1-hydroxy trinexapac acid  2-hydroxy trinexapac acid	

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			 <i>Trinexapac-ethyl</i>  <i>CGA179500</i> <i>Despite exhaustive attempts to isolate and/or synthesise the hydroxylated CGA179500 – identified by default as SYN548584- it has not been possible. The molecule appears to be unstable outside the plant matrix and reverts to CGA179500.</i> <i>As the toxicity of this molecule is likely to be equivalent to trinexapac-ethyl and of low concern and cannot be synthesised, Syngenta propose that it is removed from the definition of the residue for risk</i>	

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			<i>assessment in plant matrices.</i> Based on the supplementary information submitted, the RMS LT could assume that the toxicity of the hydroxylated CGA179500 is covered by the trinexapac acid (CGA179500) as well as the parent trinexapac-ethyl (CGA163935). Open point: RMS to update Vol 1 2.6.9.1 including the supplementary information provided by the Applicant on 31.01.2017 and to correct a conclusion regarding toxicity of the hydroxylated CGA179500.	
2(50)	Vol.3, B.6.8 Dietary metabolites 3-ethoxycarbonylpentanedioic acid	EFSA: metabolite 3-ethoxycarbonylpentanedioic acid referred as CGA300405 is a potential dietary metabolite. The weight of evidence suggests CGA300405 unlikely to be genotoxic. Please address whether the metabolite could be considered of lower, equal or higher toxicity than the parent and/or specific reference values should be set in order to conduct a consumer risk assessment.	Applicant: The applicant agrees that CGA300405 is unlikely to be genotoxic. A consumer risk assessment is not necessary for CGA300405. CGA300405 –is converted to CGA275537 a metabolite readily found in grass so contribution to this in animal feed from trinexapac use is small compared to natural quantities. Because CGA300405 exposure is not considered significant toxicity studies (or assessment) to compare it to parent were considered unnecessary.	Data requirement Based on currently available information further data would be needed to conclude on general toxicity (repeated toxicity study) for metabolite 3-ethoxycarbonylpentanedioic acid . See experts' consultation at 2(53).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
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			RMS (August 2017): The following consideration of the RMS LT in this context is given in RAR Vol 1, 2.6.9.1. <i>Toxicological evaluation of metabolite CGA300405:</i> "Hence, CGA300405 based on the results of this test battery CGA300405 is considered to be non-mutagenic and non-clastogenic/aneugenic. A conclusion on the general toxicity cannot be drawn for this metabolite as no data was provided." Since there is no repeated toxicity study performed on CGA300405 a conclusion if the metabolite is of lower, equal or higher toxicity than the parent cannot be reached by the RMS. Due to the same reason the need of specific reference values in order to conduct a consumer risk assessment cannot also be set by the RMS. Data requirement	
2(51)	Vol.3, B.6.8 Dietary metabolites	EFSA: bridging from ethyl 3,5-dioxocyclohexanecarboxylate to metabolite 3,5-dioxocyclohexanecarboxylic acid referred as Cyclodione acid is supported	Applicant: The applicant decided to use the TTC as a conservative approach for consumer risk assessment. Compared to the trinexapac ADI this is a highly	Open point: RMS to include the supplementary consideration in the text of the revised

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Cyclodione acid and CGA158377	on the basis of chemical structure similarities. Both compounds should be considered unlikely to be genotoxic. Please address whether the metabolites could be considered of lower, equal or higher toxicity than the parent and/or specific reference values should be set in order to conduct a consumer risk assessment.	conservative approach, so comparison of this metabolite to parent was considered unnecessary. The 28 day gavage NOAEL for CGA158377 was 100 mg/kg/day, and therefore it can be considered to be of equal toxicity to the parent for repeat dose toxicity. RMS (August 2017): Extensive consideration of the RMS LT in this context is given in <i>RAR Vol 1, 2.6.9.1. Toxicological evaluation of metabolite CGA113745 and the manufacturing intermediate CGA158377</i>. The NOAEL for CGA158377 is set at 100 mg/kg bw based on overall reduced bodyweight gain, the decreased mean food consumption and increased absolute and relative kidney weight for males (without accompanying histopathological effects) at 1000 mg/kg bw (highest dose tested) in 28-day oral study (Gerspach R, 1992). In a 28-days rat oral study (Basler W., 1988) on parent trinexapac-ethyl the NOAEL for males was set at 100 mg/kg bw/d, based on increased water consumption, increased in absolute and	RAR and to supplement a conclusion regarding equal short-term toxicity of CGA113745 and CGA158377 than the parent substance.

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			relative liver and kidney weight as well as liver and kidney pathology: hepatocellular hypertrophy in centrilobular regions of the liver and PAS-positive droplets in the epithelia of the collecting ducts of the kidneys at 1000/2000 mg/kg bw /d (LOAEL). The available data on general toxicity – acute oral, dermal and inhalation toxicity as well as irritation/sensitisation potential - clearly demonstrated that the compound was of comparable acute toxicity than the parent substance however this metabolite had serious eye damage and skin irritation/sensitisation potency. The short-term toxicity study in rats demonstrated that the metabolite CGA113745 and CGA158377 are of comparable / equal short-term toxicity than the parent substance. Therefore, the reference values of the parent can be applies to CGA113745 and CGA158377. Open point: RMS to include the supplementary consideration in the text of the revised RAR and to supplement a conclusion regarding equal short-term	

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			toxicity of CGA113745 and CGA158377 than the parent substance.	
2(52)	Vol.3, B.6.8 Dietary metabolites 2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid	EFSA: CGA313458 referred as 2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid is unlikely to be genotoxic. Please address whether the metabolite could be considered of lower, equal or higher toxicity than the parent and/or specific reference values should be set in order to conduct a consumer risk assessment.	Applicant: We agree what CGA313458 is unlikely to be genotoxic. CGA313458 was found in the high temperature hydrolysis study –but actual levels in processed commodities from Wheat and Barley were analysed and found to be negligible so human exposure can likewise be considered negligible. Therefore comparison of the toxicity profile of CGA313458 to the parent was not considered necessary, and repeat toxicity data were not generated. RMS (August 2017): A short consideration of the RMS LT in this context is given in RAR Vol 1, 2.6.9.1. Toxicological evaluation of metabolite CGA313458. 2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid (CGA313458) is considered to be non-genotoxic. Since there is no repeated toxicity study	Data requirement Based on currently available information further data would be needed to conclude on general toxicity (repeated toxicity study) for metabolite CGA313458 (2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid). See experts' consultation at 2(53).

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			performed on CGA313458 a conclusion if the metabolite is of lower, equal or higher toxicity than the parent cannot be reached by the RMS. Due to the same reason the need of specific reference values in order to conduct a consumer risk assessment cannot also be set by the RMS. Data requirement	
2(53)	Vol.3, B.6.8 Dietary metabolites Cyclopropane carboxylic acid	EFSA: Cyclopropane carboxylic acid is unlikely to be genotoxic on the basis of available studies. The literature search included this compound but available literature did not meet the relevance criteria according to the RMS. According to the additional search cyclopropane carboxylic acid disrupts the pyruvate metabolism (as described table 6.10-2). Please the RMS/Applicant clarifies the relevance of these mechanistic findings and clarify if further toxicological data are available on cyclopropane carboxylic acid.	Applicant: The applicant agrees that cyclopropane carboxylic acid is unlikely to be genotoxic. The applicant decided to use the TTC as a conservative approach for consumer risk assessment. Compared to the trinexapac ADI this is a highly conservative approach, so comparison of this metabolite to parent was considered unnecessary. The pyruvate metabolism disruption properties of cyclopropane carboxylic acid could potentially make it more toxic than parent, but the TTC approach used is highly conservative and is considered sufficiently protective regardless. Repeat dose toxicity studies are not available to compare to the parent.	Data requirement A 90-day rat study on cyclopropane carboxylic acid (CPCA) was submitted to JMPR for the assessment of aminocyclopyrachlor (JMPR, 2014). The study should be submitted to the RMS for an independent assessment of the study. It is noted that the EFSA guidance on residue definition has not been taken note at the Standing Committee and therefore cannot be applied. Consequently the use of the TTC as proposed in this guidance is not yet agreed for the peer review. See also data requirements 2(42), 2(45), 2(47), 2(50) and 2(52)

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		If the metabolite is a significant plant/livestock metabolite its toxicological profile should be further define in order to conduct a consumer risk assessment.	RMS (August 2017): Indeed, the literature search included Cyclopropane carboxylic acid and two following articles were retrieved in the additional search: <i>Buxton D et al. (1983)</i> and <i>Steinhelper et al. (1985)</i> (see Table 6.10-2). These authors investigated the hypoglycaemic mechanism of cyclopropane carboxylic acid and gluconeogenesis using perfused rat livers, respectively. However, they did not meet the relevance criteria and have not been discussed further due to the same following reason: as these studies used a perfused organ (rat liver) this was not considered a realistic exposure scenario, and it was not possible to equate these concentrations to an applied dose for risk assessment purposes. Cyclopropane carboxylic acid (CGA224439) was only found in high temperature hydrolysis studies, representing up to 17.7 % TRR. The consideration of the RMS LT in this context is given in RAR Vol 1, 2.6.9.1.	Experts' consultation The toxicological profile of potential dietary metabolites tricarballic acid, GA300405, CGA313458 and CPCA to be discussed by the experts. Pending on the updated literature search and data requirements on metabolites further metabolites might be included for discussion.

Section 2 – Effects on human and animal health

Toxicological data on metabolites				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			<i>Toxicological evaluation of metabolite CGA224439.</i> Cyclopropane carboxylic acid (CGA224439) is considered to be non-genotoxic. A conclusion on the general toxicity cannot be drawn for this metabolite as no data was provided. Since there is no repeated toxicity study performed on CGA300405 a conclusion if the metabolite is of lower, equal or higher toxicity than the parent cannot be reached by the RMS. Data requirement	

Medical data and information				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(54)		LV: No comments	RMS (August 2017): Noted Addressed	Addressed

Section 2 – Effects on human and animal health

Medical data and information				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(55)	Vol.3, B.6.9	EFSA: None.	RMS (August 2017): Noted Addressed	Addressed

Toxicological end points: ADI, ARfD, AOEL				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(56)	Vol. 1, CA, 2.6.11-2.6.13, reference values	NL: the references values proposed by the RMS are supported.	RMS (August 2017): Noted Addressed	See expert consultation in 2(57).
2(57)	Vol. 1, 2.6.11, p. 67, Vol. 3, B.6.3.2.3, p. 46 ff	DE: Because of the effects seen in the 1 year dog study it is proposed to regard 31.6 mg/kg bw/d as a LOAEL and the dose of 1.4 mg/kg bw/d as NOAEL ADI = NOAEL / SF = 1.4/100 = 0.014 mg/kg bw/d	Applicant: The applicant disagrees with the DE assessment of the 1 year dog study and maintains the existing 1 year dog NOAEL and ADI are retained. RMS (August 2017): The RMS disagrees with the DE proposal and proposes to remain NOEL at 1000 ppm (31.6 mg/kg bw/day) based on adverse toxic effects the next higher dose group: clinical signs (mucoid/bloody faeces) in males and females, decreased mean percent body weight gain throughout the dosing period and decreased mean body weight gain at	Expert consultation Reference values for trinexapac-ethyl (ADI, ARfD, AOEL and AAOEL) to be confirmed/discussed by the experts. See also comments 2(56), 2(58), 2(59) and 2(60).

Section 2 – Effects on human and animal health

Toxicological end points: ADI, ARfD, AOEL				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			termination in males, haematology in females, possible effect on the oestrus cycle and therefore, reduction in absolute uterus weight as well as microscopic evidence of brain histopathology (cerebral vacuolation) in both sexes. Please see comment 2(14) Expert consultation	
2(58)	Vol. 1 P 2.6.11	LV: Taking into account effects seen in the 1 yr dog study it is proposed to derive ADI from NOAEL of 40 ppm (1.4 mg/kg bw/d). Overall ADI of 0.014 mg/kg is proposed AOEL supported. Information on AAOEL is missing.	Applicant: The applicant disagrees with the LV assessment of the 1 year dog study and maintains the existing 1 year dog NOAEL and ADI are retained. RMS (August 2017): Timely response of the co-RMS LV would have been more appreciated though. Please see comments 2(14) and 2(60)	See expert consultation in 2(57).
2(59)	Vol. 1, 2.6.13, p. 68	DE: The AOEL proposed by the RMS is supported	Applicant: Agreed. RMS (August 2017): Noted	See expert consultation in 2(57).

Section 2 – Effects on human and animal health

Toxicological end points: ADI, ARfD, AOEL				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed	
2(60)	Vol.1, 2.6 AAOEL	EFSA: Please consider whether there is a need for setting an AAOEL.	Applicant: The applicant considers the setting of an AAOEL to be unnecessary as trinexapac is of low acute toxicity. RMS (August 2017): After the reassessment of the original DAR, and based on all new available information, the RMS LT considers that for the renewal of trinexapac-ethyl there is no need for setting an AAOEL. This conclusion is based on the same arguments as for the ARfD. Consideration on why AAOEL is not needed will be included in revised RAR. Open Point: RMS to update Vol 1 2.6.12 including the consideration on why AAOEL is not needed.	See expert consultation in 2(57).

Product exposure and risk assessment, including dermal absorption				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(61)		LV: No comments	RMS (August 2017): Noted	Addressed.

Section 2 – Effects on human and animal health

Product exposure and risk assessment, including dermal absorption				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed	
2(62)	Vol.3, B.6 CP; B.6.2 Dermal absorption	EFSA: None	RMS (August 2017): Noted Addressed	Addressed.
2(63)	Vol.3, B.6 CP; B.6.4. Exposure data	EFSA: none.	RMS (August 2017): Noted Addressed	Addressed.
2(64)	Vol. 3, B.6.4.1 through to B.6.6, Operator, bystander/resident and worker risk assessments	Applicant: The Applicant does not believe it is appropriate that the exposure of operators, workers, residents and bystanders is estimated using EFSA guidance applied retrospectively, for submissions made before the 1st January 2016. All risk assessments have been conducted to comply with the Council Directives that were in force at the time of submission (79/117/EEC and 91/414/EEC), and meet the criteria applied for safe exposure to aforementioned populations.	RMS (August 2017): Indeed, EFSA Guidance on exposure was not yet into force at the time of submission of dossier on 28th October 2015. At the time the dossier was evaluated by RMS LT, the new EFSA models were in force (1 st January 2016). The exposure assessments were extended with the EFSA model by the RMS itself as it was considered to be worthwhile and advisable. Furthermore, using the new EFSA guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, the risk to operators, workers, residents and bystanders was acceptable. Addressed	Addressed. At least for information purposes, exposure estimates with the EFSA guidance will be kept in the RAR, together with exposure estimates according to previous models.

Section 2 – Effects on human and animal health

Product exposure and risk assessment, including dermal absorption				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(65)	Vol. 3 CP, B.6.4.2.1 bystander exposure	NL: Although it is recognized that there is no EU agreement on which drift values to use for bystander and resident exposure we would prefer a first tier assessment with the German model applying the drift values for 1 m distance (2.77%) instead of the currently used 10 m (0.29%).	Applicant: The use of 10 m distance is consistent with the conservative 90th percentile value stated in the German guidance paper (2008) for single applications to field crops (the scenario that best represents the critical use patterns for the representative formulation). Specific national requirements will be addressed during Product Renewal (PR). RMS (August 2017): The RMS agrees with the Applicant. Addressed	Open point RMS to present both options (bystander and resident exposure estimates for both distances) in a revised RAR.
2(66)	Vol. 3, B.6.4.3, Worker exposure	DE: Worker exposure is acceptable even without workwear using a TC value of 12500 cm ² /h according to EFSA guidance. This information should be added to the results.	Applicant: The applicant does not believe it is appropriate to apply EFSA guidance retrospectively, for submissions made before the 1st January 2016. In this case, reporting the TC value of 12500 cm²/h for potential exposure is not relevant to the German and the EUROPOEM II re-entry model. RMS (August 2017): Regarding the worker assessment according to EFSA	Addressed. At least for information purposes, exposure estimates with the EFSA guidance will be kept in the RAR, together with exposure estimates according to previous models. RMS to consider adding the information on TC value and worker exposure in a revised RAR.

Section 2 – Effects on human and animal health

Product exposure and risk assessment, including dermal absorption				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			<i>Guidance Exposure Calculator (version 30 Mar 2015)</i> the TC value 1400 cm²/h x person was used, assuming the worker wearing adequate work clothing (but no PPE) that covers the arms, body and legs, when re-entering crops treated with PPP. The total potential exposure was calculated by using TC value of 12500 cm²/h and amounted 55.2% of the AOEL (please refer to Vol 3CP, B.6.7 Annex I Tables B.6.7-9], however, it was not mentioned in a summary of the estimated worker exposure Vol 3CP, B.6.4.3. In case it is considered necessary the statement could be included in the revised RAR. Open point	

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(67)		FR: Section not reviewed, no comment	RMS (August 2017): Noted	Addressed.

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed	
2(68)		LV: No comments	RMS (August 2017): Noted Addressed	Addressed.
2(69)	Vol. 3, B.6. General comment Page 6	EFSA: could the RMS clarify if new toxicity studies on trinexapac-ethyl or any of its metabolites have submitted by other applicants than Syngenta? New toxicity studies (if available) should be summarised in the B.6.	RMS (August 2017): No other new toxicity studies on trinexapac-ethyl or any of its metabolites except the genotoxicity studies mentioned below were submitted by other applicants than Syngenta. Five genotoxicity studies on the active substance were submitted by Cheminova A/S. Please see comment 2(22) Open point Two genotoxicity studies on the active substance were submitted by Helm AG (Ames tests, Spruth, B. (2015) & Schreib, G. (2014)). However, no detailed summaries for these studies were provided. The Applicant Helm AG should provide robust summaries reports in word format for two genotoxicity studies.	See open point in 2(22). Data requirement Robust study summaries to be provided to the RMS for the genotoxicity studies reported by Helm AG.

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			They will be included in the revised RAR Vol 3, B.6.4. from the confidential Vol 4 Helm AG and will not be considered as confidential any more. Additionally, the results from these two genotoxicity studies will be summarised in the revised RAR Vol 1, point 2.6.4 and the List of references (Vol 2, A.6) as well as List of Endpoints (Section 2) will be updated. Data requirement: Applicant Helm AG to provide robust/detailed summaries for two genotoxicity studies (Ames tests, Spruth, B. (2015) & Schreib, G. (2014)). Open point: RMS to update Vol 3 B.6.4. Vol 1 2.6.4 and Vol 2 A.6 as well as List of Endpoints including two genotoxicity studies of Helm AG.	
2(70)	Vol. 3, B.6. General comment Scientific open literature	EFSA: articles from 1983 and 1985 were retrieved regarding the additional search. Could the RMS clarify the date span of the different literature search on the active substances and its metabolites? Could the RMS clarify the list of metabolites	RMS (August 2017): The additional search was completed in 05.05.2015 and the search was designed to include all literature 10 years prior to this date. It should be noted that the additional search identified the study of <i>Bianchi N et al. (2015)</i> which referred to two papers and therefore the two following	See data requirement in 2(42).

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		included in the literature search? Was the list of metabolite considered complete?	articles from 1983 and 1985 were retrieved: <i>Buxton D et al. (1983)</i> and <i>Steinhelper et al. (1985)</i>. A preliminary search was conducted to identify references that included the active substance trinexapac and its four major so-called dietary metabolites according to the Applicant: 1. 3-ethoxycarbonylpentanedioic acid (referred as CGA300405) 2. 2,4-cyclopropyl-2,4-dioxo-butyl succinic acid (similar to referred as CGA313458) 3. Cyclopropane carboxylic acid (referred as CGA224439) 4. 3,5-dioxocyclohexanecarboxylic acid (referred as CGA113745) A separate search on three additional metabolites was carried separately from Initial Search & Top-Up Search; however they were not specified by the Applicant. Based on the submitted parameters (conjunction with any of the key words) the following metabolites and/or their variants were searched referred as CGA313458, variants of CGA300405, CGA224439, CGA113745 and	

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			dihydroresorcylic acid. The conclusion if the list of so-called dietary metabolites is complete could not be drawn by the section 2 during the preparation of the RAR as it principally depends on final conclusion of residue section. The RMS now considers that the list of metabolite is incomplete as the tricarballylic acid (CGA275537) should be additionally included to the literature search list. Please see comment 2(42) Data requirement: Applicant to provide a literature search on tricarballylic acid (CGA275537).	
2(71)	Vol. 4 Annex C Representativeness of the toxicological studies to the technical specification. Syngenta	EFSA comments	RMS (August 2017): Please refer to separate <i>Reporting table Confidential SYNGENTA</i>	Please refer to separate <i>Reporting table Confidential SYNGENTA</i>
2(72)	Vol. 4 Annex C	EFSA: The equivalence between technical	RMS (August 2017): Noted	Open point

Section 2 – Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Representativeness of the toxicological studies to the technical specification. Task force	materials should be reconsidered once the technical specification is agreed and supported by a complete toxicity datapackage.	Addressed	RMS to reconsider the equivalence between technical materials once the technical specification(s) is(are) agreed and supported by a complete toxicity datapackage.
2(73)	Vol. 4: C.1.4.2. Helm	HELM AG comment	RMS (August 2017): Please refer to separate <i>Reporting table Confidential HELM</i>	Please refer to separate <i>Reporting table Confidential HELM</i>
2(74)	Vol. 4: C.1.4 – C.1.5. Adama	Adama comments	RMS (August 2017): Please refer to separate <i>Reporting table Confidential Adama</i>	Please refer to separate <i>Reporting table Confidential Adama</i>
2(75)	Vol. 4, C.1.4. Cheminova source 1 (Huifeng)	Cheminova comments	RMS (August 2017): Please refer to separate <i>Reporting table Confidential source 1 (Huifeng)</i>	Please refer to separate <i>Reporting table Confidential source 1 (Huifeng)</i>
2(76)	Vol. 4, C.1.4. – C.1.5. Cheminova source 2 (Youth)	Cheminova comments	RMS (August 2017): Please refer to separate <i>Reporting table Confidential source 2 (Youth)</i>	Please refer to separate <i>Reporting table Confidential source 2 (Youth)</i>

section 3 – Residue data

3. Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(1)	Vol. 3 B7, B.7.1.1	FR: in the study K-CA 6.1/01, calculations of the % of recoveries in stored samples should be further detailed. Moreover, a detail of minor deficiencies of this study might be welcome. An example might be added to the "footnote *" of the Table B.7.1.1-1.	RMS: Noted, additional explanations will be added. Please also see 3(4) Open point: RMS to add additional details to study K-CA 6.1/01.	See 3(3)
3(2)	Vol. 3, B.7.1.1, Stability of residues in plants and plant products, Study 1	NO: Please include a column in Table B.7.1.1-1 for "Residue level in freezer storage stability sample (% of nominal spiking level, <u>uncorrected</u>)".	RMS: Table B.7.1.1-1 will be amended by column "Residue level in freezer storage stability sample (% of nominal spiking level, uncorrected)" Open point: RMS to amend table B.7.1.1-1 in a revised DRAR.	See 3(3)

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(3)	Vol. 3, B.7.1.1, Stability of residues in plants and plant products, Study 1	NO: The residue level in wheat straw samples at 24 months is 62% of nominal spiking level (uncorrected), whereas the procedural recovery for freshly spiked control samples is 92%. Therefore, residues of trinexapac acid (CGA 179500) in wheat straw are considered stable up to 12 months.	RMS: Agreed. The conclusions on storage stability in wheat straw were based on residue levels (% of nominal spiking level) for corrected results (75 % in this case). Indeed taking into account the uncorrected results, the recovery is 61.8 % (below 70%) and residues of trinexapac acid (CGA 179500) in wheat straw should be considered stable up to 12 months. Open point: RMS to amend conclusions of storage stability in a revised DRAR.	Open point: Storage recoveries in Table B.7.1.1-1 for Study 1 (K-CA 6.1/01) should report the uncorrected values. In these conditions, residues of trinexapac acid (CGA 179500) in wheat straw can be considered as stable for up to 12 months. RMS to amend the RAR and the LoEP accordingly.
3(4)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products (Sack St, 1998)	EFSA: The validation data for the method of analysis applied should be explored in more detail. Reference to the DAR is not sufficient. The fortification level of 25X LOQ used in the study is remarkably higher than the suggested level of OECD 506 (10X LOQ) and the levels tested for the validation of the analytical method (1N and 2.5N LOQ). Applicant/RMS are invited to discuss the impact on the recovery results. Please perform a complete evaluation of the study and verify equivalent conditions to current standards were met.	Applicant: This study was carried out almost 20 years ago and to guidelines which were applicable at the time and was reviewed and accepted. We appreciate that in the light of current guidance, there are insufficient recoveries in the validation to comply with current guidance. The review conclusions in terms of storage stability in plants will not change dependent on chosen fortification levels and numbers of recoveries. The recommendation is to perform a new storage stability study with the current method which has been validated to	Open point: RMS to provide detailed summary of the validation of analytical method and any deviation from guidance OECD 506 to enable conclusion on the compliance with current standards of the storage stability Study 1(K-CA 6.1/01) in a revised RAR. Data requirement: See 3(13)

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			current guidelines ready for PR. The study is in progress and should be available for PR during first quarter 2019. RMS: The study is an "old" study from the original DAR (2003). Therefore, the summary has been copied as such from the DAR into the RAR with additional remarks in the "RMS comments and conclusion" section but not marked anyhow. RMS is willing to add further clarification on the validity of the analytical method. RMS agrees with the applicant that even though the fortification level is much higher than recommended in the OECD 506 and validation of the method is not according to recent guidelines, the study could be used for the current submission with the requirement for the applicant to provide a new study (to recent guidelines) and fully covering the length of storage in field trials. See also 3(13). Open point: RMS to add further details of the validation of analytical method, deviations from the guidance and validity of the study to the study summary.	

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Data requirement: Applicant to provide storage stability study to current guidelines and covering the length of storage in supervised field trials.	
3(5)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products (Sack St, 1998)	EFSA: In Table B.7.1.1-1 results (in %) for trinexapac acid presented were adjusted by procedural recovery. Recoveries should be at least reported as uncorrected values. It is expected that in straw the (uncorrected) mean drops < 70% at 24 months. Please reconsider stability period of trinexapac acid residues in straw accordingly.	RMS: Please refer to 3(3)	See 3(3)
3(6)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products	EFSA: Storage stability data on wheat grains and straw and on OSR seeds were not provided for the major metabolite hydroxylated trinexapac acid (SYN548584) and are in principle required if residues of this metabolite are to be determined in crops.	Applicant: See 3(48) RMS: Agreed. Storage stability study for the metabolite hydroxylated trinexapac acid (SYN548584) would be required if it is included in the plant residue definition for risk assessment. This suggestion for inclusion in the RD is provisional pending the outcome of the MamTox section, see also 2(48) and 2(49) in which it is stated: Based on the supplementary information submitted the RMS LT could assume that the toxicity of the hydroxylated CGA179500 is covered by the trinexapac acid (CGA179500) as well as the parent trinexapac-ethyl	See Experts' Consolation 3(41)

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			(CGA163935). Open point: RMS to reconsider the residue definition (possible exclusion of metabolite SYN548584) for risk assessment in light of MamTox section conclusions. Expert consultation on whether or not to include metabolite SYN548584 in the residue definition for risk assessment might be needed.	
3(7)	Vol. 3, B.7.1.1. Stability of residues in plant and plant products	EFSA: Storage stability data on the major metabolites CGA313458, CGA113745 and CGA 224439 (CPCA) in the hydrolysis studies observed are missing (reported to be ongoing). These data are essential to demonstrate the integrity of the samples analysed in processing studies.	Applicant: See 3(15) RMS: Please refer to 3(15)	See 3(15)
3(8)	Vol. 3, B.7.1.2, Stability of residues in animal products, Study 1	NO: The values for milk and blood samples in the column "Residue level in freezer storage stability sample (mg/kg)*" in Table B.7.1.2-1 seem incorrect.	Applicant: Agreed; looks like the % values again. Milk should be 0.0445, 0.043, 0.045, 0.044 & 0.065 and blood 0.102, 0.099, 0.104, 0.104 & 0.101 – calculated from the information in the table, not the raw data. RMS: Indeed the residue values in table B.7.1.2-1 for milk and blood samples were not correct. Open point: RMS to amend table B.7.1.2-1	Addressed. RMS committed to amend the RAR accordingly. It is noted that the recalculated value of 0.065 mg/kg for milk proposed by the applicant is giving 130% instead of the 93% reported in the Table. This value shall be verified for correctness.

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			in a revised RAR.	
3(9)	Vol. 3, B.7.1.2, Stability of residues in animal products, Study 1	NO: In the conclusion on Page 11, the RMS writes: <i>The average recovery is below the 70 % (67 %), the range of measurements is around 70%.</i> It is difficult to find this information in the table and we are not sure what is meant by this sentence.	RMS: "the range of measurements is around 70%" means that some values are below and some over 70%. RMS wanted to highlight, that even if the mean is below 70%, not all individual values are also <70%. Individual values will be inserted in table B.7.1.2-1. Open point: RMS to amend table B.7.1.2-1 in a revised RAR	Addressed. RMS committed to amend the RAR accordingly.
3(10)	Vol. 3, B.7.1.2 Stability of residues in animal products (Sack St, 2000)	EFSA: it was concluded that the stability study was acceptable with no deviation from current guidance (OECD 506). Since deviations were noted (e.g. 5X LOQ spiking level for fat; initial value at 0 time point not determined) and reporting not sufficiently detailed (number of stored and freshly spiked samples per matrix and sampling time, validation data of the method of analysis), please perform a detailed evaluation of the study and verify equivalent conditions to current standards were met:-	Applicant: The samples were fortified and stored for the appropriate amount of time. The results from the stored sample were compared to the nominal fortification level. The study is considered to be acceptable. Applicant: The validation has the required number of recoveries at the appropriate levels. Linearity has been demonstrated and example chromatograms displayed. Final quantification is by LC/LC-UV which was considered highly specific at the time. The study is considered to be acceptable. RMS: Agrees that some deviations from OECD 506 were missed by the RMS. RMS	Open point: RMS to provide a detailed evaluation and any deviation from guidance OECD 506 of the storage stability study in matrices of animal (bovine) origin to enable concluding that stability of trinexapac acid covering the length of storage of the samples from the feeding study is adequately addressed.

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			agrees with the applicant that study is considered acceptable and is of the opinion, that additional details would not change the conclusion on the reliability of the study. Nevertheless RMS is willing to provide additional details and conclusions if the current standards were met. Open point: RMS to add sufficiently detailed evaluation of the study in a revised RAR.	

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(11)	Vol. 3, B.7.1.2 Stability of residues in animal products (Sack St, 2000)	EFSA. Table B.7.1.2 shows that at 3 months average uncorrected residue was 67% for cattle muscle. Argumentation that recoveries at 3 months from stored and freshly spiked samples were both comparable and low is questionable since mean procedural recovery in stored commodity was corrected for a theoretical initial T=0 level before being compared. Evidence of stability of trinexapac acid in muscle matrix covering the maximum length of storage of the samples from the feeding study is missing.	Applicant: Agreed; the overall recovery for stored muscle was 67%. However the guidance requires comparison of the stored result to the procedural recovery which was 82%. If the stored samples are corrected for the mean procedural recovery then the stored result is 82%. Therefore the conclusion is that stability has been demonstrated for muscle. RMS: Agrees with the applicant. Average uncorrected residue was 67% (derived from three individual results >70% and two <70%) also procedural recovery is quite low for muscle (82%), suggesting not a decline on storage, but due to analytical method. RMS considers storage stability for cattle muscle has been demonstrated. Addressed.	Addressed.
3(12)	Vol. 3, B.7.1 Storage stability of residues prior to analysis, Table B.7.1.2-2	NO: Please consider to change the value for the maximum storage period for wheat straw to 18 months.	RMS: Reconsidering the uncorrected values of residue level in freezer storage stability samples, the maximum storage period for wheat straw will be changed to 12 months in table B.7.1.2-2. Open point: RMS to amend table B.7.1.2-2 in a revised RAR.	See 3(3)

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(13)	Vol 1, Level 2.7.1 Summary of storage stability of residues	EFSA. The argument that degradation of trinexapac acid in wheat is slow and the submitted 24-months stability study is sufficient to cover also integrity of residues from trials where samples were stored up to 25.5 months is not a valid argument. The stability of trinexapac acid on cereal grain and straw covering the maximum length of storage of the samples from the residue trials shall be demonstrated.	Applicant: See 3(14) RMS: Disagree. Storage stability study shows the degradation in grain from ~90% to ~80% in 24 months period. RMS does not think that additional 1.5 month storage would lead to the degradation more than 10% and leading to lower than 70 % recovery. As this is only a theoretical assumption, new storage stability study fully covering storage period would be desirable. EFSA please clarify if additional storage stability study covering the length of storage for 25.5 months should be a data requirement , or can be submitted during product renewal. Please also see 3(14). Addressed.	Data requirement: Applicant to provide stability for trinexapac acid in cereal grains and straw covering the maximum length of storage of the samples from the residue trials. Open point: RMS to assess the data and reconsider the validity of residue data accordingly. Trials not adequately supported by storage stability shall be excluded from the assessment. See also 3(4)

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(14)	Vol 1, Level 2.7.1 Summary of storage stability of residues	EFSA: trinexapac acid was reported to be stable in high oil and high starch content commodities and in straw for 24 months. Apart of the stability period actually demonstrated, it is noted that only a single commodity (wheat grain or rape seed) instead of the two required by OECD 506 for the high starch and high oil content commodity groups was presented. Data are not sufficient to conclude on stability for the two categories.	Applicant: The storage stability data is old and no longer to current guidelines however, in principle it covers the crops in the AIR dossier – cereals and OSR. For product renewal further storage stability work will be carried out to cover all the crop groups to current guidelines. Work is in progress. See also applicants comment under 3(4). RMS: Agrees that studies from two diverse commodities are required to conclude for each high oil and high starch content categories. Does EFSA recommend to conclude on storage stability for cereal grain and rapeseeds alone and put a data requirement for applicant to provide study with additional commodities from these categories? In 3(4) applicant mentions that new study is in progress but commodities are not specified. Data requirement: Applicant to provide additional storage stability studies to cover all commodities from high oil and high starch content categories.	Addressed: RMS to amend the terminology used in the RAR reflecting the data provided. Currently, storage stability data are covering cereals and OSR seeds alone. It is not possible to conclude on stability in the high starch and high oil content commodity categories.

section 3 – Residue data

Storage stability of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(15)	Volume 1 Leve I3 3.1.4.7 Residue data	RMS: According to information from the applicant, storage stability studies for processing metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) are currently on-going. Applicant: Stability studies for processing metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) in processed commodities are completed and available. The following processing studies contain storage stability data on CGA313458 and CGA113745 (CGA313458_10011 and CGA313458_10010). Storage stability data for CPCA is in study CA876_10009. Additionally a new study investigating the storage stability of trinexapac acid in high protein crops (pulses) and high water crops is ongoing to provide data to support crops during product renewal. A one month interim report could be made available for the stop-clock.	Applicant: This study is in progress and will be extended to include all crop groups to satisfy 3(13) and 3(14) – there have been delays and therefore no one month data will be available during the stop-the clock period. RMS: Noted. As pulses and high water content commodities are not representative uses during renewal, additional studies on crops from these categories are not considered necessary. The stability studies for processing metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) in processed commodities will be evaluated and added in a revised RAR. Data requirement: Applicant to provide stability studies for processing metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) in processed commodities.	Data requirement: Applicant to provide storage stability studies for the metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) covering the length of storage of the samples from processing studies. Open point: RMS to assess the storage stability data and to conclude on the validity of the residue levels of CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) determined in the processing studies as per storage stability.
3(16)		Co-RMS (LV): No comments	RMS: Noted.	

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(17)	Vol. 3, B.7.2.1 Plants	NO: Footnotes for Table 7.2.1.-1 seem to be missing.	Applicant: Footnotes were included in the submission document (MCA Section 6) but have been restated below for reference: (a): Outdoor/field application (F) or glasshouse/protected/indoor application (G) (b): All studies that have been previously EU reviewed are considered as supplementary (c): Only seeds were analysed RMS: Agreed, footnotes are missing and will be added. Open point: RMS to insert footnotes to table B.7.2.1 in a revised RAR.	Addressed. RMS committed to amend Table 7.2.1.-1 by adding footnotes at the bottom of the table and inserting the note (b) to the table for the metabolism studies considering to provide only supplementary information (see point 3(18)).
3(18)	Vol. 3, B.7.2.1 Plants (studies 1 to 5)	EFSA: The original metabolism studies in cereals/grass (wheat, rye, rice, grass) and pulses/oilseeds (OSR) were not evaluated by the RMS. The overview tables and remarks from the DAR (Netherlands, 2003) were reported in the RAR and not commented. Please perform an independent, objective and transparent assessment of these studies and a detailed analysis for compliance with current	RMS: The original metabolism studies were checked for compliance to OECD 501 by RMS LT. Additional observations on deviations from the OECD 501 were inserted in the "Guidelines and limitations" sections, but not marked anyhow. It seemed not necessary to analyse these studies in detail, as new metabolism studies (fully compliant with OECD	Open point: RMS to provide a detailed evaluation and any deviation from guidance OECD 501 of the submitted metabolism studies in cereals/grass (wheat, rye, rice, grass) and pulses/oilseeds (OSR) and to conclude on acceptability and their appropriateness to derive the residue definition for at least the representative uses.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		scientific and technical knowledge. Otherwise the acceptability of these studies for the renewal of a.s. could be decided on.	guidelines) were presented for renewal. As all the original "old" metabolism studies had some deviations from the OECD guidelines, applicant's position was to consider these studies as supplementary only. RMS position would be to consider them at least partially reliable (as they provide at least some information on metabolism) but only together with new metabolism studies. Open point: RMS to insert additional comments on the studies acceptability and compliance to current guidelines.	The RAR and the LoEP shall be revised accordingly. See Experts' consultation 1
3(19)	Vol. 3, B.7.2.1, study by Krauss J.H. (1993), page 24	Co-RMS (LV): In the test system (25 page) there are additional stem injection and <i>in vitro</i> incubation experiments described for elucidation of the metabolic pathways. Results of these additional experiments isn't mentioned at all. Are they available?	Applicant: Stem injection experiments were performed in order to generate grain specific metabolite fractions. As a result of this work, metabolite fraction II3 was isolated in sufficient amounts to identify it as CGA329773. This was then used to confirm its presence in grain and straw derived from field grown spring wheat. RMS: Please refer to applicant explanation above. Addressed.	Addressed.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(20)	Vol. 3, B.7.2, spring wheat metabolism Table B.7.2.1-4, p. 29	DE: It is not clear to us what is the amount of conjugates included in the residue fraction of CGA179500 (and others).	Applicant: This study is considered supplementary. A new wheat metabolism study (representative for cereals) was conducted (Piskorski, 2015) and levels of all metabolites (free and conjugated) are clearly defined. Based on the Krauss study (1993), the levels of metabolites present in their free and conjugated forms are detailed in the below attachment.  Wheat Metabolite Summary.docx RMS: the amount of free and conjugated forms of identified metabolites are clearly stated in the attachment above. Although it should be noted, that the correct values for CGA179500 in husks are 10.0% free and 6.7% released from debris following Soxhlet and autoclave extraction leading to total of 16.7%TRR. Open point: RMS to include additional information on exact amounts on free and conjugated forms of identified metabolites in table B.7.2.1-4 in a revised RAR.	See 3(18)
3(21)	Vol. 3, B.7.2, rice	DE: It is not clear to us what is the amount	Applicant: This study is considered	See 3(18)

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	metabolism Table B.7.2.1-5, p. 34	of conjugates included in the residue fraction of CGA179500 (and others).	supplementary. A new wheat metabolism study (representative for cereals) was conducted (Piskorski, 2015) and levels of all metabolites (free and conjugated) are clearly defined. Within the Gross study (1996), hydrolysis of conjugates was not addressed at the 1x rate but was investigated at the 4x rate. The levels of metabolites present in their free and conjugated forms are detailed in the attachment.  Rice Metabolite Summary.docx RMS: The amount of free and conjugated forms of identified metabolites are clearly stated in the attachment above. Open point: RMS to include additional information on exact amounts on free and conjugated forms of identified metabolites in table B.7.2.1-5 in a revised RAR.	
3(22)	Vol. 3, B.7.2, grass metabolism Table B.7.2.1-7, p. 39	DE: It is not clear to us what is the amount of conjugates included in the residue fraction of CGA179500 (and others).	Applicant: This study is considered supplementary. A new wheat metabolism study (representative for cereals) was conducted (Piskorski, 2015) and levels of	See 3(18)

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			all metabolites (free and conjugated) are clearly defined. Based on the Ray study (2003), the levels of metabolites present in their free and conjugated forms are detailed below:  Grass Metabolite Summary.docx RMS: The amount of free and conjugated forms of identified metabolites are clearly stated in the attachment above. Open point: RMS to include additional information on exact amounts on free and conjugated forms of identified metabolites in table B.7.2.1-7 in a revised RAR.	
3(23)	Vol. 3, B.7.2, grass metabolism	DE: The sentence " <i>Considering that amenity grass is not intended for livestock feeding, no intake of CGA 165935 residues via amenity grass by livestock is anticipated</i> " should be deleted, as grass is representative for cereals.	Applicant: Noted RMS: Agreed. Sentence will be deleted. Open point: RMS to delete the sentence in a revised RAR.	Addressed. RMS committed to amend the RAR accordingly.
3(24)	Vol. 3, B.7.2.1 Plants New metabolism study in oilseeds rape (study 6)	EFSA: To cover the entire group of pulses/oilseeds which includes crop parts potentially used as feed items (e.g. rape forage and legume forage), please address	Applicant: Commercially Oilseed rape varieties grown for seed are not fed at the forage stage to animals. This use is not on the label of	Addressed.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		the metabolic pathway of trinexapac-ethyl in OSR relevant plant parts.	trinexapac-ethyl products – therefore metabolism data in forage is not needed and was not included in the metabolism study for this reason. RMS: Agrees with the applicant. Additionally the old metabolism study on oilseed rape (Nicollier 1991 and 1993) analysed green parts and flowering parts 14 DAT and found only parent trinexapac-ethyl at low levels (0.012 mg/kg (1.5% TRR) and 0.068 mg/kg (1.0% TRR) for green and flowering parts respectively. Addressed.	
3(25)	Vol. 3, B.7.2.1 Plants (studies 6 to 7)	EFSA: The code CGA275537 is assigned to tricarboxylic acid (e.g. p. 45, 47, 51) and tricarballylic acid (p. 52, LoEP). RMS is invited to verify that the code is unequivocally assigned to the correct common name(s).	Applicant: CGA275537 contains three carboxylic acid functional groups and on pages 45, 47 and 51, the generic term 'tricarboxylic acid' has been used to describe it. In the LoEP (page 52) the term tricarballylic acid is used and is the common name for the metabolite CGA275537. It is confirmed that in this submission, tricarboxylic acid and tricarballylic acid both refer to the same metabolite CGA275537. RMS: Tricarballylic acid is a glutaric acid in which one of the β-hydrogens is substituted by a carboxy group. Tricarboxylic acid will be changed to	Addressed. RMS committed to verify that the term "tricarballylic acid" is used for the metabolite code CGA275537 throughout the revised RAR.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			tricarballic acid where appropriate. Open point: RMS to correct the name for CGA275537 in a revised RAR.	
3(26)	Vol3CA B.7.2.1 metabolism study in spring wheat	FR: In the study 7 (Piskorski R. (2015a)), extractability at 64.8% TRR in straw indicated in RMS comments and conclusion does not correspond to extractable radioactivity specified in table B.7.2.1-11 for straw. Please clarify.	Applicant: In Table B.7.2.1-11, the extractability values quoted for straw and grain have unintentionally been swapped. Therefore the correct extractability values for straw is 64.8% TRR and for grain is 84.1% TRR. RMS: there is a mistake in table B.7.2.1-11 as line for grain and straw are switched. The correct extraction for straw is indeed 64.8%. This will be corrected. Open point: RMS to correct table B.7.2.1-11 in a revised RAR.	Open point: RMS committed to report the correct extractability values for straw and grain of the metabolism study in spring wheat (Study 7) in a revised RAR. See also 3(18) and Experts' consultation 1
3(27)	Vol. 1, Level 2.7.2 Metabolism in plants	EFSA: For sake of clearness, please add the (N) application rate at which the new metabolism study on wheat was conducted in relation to the cGAP in barley.	Applicant: 1.06 N (211g/ha) RMS: 1.06N rate for wheat in relation to the cGAP in barley will be added. Open point: RMS to add N rate to wheat metabolism study.	Addressed. RMS committed to add that the wheat metabolism study was conducted at 1.06N rate in relation to the cGAP for barley (0.211 vs 0.200 kg/ha).
3(28)	Vol. 3, B.7.2.1 Plants Summary and conclusions and Vol. 1, Level 2.7.2	EFSA: It is noted that use on grass is not authorised in EU (see MRL review). Hence, the information that metabolism study in grass was 2.8N the NEU/SEU GAP should	Applicant: Noted RMS: sentence will be deleted. Open point: RMS to amend RAR	Open point: RMS committed to revised the RAR accordingly.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Metabolism in plants	be deleted.	accordingly.	
3(29)	Vol. 3CA B7, Appendix I (Page 269 section 2 metabolites)	Applicant: The position of the OH group in the hydroxylated trinexapac acid component could not be confirmed by chromatographic means as no reference standard was available, however LCMSMS analysis and chemical characterisation has enabled us to conclude on the structure of the grain metabolite, as detailed in the attached document.  Position paper on identification of hyc Exhaustive attempts have been made to synthesize all feasible hydroxylated standards, but it has not been possible to synthesize SYN548584, as detailed in the attached statement. Non-GLP work has shown that the component seen in the GLP study does not co-elute with SYN549426 or SYN549427 standards. GLP study is now complete and available (CGA163935_10838) and confirms the above.	RMS: The documents attached in the comment were provided to RMS on 31.01.2017 and was reported (summarised) in Vol 1 2.7.3 "Definition of the residue". As this was provided to the residue section and nothing submitted to MamTox section, the conclusions on the toxicity of this metabolite could not be finalised. Please also refer to 2(49). The GLP study (CGA163935_10838) showing same results as the non-GLP work should be provided. Data requirement: Applicant to provide GLP study (CGA163935_10838) to section 1 Physical/chemical properties. Open point: RMS to evaluate the above mentioned study and report it in a revised RAR.	Data requirement: Applicant to submit the GLP study (CGA163935_10838) related to hydroxylated trinexapac acid (SYN548584). Open point: RMS to evaluate the information in a revised RAR.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		 Synthesis summary for postulated hydr		

section 3 – Residue data

Metabolism, distribution and expression of residues in poultry, lactating ruminants, pigs and fish				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(30)	Vol. 3, B.7.2.2.1. Poultry (study 1 and 2)	EFSA: RMS concluded that study 1/2 assessed under Directive 91/414 was acceptable with limited deviations (number of animals, duration, dosing). Missing details (e.g. on method of analysis, capability to determine free and conjugated forms of metabolites; time from collection to sample analysis; total TRR identified/characterised; poor extractability in eggs, fat and skin/fat with no apparent attempts for further extraction efforts to characterise/identify the non-extracted residues; storage stability in animal matrices) do not allow concluding on acceptability and validity. Please provide detailed evidence of equivalence to OECD 503.	Applicant: Study 1/2 are considered supplementary studies. The two dose rates in the EU reviewed study (Cameron, 1992) were either below the recommended minimum as per OECD503 or unrealistically high compared to the actual animal dietary burden intakes. Therefore, another metabolism study on poultry (Powell, 2006) was conducted in order to use a more representative dose rate that also meets the requirements in OECD guidelines. The metabolic profile observed in analysed tissues was broadly similar across Muller (1992) and Powell (2006) with CGA163935 (parent) and CGA179500 (trinexapac acid) identified as the major components of the residue. RMS: Agrees, there are missing details in the studies summaries. RMS will add additional details to the summaries, but this would probably not change the conclusions, as the results are comparable to additional new study (Powell, 2006; study 3). Open point: RMS to add detailed evidence of equivalence to OECD 503 in a revised RAR.	Open point: RMS to provide a detailed evaluation and any deviation from guidance OECD 503 on the submitted metabolism studies in poultry and ruminants and to conclude on acceptability and their appropriateness to derive residue definition in products of animal origin. The RAR and the LoEP shall be revised according to the acceptability conclusions. See also Experts' consultation 1

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(31)	Vol. 3, B7.2.2.1 Poultry / LoEP, Metabolism in livestock	NO: Proposed time needed to reach a plateau concentration in eggs is 2-8 days (LoEP). However, it has been shown that a maximum concentration level was reached at different time point (3-10 days) in each animal (see Table B.7.2.2.1-6). It is therefore difficult to establish a plateau concentration from the available studies.	Applicant: Residues in egg whites have been plotted in the attached document for each individual hen. The data demonstrates that although there is some variability (mainly attributable to low residue levels), plateau is reached rapidly in egg whites in all hens, due. In addition mean residues in egg whites across all hens has been plotted to take account of biological variability and clearly demonstrates that plateau is reached rapidly.  Hen Egg White Data.xlsx RMS: It is indeed difficult to establish a plateau from the available studies. Although max values is reached 3 to 10 days in each animal, the mean concentration curve is quite stable during the experiment. RMS is willing to reconsider the plateau to 3-8 days if required by EFSA, but agrees with the applicant that plateau is reached rapidly as quite high values is observed at 1 day in 3 of 5 hens. Addressed.	Addressed. EFSA agrees with RMS that establishing the exact time when the plateau concentration was reached in eggs from the available metabolism studies is difficult.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
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3(32)	Vol. 3, B.7.2.2.2. Lactating ruminants (study 1 and 2)	EFSA: RMS concluded that study 1/2 assessed under Directive 91/414 were acceptable with limited deviations (duration, low identification rate). Missing details (e.g. time of sacrifice of animals, time from collection to sample analysis; method of analysis, efficacy of extraction, capability to determine free and conjugated forms of metabolites; total TRR identified/characterised; poor extractability in fat with no apparent attempt for further extraction efforts; information on the storage stability in animal matrices) do not allow concluding on acceptability and validity. Please provide detailed evidence to demonstrate the equivalent conditions to OECD 503.	Applicant: Study 1/2 are considered supplementary studies. The two dose rates in the EU reviewed study (Cameron, 1992) were either below the recommended minimum as per OECD503 or well in excess of the actual animal dietary burden intakes. For the higher dose experiment, some residues > 0.01 mg/kg or 10% TRR were not identified, but taking account of the the exaggerated dose level these components are unlikely to be significant at realistic dietary burdens. The findings were that the major component of the residue in milk and tissues was CGA179500 (trinexapac acid). An additional study on ruminants (Ray, 2002) was conducted at around 100 mg/kg in the feed with higher accountability of the residue. As per Muller (1993a) the major component of the residue was defined as CGA179500. RMS: agrees, there are missing details in the studies summaries. RMS will add additional details to the summaries, but this would probably not change the conclusions, as the results are comparable to additional study (Ray, 2002; study 3).	See 3(30)

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
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			Open point: RMS to provide detailed evidence to demonstrate the equivalent conditions to OECD 503 in a revised RAR.	
3(33)	Vol. 3, B.7.2.2.2 Lactating ruminants (study 2 and 3)	EFSA: RMS reported that plateau in milk was reached after 2 or 3 days. However, it cannot be seen from the documentation provided. A table showing the daily TRR and trinexapac levels in milk collected over the 4 days of study 2 and, additionally, study 3 shall be provided to substantiate the conclusion.	Applicant: Data from Cameron (1992), Muller (1993a) and Ray (2002) has been used to calculate residues in milk for a 24 hour period. These have been plotted in the attached document. The data demonstrates that plateau is reached rapidly in milk in both Study 2 and 3.  Goat Milk data.xlsx RMS: In the attached document above it is clearly showed, that in both studies plateau is reached rapidly in milk. These tables/graphs will be added for clarity. Open point: RMS to add additional details to study 2 and 3 in a revised RAR.	Addressed. RMS committed to add additional details on the TRR and trinexapac acid amounts found in milk collected daily in study 1, 2 and 3.
3(34)	Vol 3, B.7.2.2.4 Fish and Vol. 1, Level 2.7.2. Metabolism in animals	EFSA: Vol 3 of the RAR shall include the scientific assessment of the available experimental studies. If the applicant is of the opinion that the risk	Applicant: Further guidance and opinion has been published since this submission was made. Please see the information below and the reasoning as to why we do not	Data requirement: Applicant to submit information against the data requirement of Regulation (EU) No 283/2013. The argument that no

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		assessments can be completed without submission of data on metabolism, distribution and expression of residues in fish/feeding studies with fish, the justification supporting this opinion should be provided in Vol 1. It is noted that the argument that no agreed test method or guidance is available as reported in Vol 1 is not considered a valid justification.	feel we are able to provide the information suggested. Document SANCO/10181/2013 Rev. 2.1, of 13 May 2013, states: <i>In some cases, agreed test methods or guidance documents are not yet available for particular data requirements. In these cases, waiving of these particular data requirement points is considered acceptable as long as no test methods or guidance documents are published in the form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02.</i> It is also recorded in the Summary Report of the Standing Committee meeting on Plants, Animal, Food and Feed (Section Phytopharmaceuticals - Pesticides Residues), held in Brussels on 24-25 November 2014, under item A.24, that " ... the Commission working document on the nature of residues in fish was discussed in 2013 and it was concluded that it is not yet finalised and ready to be noted as a guidance document." Additionally the report states under item A.24 the Commission emphasised that for the time being there are no agreed test guidelines and that hence the pertinent data requirements can be waived [as per document SANCO/10181/2013 Rev 2.1]." In the Summary Report of the SCoPAFF meeting (Section Phytopharmaceuticals - Plant Protection Products - Legislation), held in Brussels on 26-27 January 2015, it is reiterated, under item A.26, "... some RMS are requesting studies on data requirements for which currently there is no agreed methodology and they consider a dossier incomplete if these data are not provided. The Commission explained that this is not consistent with the Guidance Document SANCO/10181/2013, which was taken note of by Member States." The following statements were also made by the Commission: "In particular cases, ad-hoc studies could be requested, as it is always the case in justified situations. ... However, the Commission referred to the general policy of reducing animal testing and asked Member States to consider this when asking for additional studies on vertebrates."	agreed test method or guidance is available is not considered a valid justification. Detailed circumstances in which animal fish metabolism and feeding studies are triggered are described in SANCO/11187/2013. Open point: RMS to assess information provided in a revised RAR.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			We believe that it is essential that guidance is suitably discussed and peer reviewed, considering both benefits to the assessment of consumer safety and the minimisation of vertebrate testing, before being applied. In addition there are currently no definitive triggers in Regulation (EC) No. 283/2013 on which to base a decision as to whether a "fish metabolism" study is required or not. In order to properly assess the potential transfer of pesticide residues from plant-protection-product treated feed items into the consumable tissues of farmed fish we believe that the following need to be in place: A robust and representative dietary burden calculation method (including the underlying feeding-practice data); An agreed and practicable method for studying the nature of residues in fish; and (depending on the potential for residues to transfer into fish tissues) An agreed and practicable method for quantitatively studying the transfer of residues of concern into fish tissues. RMS: Argumentation from the applicant will be included in Vol 1. RMS is of the opinion that it is not correct to ask metabolism/feeding study on fish, as it is not clear for the applicant how to conduct such studies and for the RMS how to evaluate them. Open point: RMS to add applicant justification in Vol 1 in a revised RAR leaving only the statement of the current situation in Vol 3 (no studies provided).	
3(35)	Vol 1, Level 2.7.2. Metabolism in animals	EFSA: Metabolites SYN548584, CGA275537, CGA300405 and CG351210 are major plant metabolites. The need for	Applicant: The metabolites mentioned are major in some feed items analysed in the metabolism studies however, for different	Open point: RMS to assess the argumentation provided by the applicant in a revised RAR.

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		metabolism data in livestock dosed with a mixture of compounds reflecting the level of their exposure in feed items of the treated crops shall be addressed.	reasons noted below we do not believe an additional livestock metabolism study is necessary or ethical:- A position on ruminant metabolism livestock metabolism studies dosed with CGA275537 and CGA300405 not being required is outlined in the attached document.  CGA275537_CGA300405 ruminant.docx As SYN548584 has been found to be unstable outside the plant matrix it would be physically impossible to carry out a livestock metabolism study using this unstable metabolite. The majority of CGA351210 is found in OSR pods and stalks. These items are not fed to animals so would not add to the dietary burden. There is a minor quantity 5.6% TRR found in the OSR seed. This adds to the dietary burden in the form of meal remaining after the oil is processed but is not considered a major increase – therefore a major vertebrate study should not be required. RMS: Agrees with the applicant, that additional ruminant metabolism study	

section 3 – Residue data

Metabolism, distribution and expression of residues in plants				
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			dosed with SYN548584, CGA275537, CGA300405 and CG351210 is not necessary. Explanations provided will be included in a revised RAR. Point is considered addressed .	
3(36)		Co-RMS (LV): No comments	RMS: Noted.	
3(37)		FR: No comment	RMS: Noted.	

Residue definition				
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3(38)	Vol. 1, Level 2.7.3 Definition of residues (2) trinexapac acid, free and conjugated	EFSA: In Table 2.7.3-1, the residue definition for risk assessment includes the metabolite hydroxylated-CGA179500 (SYN548584) but CFs were reported to be calculated based on the residue levels of trinexapac acid (free) and total trinexapac acid (free and conjugated) only (see footnote (e) of the table). Apart of the calculation of PFs using results from processing studies analysed for trinexapac acid only which acceptability is to be demonstrated, it is not clear how CFs for risk assessment shall be	Applicant: Noted – RMS to clarify. Applicant: The following attempts to explain how free trinexapac acid (CGA179500) residues can be converted to a total residue for risk assessment including the SYN548584 component.	Open point: RMS is requested to reconsider the residue definition for enforcement and for risk assessment in raw commodities and processed products and to provide detailed explanation on how the different CFs used in the assessment were derived in a revised RAR and LoEP See also 3(39), 3(40), 3(46), 3(51), 3(53), 3(59), 3(71), 3(76), 3(80) and Experts' Consultation 2

section 3 – Residue data

Residue definition				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		calculated, since SYN548584 was not analysed in processed products.	As SYN548584 has been found to be unstable outside the plant matrix, levels in residue trials can only be estimated by using conversion factors based on the levels of SYN548584 found in the wheat metabolism study. Risk assessment DOR is proposed as Sum of trinexapac acid (free and conjugates) and OH-trinexapac acid, expressed as trinexapac acid. So it was necessary to use measured residues of trinexapac free in cereal grain to give an additional component in the Risk assessment (RA) for the presence of the unmeasurable SYN548584. This was done by multiplying the MRL for wheat and barley grain by 1.44. (From wheat metabolism study: Residues of free trinexapac acid = 0.401 mg/kg. Residues of SYN548584 = 0.175 mg/kg. Total residue for RA = 0.401 + 0.175 mg/kg = 0.576 mg/kg. Hence to convert free trinexapac residues to (free trinexapac residue plus SYN548584) the free trinexapac value should be multiplied by $0.576/0.401 = 1.44$ (1.436 to 3 decimal places)). RMS: Indeed, residue definition for risk assessment in processed commodities should not include hydroxylated trinexapac	

section 3 – Residue data

Residue definition				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			acid (SYN548584) as it was not found in processing studies. SYN548584 is not stable, could not be synthesised and therefore could not be analysed in processing studies (as well as residue trials), see also 3(29), therefore the CF could be derived based on metabolism study in RAC only. Conversion factors reported in Table 2.7.3-1 are to convert residue values from MO to RA - from „free trinexapac acid“ to „free and conjugated trinexapac acid“. As the method does not discriminate acid and salts, it seems that the wording of residue definition „sum of trinexapac acid and its salts, expressed as trinexapac acid“ for monitoring and „sum of trinexapac acid, its salts and conjugates, expressed as trinexapac acid“ for risk assessment would be more appropriate. Please also refer to 3(6) and 3(44). Open point: RMS to reconsider the proposed residue definitions for monitoring and risk assessment for both raw and processed commodities.	
3(39)	Vol 1 Level 2.7.3 Definition of residues (6) hydroxylated CGA179500 (SYN548584)	EFSA: Hydroxylated trinexapac (SYN548584) represented 12% TRR (0.18 mg eq/kg) in wheat grain from the metabolism study at 1N the cGAP. Its concentrations were only	Applicant: See 3(38) RMS: Please refer to 3(38)	See 3(38) and Experts' consultation 2

section 3 – Residue data

Residue definition				
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		theoretically calculated in cereal grains treated according to the cGAP using a CF of 1.434. Please provide information on how this value was derived.		
3(40)	Vol. 1, Level 2.7.3 Definition of residues in plants	EFSA: Although the nature of residues in processed products was different than in primary crops, the residue definition (RD) for risk assessment in primary and processed products has been proposed as "sum of trinexapac acid (free and conjugated) and hydroxylated trinexapac acid, expressed as trinexapac acid" with CF of 2.5 (grain) and 5 (straw). In Table 2.7.3-1 of summary of processing studies RD is reported as "trinexapac acid (free and conjugated)" with CF of 2 (grain) and 4 (straw). Please clarify the RD proposed for enforcement and risk assessment in processed products and address the discrepancy of RD and CFs.	Applicant: There appears to be some confusion - The RD is stated as "Residue definition for risk assessment: sum of trinexapac acid (free and conjugated) and OH-trinexapac acid, expressed as trinexapac acid". In Table 2.7.3-1 of document RAR Vol 1 2017-03-31 the CF of 2.5 (grain) and 5 (straw) are applicable for converting free trinexapac acid residues to the risk assessment RD of sum of trinexapac acid (free and conjugated) and hydroxylated trinexapac acid, expressed as trinexapac acid. CF of 2 (grain) and 4 (straw) are applicable for converting free trinexapac acid residues to trinexapac acid (free and conjugated) values (at end of section 2) Trinexapac acid, free and conjugated (CGA179500). RMS: The discrepancy of CF is well explained by the applicant. For discrepancy of residue definitions please refer to 3(38). Addressed.	See Experts' consultation 2

section 3 – Residue data

Residue definition				
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3(41)	Vol 1, Level 2.7.3 Definition of residues	EFSA: The proposed residue definitions for risk assessment in plants, processed and products of animal origin need to be reconsidered pending upon further discussion and decision in Mam-Tox Section 2 on the toxicological proprieties of the metabolites observed in the plant/livestock metabolism and hydrolysis studies but not in rat metabolism.	Applicant: Agreed RMS: Agreed. Open point: RMS to reconsider the residue definitions proposed after the decision in Mam-Tox Section 2 on the toxicological proprieties of the metabolites observed in metabolism and hydrolysis studies, please also see 2(49)-2(53). Expert consultation on residue definitions might be needed.	Experts' consultation 2. It is proposed to discuss the residue definition for enforcement and risk assessment in plants, processed products and products of animal origin in an expert meeting also considering the appropriateness of the metabolism studies the magnitude of residues and the toxicological proprieties of the identified relevant metabolites. See 2(42), 2(43), 2(45), 2(49), 2(50), 2(51), 2(52) and 2(53). See also Experts' Consultation 1
3(42)	Vol. 1 level2, 2.7.3 LOEP	FR: considering the available metabolism studies the residue definition proposals might be restricted to cereals and oilseeds groups only. Additional metabolites might be included in residue definition in case further uses are intended in the future.	Applicant: Noted RMS: Agrees that from the existing metabolism studies, the definition of residues could be set restricted to cereals and oilseeds. Open point: RMS to reconsider setting residue definitions only to cereals and oilseeds.	See Experts' consultation 2 Open point: RMS to reconsider proposing residue definitions restricted to cereals and oilseeds in the revised RAR.
3(43)	Vol. 1, 2.7.3, p. 77 residue definition	DE: It is written by RMS that the residue definition for plants (monitoring and risk assessment) was changed during the review of Art. 12 assessment in 2012. Please note that the original proposal in	Applicant: Noted RMS: Noted. Additional explanations on residue definitions will be added. Open point: RMS to amend the RAR	Addressed.

section 3 – Residue data

Residue definition				
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		EFSA Scientific Report (2005) 57, 1– 70 was already " <i>Trinexapac and its salts in food of plant (cereals, only)</i> ". Only in the LoE the simplified wording " <i>Trinexapac</i> (CGA 179500)" is used.	accordingly.	
3(44)	Vol. 1, 2.7.3, p. 77 residue definition	DE: As residue definition for monitoring we would prefer the wording " <i>Sum of trinexapac acid and its salts, expressed as trinexapac acid</i> ". The residue analytical method does not discriminate, so results obtained cover the acid plus their salts.	Applicant: Noted RMS: Noted. At the time of proposing the Mo RD it was not taken into account, that the analytical method for monitoring does not discriminate and results cover the acid plus its salts. RMS agrees that the wording of "Sum of trinexapac acid and its salts, expressed as trinexapac acid" would be more appropriate. Open point: RMS to reconsider wording of Mo RD taking into account, that analytical method for monitoring covers both acid and salts.	See Experts' consultation 2
3(45)	Vol. 1, 2.7.3, p. 77 residue definition for risk assessment	DE: We agree to the approach of the RMS to consider on a tentative basis the hydroxylated acid by a conversion factor in absence of definitive structural elucidation and synthesis of 1-OH reference material and to consider toxicological expert judgement for risk assessment. Indicative residue trials might give confirmation on the proposed quantitative non-relevance.	Applicant: In the light of further investigation and attempts to synthesize SYN548584, it is now not possible to analyse for this molecule in residue trials. If it is to remain in the DOR for RA, an estimated conversion factor is the only solution available. Please see also 3(38) RMS: Noted. See also 3(6), 3(29) and 3(38).	See Experts' consultation 2

section 3 – Residue data

Residue definition				
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3(46)	Vol. 3 B7, B.7.3 (table B.7.3.2-4) Vol. 1.2.7.3	FR: Calculations of the proposed CF might be further detailed in these sections.	Applicant: How the conversion factors were derived would be useful. The factors used are clearly noted in the footnotes to tables B7.3.2-3 and the calculated results shown in the appropriate columns. RMS: Noted. Additional explanations on the calculation of CF will be added. Open point: RMS to amend the RAR accordingly.	See 3(38)
3(47)	Vol. 3 B7, B.7.3.2 (table B.7.3.2-4) LOEP p22	FR: The monitoring RD for plant and also for animal should specify that only "free" trinexapac acid is included to avoid any confusion.	Applicant: Noted RMS: Noted. Open point: RMS to add explanations to residue definitions in a revised RAR.	See Experts' consultation 2
3(48)	Volume 1, Level 3 Residue Definition AnnexII 3.9 and 3.1.4.7	Applicant: RMS: Due to the lack of information on metabolite hydroxylated-CGA179500 (hydroxylated trinexapac acid) (actual amounts in residue trials – as analytical standards are not yet available and general toxicity), residue definition for risk assessment could not be finalized. This metabolite is provisionally proposed for inclusion in the residue definition for risk assessment for plant matrices. and	RMS: Noted. Please refer to 3(6) and 3(29)	See Experts' consultation 2

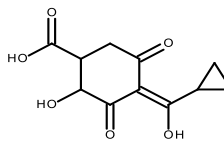
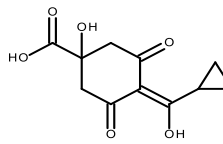
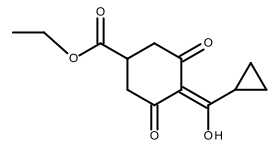
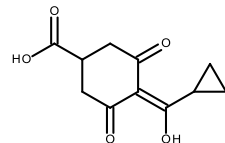
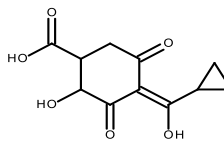
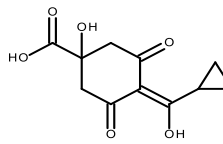
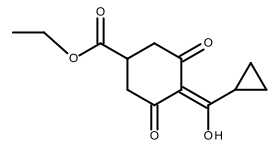
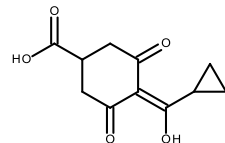
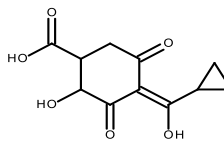
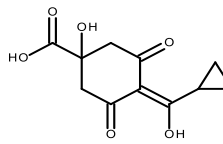
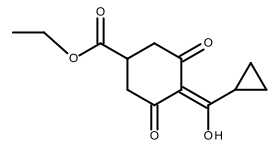
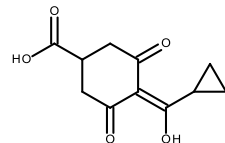
section 3 – Residue data

Residue definition				
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	and 3.1.5 - Issues that could not be finalised	Toxicological evaluation of metabolite hydroxylated CGA179500 need to be provided for final decision making of the residue definition. RMS: In plants, residue definition for risk assessment could not be finalised due to missing information on metabolite hydroxylated CGA179500. Hydroxylated CGA179500 was detected in edible plant parts (wheat grain at 12.1 % TRR). As analytical standards are not yet available, OH-CGA179500 could not been measured in the residue trials. Although OH-CGA179500 was not observed in the rat, no alerts were identified for genotoxicity (using (Q)SAR analysis (DEREK, LHASA Ltd)). A final conclusion on the genotoxic potential cannot be drawn for this metabolite based on the information provided. Consequently, a decision on the inclusion of hydroxylated CGA179500 into the residue definition cannot be made until the applicant has provided a toxicological characterisation of hydroxylated CGA179500. Applicant response/further explanations Applicant: In terms of general toxicity,		

section 3 – Residue data

Residue definition				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		hydroxylated trinexapac acid could potentially exist as a 2-hydroxy or 1-hydroxy form. It is structurally similar to trinexapac acid (CGA179500) and trinexapac-ethyl. Hydroxy trinexapac acid differs from CGA179500 in the addition of a hydroxyl group on the cyclohexane ring. The addition of a hydroxyl group is unlikely to result in increased toxicity, and may make the metabolite more readily excreted (the hydroxyl group may be available for conjugation and aid rapid excretion). CGA179500 is the major rat metabolite of trinexapac-ethyl, and therefore the toxicity profile of trinexapac-ethyl effectively covers both molecules. Both hydroxy trinexapac acid potential metabolites would be expected to be of equivalent or possibly lower toxicity than trinexapac-ethyl/CGA179500. Trinexapac-ethyl is non-genotoxic, of low acute oral toxicity, and neither carcinogenic or reproductively toxic. Furthermore, new in vitro genotoxicity studies have been conducted and show		

section 3 – Residue data

Residue definition												
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)								
		CGA179500 to be non-genotoxic (Ames, HPRT and in vitro micronucleus, studies in reporting phase, see also comment Vol. B.6.8.1.4.3 Genotoxicity). Therefore the hydroxylated trinexapac acid metabolites would be expected to be of similarly low concern. <table><tr><td></td><td></td></tr><tr><td>1-hydroxy trinexapac acid SYN548583</td><td>2-hydroxy trinexapac acid SYN548584</td></tr><tr><td></td><td></td></tr><tr><td>Trinexapac-ethyl</td><td>Trinexapac acid CGA179500</td></tr></table> Despite exhaustive attempts to isolate and/or synthesise the hydroxylated CGA179500 – identified by default as SYN548584 - it has not been possible. The molecule appears to be unstable			1-hydroxy trinexapac acid SYN548583	2-hydroxy trinexapac acid SYN548584			Trinexapac-ethyl	Trinexapac acid CGA179500		
												
1-hydroxy trinexapac acid SYN548583	2-hydroxy trinexapac acid SYN548584											
												
Trinexapac-ethyl	Trinexapac acid CGA179500											

section 3 – Residue data

Residue definition				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		outside the plant matrix and reverts to CGA179500. See 3CA B7 Appendix I above. As the toxicity of this molecule is likely to be equivalent to trinexapac-ethyl and of low concern and cannot be synthesised, the applicant propose that it is removed from the definition of the residue for risk assessment in plant matrices.		
3(49)		Applicant: DOR information is missing in dRAR (Vol 3 Annex B.7) Please see applicant dossier MCA Section 6 CA 6.7	Applicant: We see that the DOR information is located in Volume 1 only. The applicant would like to see the full version in B7 and a summary in Volume 1. RMS: According to SANCO/12592/2012-rev.0 information on definition of residue should be presented only in Vol 1. Addressed.	Addressed.
3(50)		Co-RMS (LV): No comments	RMS: Noted.	

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(51)	Vol. 3 B7, B.7.3.1 barley and B.7.3.2 wheat	FR: In table B.7.3.1-3 and table B.7.3.2-3, CF are proposed to estimate residue level of OH-CGA179500, CGA300405, CGA275537. It is mentioned in the text above "Values in the grey cells are residue levels estimates calculated using trinexapac acid (free) data and conversion factors (refer to Appendix I for details)". Nevertheless no paragraph explaining the CF calculation was found.	Applicant: In this version of the dRAR the details of how the conversion factors were estimated from the levels found in the metabolism studies seem to have been omitted. Appendix I in this version covers the literature search. The information requested is in Vol I 2.7.3 RMS: Indeed a reference to Appendix I is not correct and will be deleted, additionally explanations on the CF will be provided in the footnote to the tables B.7.3.1-3 and B.7.3.2-3. Open point: RMS to add explanations to tables B.7.3.1-3 and B.7.3.2-3 in a revised RAR.	See 3(38)
3(52)	Vol. 3 B7, B.7.3.1 barley and B.7.3.2 wheat	FR: in table B.7.3.1-3 and table B.7.3.2-3, it was noticed that for some residue trials the residue level measured for CGA179500 (free) were above the residue level measured for CGA179500 (free and conjugated). As this case is not consistent, a justification (regarding sample or analytical method) will be welcome.	Applicant: Trials and analysis have been checked and the levels reported are correct. RMS: Trials were checked by the RMS, the reason why measured "free" residues is in few cases higher than "free and conjugated" is unclear. It could be due to variability in analytical method. Addressed.	Addressed.

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(53)	Vol 3, B.7.3	NL: conversion factors should not be derived from metabolism studies, but from supervised residue trials. A reference is made to Appendix I, but Appendix I contains the literature search and no information on conversion factors.	Applicant: Please see 3(38) for conversion factor from free trinexapac acid residues to SYN548584 residue for use in RA which includes trinexapac acid free and conjugated plus SYN548584. Please also see 3(51). RMS: Conversion factors could not be derived from supervised residue trials as metabolites OH-CGA179500, CGA300405 and CGA275537 were not measured in residue trials. These calculations with conversion factors from metabolism studies were chosen as an alternative provided by the applicant only to demonstrate, that theoretical calculations show insignificant exposure to consumer. A reference to Appendix I is not correct and will be deleted, additionally explanations on the CF will be provided in the footnote to the tables B.7.3.1-3 and B.7.3.2-3. Open point: RMS to add explanations to tables B.7.3.1-3 and B.7.3.2-3 in a revised RAR.	See 3(38)

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(54)	Vol. 3, table 7.3.1-3 and 7.3.2-3	NL: the levels of relevant metabolites from supervised residue trials should not be calculated/estimated using conversion factors.	Applicant: The metabolites relevant to the DR are free trinexapac acid, free and conjugated trinexapac acid and SYN548584. Only the contribution of SYN548584 has been calculated –as it is now known it cannot be synthesized. – This remains the only way it can be accounted for in the risk assessment. Free trinexapac acid and free and conjugated trinexapac acid were analysed for and reported in the table 7.3.1-3 RMS: Agrees with the applicant, please also see 3(53)	See 3(53)
3(55)	Vol 3, B.7.3.2, study 3	NL: although recoveries in grain for the analytical method used are within the limits reported in the guideline, they are overall low (62-85%), possibly resulting in an underestimation of residue levels in grain.	Applicant: Noted – As residues are low any differences are likely to fall within statistical variation. RMS: As recoveries in grain for the analytical method used are within the limits reported in the guideline, the study 3 is considered reliable. Point is considered addressed.	Addressed.

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(56)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: Evidence that the conditions of OECD 509 are met in the supervised residue field trials (only study 6 on barley and study 4 on wheat were reported to be conducted according to OECD 509) and that samples of grains and straw are covered by acceptable storage stability data shall be provided.	Applicant: Noted – The RMS to re-assess. RMS: All supervised residue trials meet the conditions of OECD 509, for mistake it is reported only for study 4 and 6. Samples of grains are considered to be covered by storage stability studies (for 25.5 months storage samples please refer to 3(13). Although straw samples are in most cases not covered by existing storage stability studies (see also 3(4)). Data requirement: Applicant to provide storage stability studies covering the length of storage of straw samples in residue trials. See also data requirement under point 3(4). Open point: RMS to add additional comments on the reliability and storage of the residue studies in a revised RAR.	Open point: RMS to amend the RAR revising information on the guidance followed to conduct the supervised residue field trials on barley and wheat. According to the applicant, all trials were conducted according to OECD 509. Data requirement: See 3(4) and 3(13)

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(57)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: Trials with samples analysed for hydroxylated trinexapac acid (SYN548584) are missing and they may be required (see comment under Vol 1, Level 2.7.3 Definition of residues).	Applicant: Not possible as analytical standard cannot be made. See 3(48) RMS: although metabolite hydroxylated trinexapac acid (SYN548584) should be measured in residue trials, it is not possible in the current situation as it is not stable and the analytical standard is not available. Definition of residues might be reconsidered accordingly, see also 3(48). Expert consultation on whether metabolite hydroxylated trinexapac acid (SYN548584) should be included in the residue definition for risk assessment might be needed.	See Experts' consultation 2

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(58)	Vol. 3, B.7.3 Annex B7 (AS) Residue data, barley and wheat	EFSA: Details of the locations where each single residue trial was conducted were not reported. The information is essential to verify the independency of the residue trials on wheat and barley.	Applicant: Postcodes for all trial sites are noted in B7 pages 133-120 for barley and 137-145 for wheat. RMS: As postal codes are not visually informative, RMS will insert a map with marked places of each single residue trial. As all residue trials have different postal codes, RMS assumes them to be independent. Data requirement: As some trials are located in nearby areas, applicant is asked to provide details of the locations where each single residue trial was conducted (distance from the near located trial sites, for example 4 wheat trials conducted in UK and FR each, 3 barley trials conducted in UK and FR each.) Open point: RMS to add additional information on residue trials location in a revised RAR.	Data requirement: Applicant to provide details of the location where each single residue trial was conducted and the distance from the located near sites. Open point: RMS to add information on the trial location and to conclude on the total number of valid and independent residue trials available per each crop and geographical region in a revised RAR.

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(59)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: The calculation of theoretical concentrations of hydroxylated trinexapac acid and the CFs from enforcement to risk assessment reported in Tables B.7.3.1.-3 (barley) and B.7.3.2.-3 (wheat) were provided in Appendix I. Reference is mismatched (Appendix I of Vol 3 refers to literature review). Please help retrieving the calculations.	Applicant: See 3(51) and 3(58) RMS: Please refer to 3(53)	See 3(38) and 3(53)
3(60)	Vol. 3, B.7.3 Magnitude of residue trials in plants, barley	EFSA: It is noted that trial in NC13038-02 (study TK0178795) in winter barley residues of trinexapac acid alone as well as total free and conjugated were <LOQ in grains and straw. Considering the residue levels observed in all the other trials, it shall be verified if the trial had failed to determine residues and shall be disregarded or observations are within normal agricultural practice variability.	Applicant: Noted. The RMS to assess RMS: No information on failing to determine residues could be found in the study report. RMS considers these <LOQ values are within normal agricultural practice variability. Please also note that residue in grain values in study 36190 trial 1 are 0.01 and 0.02 mg/kg for trinexapac acid free and trinexapac acid free plus conjugates respectively, and below LOQ for straw. Addressed.	Addressed.
3(61)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: EFSA: According to the proportionality principle, not only the overdosed, but also residues from trials on wheat and barley conducted at the nominal application rate ($\pm 25\%$) should be scaled (entire SEU dataset).	Applicant: Noted. RMS: Agreed. All residue values will be scaled. See also 3(62) Addressed.	See 3(62)

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(62)	Vol. 3, B.7.3 Magnitude of residue trials in plants	EFSA: Since the SEU and NEU GAP on winter barley and wheat are the same, NEU and SEU (after scaling) datasets should be statistically tested if a more robust MRL/input values can be derived from combined dataset. It is advisable that if NEU/SEU data belong to similar populations (U-test, 5%), also the NEU dataset is scaled to exact application rate (entire NEU/SEU dataset).	Applicant: Noted. RMS: NEU and SEU datasets on barley are similar according to U-test. NEU and SEU datasets on wheat are also similar according to U-test, although one value of 0.39 mg/kg seems to be an outlier. The MRL proposal based on combined datasets (without an outlier) is 0.4 mg/kg for wheat and 0.8 mg/kg for barley. Open point: RMS to report the scaled values of all datasets in the RAR Vol. 3, B.7.3 and correct MRL calculations in LoEP accordingly.	Open point: RMS to proportionally scale residue values of the entire SEU datasets to nominal application rates and, if statistically appropriate to merge datasets, to scale NEU datasets prior to the merge. Results should be checked carefully as being a potential outlier and exclusion from dataset justified (i.e. accidental contamination). MRL proposals for wheat grain and straw, input values for the exposure assessment and the livestock dietary burden calculation and the proposed CF shall be recalculated accordingly in the revised RAR. See also 3(13), 3(38), (58) and Experts' consultation 2
3(63)	LOEP p22 and p31	FR: the CF mentioned for grain and straw to convert residue level from monitoring RD to Risk RD seem overestimated compared to the estimated CF proposed in Vol. 3 B7, B.7.3.1 barley and B.7.3.2 wheat table B.7.3.1-3 and table B.7.3.2-3. The detail of the proposal CF value should be added.	Applicant: Agreed – There is some confusion between different versions of the documents and between the previous version of the dRAR Volume 3 B-7, the dRAR Volume 3 B-7 (submitted to EFSA), the LOeP and the dRAR Volume 1 (submitted to EFSA). To clarify by the RMS. In LOEP the CF mentioned for grain and straw to convert residue level from	See 3(38)

section 3 – Residue data

Residue trials in plants and identification of critical GAP				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			monitoring RD to Risk RD are 2.5 and 5 respectively – however on page 31 an average grain conversion factor calculated from the 8 values given would be 1.84 and for straw 4.17 – rounding these up could give 2 and 4, respectively. There appears to be an Appendix missing which explains how the conversion factors were calculated from the metabolism studies. The RMS should include the missing Appendix to the dRAR. RMS: Proposed CF in Vol 3 B.7.3.1 and B.7.3.2 were calculated separately for wheat and barley, NEU and SEU datasets leading to 8 values (median conversion factors, which are also stated in LoEP 31 p.). In the LoEP RMS took the most critical of those values, which is barley grain NEU 2.46 and barley straw NEU 4.88. These values were rounded to CF 2.5 and 5 respectively. If this approach is not appropriate, RMS is willing to change the proposed CF values to mean or median values calculated from combined datasets (wheat and barley from NEU and SEU). Point is considered addressed.	
3(64)		Co-RMS (LV): No comments	RMS: Noted.	

Feeding studies in poultry, ruminants, pigs and fish				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(65)	Vol 3, B.7.4.1 Poultry	EFSA: Since Vol 3 of the RAR includes the scientific assessment of the available experimental studies, RMS is asked to report current situation (no feeding study available, as done for pigs and fishes). Any justification for waiver of submission of data on feeding studies with poultry should be provided in Vol 1.	Applicant: Please see dRAR Volume 1 page 99. RMS: Agreed. Only the current situation on feeding studies with poultry will be stated in Vol 3. Open point: RMS to amend Vol3 B.7.4.1 accordingly.	Addressed. RMS committed to amend Vol 3, B.7.4.1 accordingly.
3(66)	Vol 3, B.7.4.2 Ruminants (study 1)	EFSA: The feeding study on cows was conducted according to SANCO guidance 70/31/VI/95. RMS is invited to provide additional information and detailed evidence to demonstrate that equivalent conditions to OECD 505 are met. (e.g., but not exclusively: provide the dose levels as mg/bw and the body weight of the animals; detailed description of the validation of the analytical method; compliance of type of tissue sampled for analysis; milk data and plateau analysis; individual levels for each sample not merely the mean and average of the 3 as in Table B.7.4.2-2)	RMS: Additional information and detailed evidence to demonstrate that equivalent conditions to OECD 505 are met will be provided in Vol3, B.7.4.2 Open point: RMS to include additional information to Vol3, B.7.4.2 in a revised RAR.	Open point: RMS to include additional information on the feeding study in ruminants to enable an evaluation of equivalence to OECD 505 and to conclude on acceptability and the resulting residues in products of animal origin taking into account the LOQ of the analytical method used. See also Experts' consultation 2

Feeding studies in poultry, ruminants, pigs and fish				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(67)	Vol 3 CA B7 B7.4.3 Ruminant feeding study	Applicant: Absolute calculation of the expected residues levels in animal tissues based on the dietary burden and feeding study results should be presented for lactating ruminants. Refer to page 23 in MCA-section 6 document.	RMS: Absolute calculation of the expected residues levels in animal tissues based on the feeding study results is presented for lactating ruminants, although dietary burden is presented for lamb as being the most critical. These values could be changed to lactating ruminants and having no impact on the conclusions. Point is considered addressed .	Addressed.
3(68)	Vol.1 2.7.5 (Table 2.7.5-1 Table 2.7.5-2) and LoEP p28 and LoEP p29	FR: in the tables presenting "Inputs for animal burden calculations", please add the residue definition used for DB calculation (plant RA: Sum of CGA179500 (free & conj.) and OH-CGA179500). in the tables "Residues from livestock feeding studies ", please added the residue definition (animal RA: CGA179500 (<u>free</u>)).	Applicant: Agreed. RMS: Agreed. Residue definition used will be added. Open point: RMS to add residue definition used in the tables 2.7.5-1 and 2.7.5-2 and LoEP.	Open point: RMS to add the residue definition in Table 2.7.5-1/2 and in the LoEP.
3(69)		Co-RMS (LV): No comments	RMS: noted.	

section 3 – Residue data

Effects of processing				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(70)	Vol. 3, B.7.5.3 Magnitude of residue in processed commodities	EFSA: The original processing studies (study 1-to 8, and 13) were reported not to be evaluated by the RMS. Study 9, 14, and 15 were conducted according to US-EPA guidance. Furthermore, these studies analysed trinexapac free acid only. An independent, objective and transparent assessment of these studies and a detailed analysis for compliance with current scientific and technical knowledge shall be conducted. Evidence of equivalence to OECD 508 to be provided.	Applicant: Noted. RMS: Re-assessment of these studies, more details and equivalence to OECD 508 will be provided. Open point: RMS to provide detail analysis and evidence of equivalence to OECD 508 in a revised RAR.	Open point: RMS to provide a detailed evaluation and any deviation from guidance OECD 508 for the original processing studies and to conclude on acceptability and their valid to derive reliable PFs/CFs according to the residue definitions. The RAR and the LoEP shall be revised accordingly.
3(71)	Vol. 3, B.7.5.3 Magnitude of residue in processed commodities	EFSA. None of the samples from the processing studies was analysed for hydroxylated-CGA179500 (SYN548584). The nature and magnitude in processed products need to be addressed.	Applicant: As it is now known that SYN548584 cannot be synthesised – therefore analytical standard is not available – hence it is not possible to analyse samples for it. RMS: Agrees with the applicant, although required it is not possible to analyse SYN548584 in samples of processed commodities. It could be calculated only using the same conversion factor as for raw commodities. Point is considered addressed .	See Experts' Consultation 2

section 3 – Residue data

Effects of processing				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(72)	Vol. 3, B.7.5.1, study by Scullion (2012), page 163	Co-RMS (LV): According to OECD 507 "The same labelling positions as in the available metabolism studies are preferable and should be used." This time radiolabel position was different. Could you, please, explain how these divergences influence the significance of this study compared to other high temperature hydrolysis studies? Especially, because metabolite CGA224439 is identified only in this study, maybe CGA224439 could be major metabolite also in plant metabolism if used radiolabel position has been as in this study?	Applicant: When the task force was formed it was noted that one study carried out with a different label had produced the CGA224439. An analytical method was developed to investigate levels of CGA224439 in the exaggerated rate wheat and barley processing studies. CGA224439 was found in the pre-processed grain as well as in some of the processed fractions at low levels. A risk assessment was carried out using the TTC approach – which provides a very low default endpoint – and showed no risk to the consumer from the levels of CGA224439 estimated in grain – treated at the cGAP application rates. We believe this metabolite is of no concern. RMS: Agrees with the applicant. Point is considered addressed.	Experts' consultation 1: To discuss if the submitted metabolism studies with radiolabelled test substance in the cyclohexane ring only are appropriate to firmly address the metabolic pathway of the active substance and conclude on the residue definition for the representative use and for animal products, considering that according to OECD 501, 502 and OECD 503 separate studies labelling each ring or side chain of the molecule will normally be required, unless no cleavage is anticipated. It is note that apparently CPCA (CGA224439), when analysed, was found in grain prior to be processed and it is not clear if derived from hydrolysis degradation pathway only and its toxicological relevance. See 2(42), 2(53) and Experts' Consultation 2
3(73)	Vol. 3, B.7.5.1, study by Scullion (2012), page 169	Co-RMS (LV): There's a small typo for parent concentration (mg/L) in Table B.7.5.1-5 on pH 4 (90°C) column. (0.087 mg/L instead of 0.87 mg/)	Applicant: Noted. RMS: Noted, will be corrected. Open point: RMS to correct the residue value in table B.7.5.1-5 in a revised RAR.	Addressed. RMS committed to correct Table B.7.5.1-5 accordingly in a revised RAR

section 3 – Residue data

Effects of processing				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(74)	Vol. 3, B.7.5.3 Magnitude of residue in processed commodities (study 10-12, barley; study 16-18, wheat)	EFSA: Samples of grains from 2 field trials on barley and 2 field trials on wheat were collected and split each into 2 subsamples prior to undergo the different processing. It is questionable that these studies are providing 4 independent results per each processed commodity.	Applicant: OECD 508 requires "At least 2 independent trials with RAC samples from 2 separate field sites...." This requirement was met for both Barley and Wheat. Two data points are used to give the processing factors unless the data vary considerably – only then is a third trial required. In the trials presented additional variability was introduced by processing duplicate samples. RMS: agrees with the applicant. Even if considering these 4 subsamples as representing only 2 trials, the requirement on OECD 508 is still fulfilled. Point is considered addressed.	Open point: RMS and recalculate PF and CF considering that only two studies (each with 2 sampling replicate values) were conducted. The RAR and LoEP shall be revised accordingly.
3(75)	Vol. 3, B.7.5.3, study by Mayer T. (2010a), page 203	Co-RMS (LV): No comments	RMS: Noted.	
3(76)	Vol. 1, Level B.7.6 Summary of effects on processing	EFSA: The validity of the processing trials in wheat and barley and PFs/CFs can only be verified when clarification of questions and submission of further information as identified during the commenting of the RAR become available. For the time being review for completeness and correctness is not possible.	Applicant: Noted. RMS: Noted. Please also see 3(70)	See 3(13), 3(38), 3(70), 3(71), 3(74), 3(80) and Experts' consultation 2

section 3 – Residue data

Residues in rotational crops				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(77)	Vol. 3, B.7.6.1. Metabolism in rotational crops (study 1)	EFSA: RMS concluded that the rotational crop study assessed under Directive 91/414 was acceptable. This study was underdosed (0.75N) and conducted according to US-EPA guidance. Evidence of equivalence to current data requirements (OECD 502) should be provided.	Applicant: The new study was carried out to current guidance and to cover a higher application rate. The old study was submitted for completeness. RMS: The applicant position is to consider this study as supplementary only. As this study conducted within 25% rule and provides at least some information on metabolism in rotational crops and was considered acceptable by RMS NL(2003), results are in line with the new study, RMS position would be to consider this “old” study at least partially acceptable. Open point: RMS to provide evidence of equivalence to current data requirements (OECD 502) in a revised RAR.	Open point: RMS to provide evidence of compliance of the rotational crop metabolism studies submitted to OECD 502 and to conclude on acceptability and that metabolism of trinexapac- ethyl in rotational crops is appropriately addressed. The RAR and the LoEP shall be revised accordingly. See Experts’ consultation 1

section 3 – Residue data

Residues in rotational crops				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(78)	Vol. 3, B.7.6.1, study by Quistad G.B., Kovatchev A. (2010), page 230	Co-RMS (LV): In results section it's stated: " <i>Total residues determined by initial combustion and sum of fractions in rotational crop RACs are given in Table A3.12-2</i> ". Table A3.12.-2 doesn't exist. In the same paragraph, fourth line, please correct "Tables B.7.6.1-3 to B.7.6.1-x" to "Tables B.7.6.1-3 to B.7.6.1-5".	Applicant: We believe there is some confusion with versions of the dRAR Volume 3 CA_B7_2017. The version on the EFSA web site is 2017-03-31 and this mentions Table B7.6.1-3 – rather than A3.12-2". The table numbers also read correctly in the 2017-03-31 version. The co-RMS (LV) may have been referring to an earlier dRAR version. RMS: Agrees with the applicant. All mentioned table numbers are correct in the version on the EFSA web site (2017-03-31). Point is considered addressed.	Addressed.
3(79)	Vol. 3, B.7.6.2 Magnitude of residues in rotational crops and Vol.1, Level 2.7.7 Summary of residues in rotational crops	EFSA: For sake of transparency, please report that the new confined rotational crop study was conducted at 1.5N (300 g/ha instead of 200 g/ha) the maximum rate of the representative crops (barley).	Applicant: Noted. RMS: Agreed. Open point: RMS to amend the text in a revised RAR.	Addressed. RMS committed to amend the RAR accordingly.

section 3 – Residue data

Residues in rotational crops				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(80)	LOEP p22 and p32	FR: in Vol.1 is stated that the RD for processed commodities is in line with the RD for raw commodities. So it is concluded that no specific RD is proposed for processed commodities. This information should clearly be mentioned in LOEP (p22 and p32).	Applicant: Noted. RMS: Noted. Open point: RMS to add clarifications in LoEP (p22 and p32)	See 3(38) and Experts' consultation 2
3(81)	Vol 1 Level 3 3.1.4.7 Residue data	Applicant: RMS: According to information from the applicant, magnitude of metabolite CGA113745 in processed barley and wheat commodities studies are currently on-going. Interim reports provided. Anticipated date of completion – not stated. Applicant: These studies are completed and are available for CGA113745 and CGA313458 (CGA313458_10011 for wheat and CGA313458_10010 for barley). These studies also include storage stability data. For completeness the following processing studies are also available for CPCA (CGA224439): CA876_10003 (wheat) and CA876_10004 (barley).	RMS: Noted. Data requirement: Applicant to provide magnitude of metabolite CGA113745 and CGA313458 in processed barley and wheat commodities studies. Open point: RMS to evaluate these studies and report in a revised RAR.	Data requirement: Applicant to provide magnitude of residues of the metabolite CGA113745 and CGA313458 in barley and wheat processed commodities. Open point: RMS to evaluate these studies in a revised RAR.
3(82)		FR: No comment	RMS: Noted.	

section 3 – Residue data

Summary of other studies				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(83)	Vol 1; Level 2.7.8. Summary of other studies	EFSA: Although cereals are considered of low attractiveness to bees for pollen/nectar, data indicate translocation of the residues throughout the plant parts as attested by residues observed in cereals (TRR 1.4 mg eq/kg in metabolism at 1N; highest residue trinexapac (free and conjugated) 1.1 mg/kg in residue trials). Therefore, data to exclude of pollen/nectar collection by bees as required in the EFSA guidance on the risk assessment of PPP on bees need to be addressed. The argument that not agreed test method or guidance is available is not considered a valid justification.	Applicant: A Honey residue study is in progress and will be available during first quarter 2018. RMS: Since according to EFSA The argument that no agreed test method or guidance is available is not considered a valid justification, the applicant should provide a justification as to address this point. Data requirement: Applicant to provide residue study in honey. Open point: RMS to evaluate this study and report in a revised RAR.	Data requirement: Applicant to provide the residue study in honey. Open point: RMS to evaluate the study on honey in a revised RAR.
3(84)		FR: No comment	RMS: Noted.	
3(85)		Co-RMS (LV): No comments	RMS: Noted.	

Estimation of the potential exposure through diet and other sources				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(86)	Vol 3 CA B-7	Applicant: No chronic risk assessments for trinexapac-ethyl have been presented, refer to page 36 of MCA-section 6 and Appendix 2	RMS: Noted.	Addressed.

Estimation of the potential exposure through diet and other sources				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(87)	Vol.1 2.7.5 (Table 2.7.10-1)	FR: in the tables, please add the residue definition considered.	Applicant: The RMS to add. RMS: Noted. Open point: RMS to add residue definition considered in table 2.7.10-1.	See 3(91)
3(88)	Vol. 1, Level 2.7.9 Estimation of potential and actual exposure throughout the diet and other concerns	EFSA: The consumer risk assessment for trinexapac acid is pending clarification of questions and submission of further information as identified during the commenting of the RAR, in particular with regards to the levels and toxicological relevance of metabolites observed in plants, livestock and processed products.	Applicant: Noted. RMS: Noted, see also 3(41).	See Experts' consultation 2

Estimation of the potential exposure through diet and other sources				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(89)	Vol. 1, Level 2.7.9 Estimation of potential and actual exposure throughout the diet and other concerns	EFSA: For acute/chronic risk assessment of the processing metabolite CPCA, the TTC concept comparing predicted dietary exposure levels through processed products from cereals treated according to representative uses with a threshold (Cramer II, 1.5 µ/kg bw) is not acceptable. There is currently not implemented guidance on the subject tool and the metabolites is common to other a.s.	Applicant: The applicant does not understand why this approach is now considered unacceptable as it was first suggested by EFSA, gives a very conservative endpoint, which in this case results in a very low risk assessment for the consumer. Please advise how we should proceed. RMS: EFSA please advise how acute/chronic risk assessment of the processing metabolite CPCA should be assessed. Open point.	See Expert consultation 2. Since the EFSA PPR GD (2016) guidance on the residue definition is not yet adopted by Member States and the Commission, it cannot be used to assessment the risk for of dietary metabolites. To perform a comprehensive dietary risk assessment, the toxicological relevance and the magnitude of residues of CPCA in the relevant commodities for the representative uses should be established. See 2(53)
3(90)		Co-RMS (LV): No comments	RMS: Noted.	

section 3 – Residue data

Proposed MRLs and compliance with existing MRLs				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(91)	Vol.1 2.7.5 (Table 2.7.10-1) LOEP p34	FR: in the tables, please add the residue definition considered.	Applicant: The RMS to add. RMS: Noted. Open point: RMS to add the residue definition considered in table 2.7.10-1 and LoEP p34.	Addressed. RMS committed to add the residue definition considered in table 2.7.10-1 of Vol 1 and in the LoEP.
3(92)	Vol. 1, Level 2.7.10	EFSA: The proposed MRL values and residue definitions in cereals can be verified when a confirmation of a complete set of valid and independent trials with samples analysed according to the residue definition for enforcement and risk assessment is available and meets currently applicable guidance for AIRIII.	Applicant: A complete set of valid and independent trials with samples analysed according to the residue definition for enforcement have been supplied. The proposed DOR for RA included SYN548584 which cannot be synthesised and therefore not measured in residue or processing trials. If SYN548584 remains in the DOR for RA then estimates of possible residue levels based on the metabolism study will be necessary. RMS: A complete set of valid residue trials with samples analysed according to the residue definition for enforcement have been provided. Due to the independency of these trials please refer to 3(58). Samples could not be analysed according to the proposed residue definition for risk assessment as analytical standards for metabolite SYN548584 are not available, also see 3(57).	See 3(4), 3(13), 3(58) and Experts' Consultation 2

section 3 – Residue data

Proposed MRLs and compliance with existing MRLs				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed.	
3(93)		Co-RMS (LV): No comments	RMS: Noted.	

Proposed import tolerances and compliance with existing import tolerances				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(94)		FR: No comment	RMS: Noted.	
3(95)		Co-RMS (LV): No comments	RMS: Noted.	

section 3 – Residue data

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(96)	Vol. 3, B7, paragraph 5	NL: it is reported in the text that the literature search is provided in Appendix III, but in reality this is Appendix I.	Applicant: Agreed – Text has been carried over from an earlier version where there were 3 Appendices. RMS: Indeed, the correct reference is Appendix I. Open point: RMS to correct reference in a revised RAR.	Addressed. RMS committed to report the correct reference in a revised RAR.
3(97)	Vol. 3, B.7.8 Reference relied on. Literature search and Appendix I Literature data	RMS is asked to confirm that the open literature found by the applicant during the rapid assessment has been screened and none was of potentially relevant or unclear for relevance (no details reported also in the literature search available on the "K"-drive).	Applicant: Noted RMS: All information provided by the applicant is included in Appendix I. No additional data on literature found by the applicant during the rapid assessment was provided and screened by RMS. RMS cannot confirm if any of them were potentially relevant or unclear for relevance, all findings were excluded as being "obviously irrelevant records" based on titles. Data requirement: Applicant to provide more details on the assessment of literature search.	See 3(98)

section 3 – Residue data

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(98)	Vol. 3, B.7.8 Reference relied on. Literature search and Appendix I Literature data	EFSA: Literature search on major metabolites identified in plants such as hydroxylated trinexapac acid (SYN548584) and CGA 275537 was not conducted. It seems that the search was done combining a.s. with the metabolites plus main categories (e.g. METABOL? OR RESIDUE). Thus, limiting the records found. Please provide clarification regarding the exclusion criteria and strategy applied in the literature search.	Applicant: An additional Literature search will be carried out including SYN548584 and CGA275537 and additionally CGA329773 CGA351210 SYN540405 NOA433257 SYN540406 CGA300405 This data will be provided during the stop-the clock period. Exclusion criteria are noted in RMS: Criteria for relevance are listed in Appendix1 dRAR Volume 3 B-7 although not specified which were used for exclusion of found records. Data requirement: Applicant to provide literature search results for the above mentioned metabolites and more clarification regarding the exclusion criteria and strategy applied in the literature search.	Data requirement: Applicant to carry out more extensive literature search involving additional metabolites as proposed and combining different terms with the metabolites. Results for all potentially relevant or unclear for relevance of the open literature and inclusion/exclusion criteria to be documented. Open point: RMS to assess appropriateness of the methodology and the results of the open literature research conducted by the applicant in a revised RAR.

section 3 – Residue data

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(99)	LoEP. Section 3 Residue pattern in processed commodities	EFSA: it is reported that metabolite CGA224439, included in the table summing up results of the hydrolysis study (see p. 21) was not included in "standard reference compound lists". The remark is not clear. Nevertheless, in principle the lists should include all cited compounds.	Applicant: CGA224439 was included in the submitted N3 document of the supplementary dossier. RMS: With this remark RMS wanted to highlight that in one processing study trinexapac-ethyl was radiolabeled in the different position than in metabolism studies, and only in this study metabolite CGA224439 was measured. This metabolite was not included in "standard reference compound lists" in provided metabolism studies, therefore it is not clear if this metabolite was not found in metabolism studies because it was not present, or it was not found because it was not searched for. Addressed.	Addressed. RMS is kindly requested to verify the relevance of reporting the remark "CGA224439 was not included in standard reference lists" reported in the section "Residue pattern in processed commodities similar to residue pattern in raw commodities" after the end of the Table summarising processing studies in Section 3 of LoEP). The metabolite CGA224439 (Cyclopropane carboxylic acid) is included in the list of compound codes of the LoEP.
3(100)	LoEP Section 3 Stability of residues (p. 24)	EFSA: LoEP to be amended by including the matrix "eggs" as per template LoEP (SANCO/12483/2014 rev. 3)	Applicant: The RMS to amend. RMS: Agreed. Open point: RMS to include matrix "egg" as per template LoEP (SANCO/12483/2014 rev. 3)	Addressed. RMS committed to include an additional row for "eggs" in the LoEP (Section 3, Stability of residues).
3(101)		FR: No comment	RMS: Noted.	
3(102)		Co-RMS (LV): No comments	RMS: Noted.	

section 4 – Environmental fate and behaviour

4. Environmental fate and behaviour

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(1)		LV: Section not reviewed, no comments	-	Noted.
4(2)	Vol. 3 – B.8 (A.S), B.8, Fate and behaviour in the environment	Applicant: Page 6, Table 8-1, WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	LT: Table updated. Addressed.	Open point: RMS to provide an amended RAR clarifying that metabolite WaterM3Hydrolysis has been identified as SYN549299 and giving further details. The name of this metabolite should be used consistently in the whole RAR and also in the LoEP. See also comments 4(39), 4(40) and 4(41).
4(3)	Vol. 3 CA, 8.1	NL: as a general comment, it is noted that no acidic soil has been selected in the degradation test. Is the soil selection criterion in accordance with the relevant recommendations in OECD 307?	Applicant: The Applicant confirms that the soils used in all the aerobic soil degradation studies do not have pH values measured under 6.0; however, all the soils used in the aerobic degradation studies comply with the OECD guidance which recommends that the pH values are selected between 5.5 and 8.0. When analysing the whole data set supplied in the dossier for the degradation rates, there is no indication that the rates obtained are dependent of the pH and therefore the soils presented in the	Data requirement: Applicant to provide for parent compound and metabolites degradation studies using acidic soils.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			latest submission are appropriate for use in the risk assessment. LT: RMS agrees with the applicant. Addressed.	
4(4)	Vol. 3, B.8 (CA), 8.1.1.1 Degradation of the active substance in aerobic soil, Spare 1992a, p 17	EFSA: Soil bacterial biomass was determined pre-dosing to be $>3 \cdot 10^8$ CFU/g (first aerobic incubation) and after 90 days of aerobic incubation soil bacterial biomass was $>3.0 \cdot 10^8$ CFU/g. It seems strange that after 90 day the bacterial biomass did not change. Please, check the values.	Applicant: The technique used for the determination of total bacterial biomass was not quantitative enough to provide a definitive biomass value, but only a greater than value. Therefore, it cannot be concluded that the biomass did not decline, as would be expected in a laboratory incubation. The important point is that the microbial viability is sufficient at the end of the incubation for the degradation potential to be retained. Indeed, when directly comparing the viable samples with the sterile samples in the experiment, results clearly show a significantly higher biomass, therefore validating the study outcomes. LT: Following values are provided in the original study report. More detailed explanation is provided by the applicant.	See open point in comment 4(10).

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed.	
4(5)	Vol. 3, B.8 (CA), 8.1.1.1 Degradation of the active substance in aerobic soil, Hellstern 2008, p 19 List of endpoints, Route of degradation (aerobic) in soil, p 35	EFSA: High percentage of non-extractable residues was found in the study by Hellstern 2008. For extraction it was used the same method as in Mamouni 2000, which was questioned already in the first evaluation. Therefore, more clarifications on the extraction method used should be provided.	Applicant: The Applicant would like to highlight that the Hellstern (2008) aerobic soil degradation study was carried out as an Annex II study and that, at the time, the Mamouni (2001) study was the most up to date experiment available from the DAR published in 2005. Therefore, the same protocol and the same extraction method were used in these two studies. The Task Force recognise that there is uncertainty arising with the levels of non-extractable residues in the Mamouni (2001) study, and therefore the Hellstern (2008) study. As a result, it was decided in conjunction with the RMS not to use the study for deriving endpoints for trinexapac-ethyl and CGA179500. However, the study is still considered fit for purpose in assessing the route of degradation of trinexapac-ethyl and CGA179500. LT: More clarification is provided by the applicant.	Addressed.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed.	
4(6)	Vol. 3 – B.8 (A.S), B.8.1.1.1, Degradation of the active substance in aerobic soil	Applicant: Page 25 the Applicant would like to comment that even though DT ₅₀ values originating from the Hellstern (2008) study are considered unreliable due to the amount of non-extractable residues (referred in the rest of this document as NER), the study is still considered fit for purpose in assessing the route of degradation of trinexapac-ethyl.	LT: Noted. RMS agrees with the applicant that study can be used for the evaluation of the route of degradation of trinexapac-ethyl. Data from Hellstern (2008) were used for route of degradation in soil and were included in the LoEP (please see LoEP, p 35). Addressed.	Addressed.
4(7)	Vol. 3, B.8 (CA), 8.1.1.1 Degradation of the active substance in aerobic soil, Adam 2014, p 25 List of endpoints, Route of degradation (aerobic) in soil, p 35	EFSA: In the comment concerning the study by Adam (2014) it was reported that not validated extraction methods were used. High percentage of non-extractable fraction was detected at first sampling point for 18 Acres and Sarpy soils. It was explained that current extraction procedure was improved, however more clarifications on the improvement should be provided. It is not clear to which selected samples the last extraction method was applied.	Applicant: The Applicant would like to share additional information which was provided to the RMS when comments were made in the first draft version of the dRAR:  Non extractable residues document In this document, there are more details on the different extraction methods used in the three aerobic degradation studies Hellstern (2008), Adam (2014) and Walther (2008). The document also provides more information on the extraction efficiency for all the methods compared. After sharing the document with the RMS,	Open point: RMS to provide an amended RAR including additional information on the different extraction methods used in the aerobic degradation studies by Hellstern (2008), Adam (2014) and Walther (2008).

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			it was agreed with the Task Force that due to the unexplained high percentage of non-extractable residues present in the first sampling points for the 18 Acres and the Sarpy soils, they would not be considered reliable to generate endpoints for parent and metabolite CGA179500. The Gartenacker, the East Anglia and the Capay soils on the other hand were deemed reliable. With regards to the last extraction method, GRM020.03A, it was not applied to any soils degradation studies. GRM020.03A is a monitoring method for the determination of the active substance and/or metabolites in soil, and is presented in document Vol. 3, CA B.5.2.3 – Method for the determination of residues in soil. LT: More clarification is provided by the applicant. Addressed.	
4(8)	Vol. 1, 2.8.1 Summary of fate and behaviour in soil	Applicant: Page 117 the Applicant disagrees with the modelling soil endpoint derived by the RMS for trinexapac-ethyl. Please refer to point (10) of this table for further details.	LT: RMS agrees with the applicant, endpoint updated. Addressed.	See open point in comment 4(10).

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(9)	Vol. 1, 2.8.5 Definition of the residues in the environment requiring further assessment	Applicant: Page 122 the Applicant does not agree with the definition of residue for soil and surface water. CGA300405 should not be assessed in soil, while CGA275537 should not be assessed in soil or surface water. Please see point (16) of this table more further details. Therefore the Applicant does not believe exposure calculations should be calculated in soil for metabolites CGA300405 and CGA275537 and in surface water for CGA275537.	LT: Noted, however RMS is still of the opinion that metabolites CGA300405 and CGA275537 should be assessed in soil and surface water, since they both were found >10% in soil photolysis study. Addressed.	Addressed. See comment 4(23).
4(10)	LoEP, Section 4, Rate of degradation in soil (aerobic) laboratory studies active substance	Applicant: Page 36 the Applicant disagrees with the endpoint derived by the RMS for trinexapac-ethyl. The two values obtained in the Spare (1990) study originate from the same soil (Maryland) and therefore should be pre-geomeaned prior to any further averaging with the rest of the values. As a result, the final geometric mean DT₅₀ value for trinexapac-ethyl should be 0.14 days. The difference in the calculations is not significant and does not impact the overall risk assessment but the value should however be updated for completeness.	LT: RMS agrees with the applicant, LoEP updated. Addressed.	Open point: RMS to provide an amended RAR and LoEP deleting the degradation endpoints derived from the second incubation of Maryland soil in the study by Spare (1992a), because it cannot be concluded that the biomass did not decline and the storage time for the second aerobic incubation was too long and at high temperature (2 months at 25°C). Therefore the geometric mean DT₅₀ value for trinexapac-ethyl will be 0.13 days.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
				See also comment 4(4).
4(11)	Vol. 3 – B.8 (A.S), B.8.1.1.1, Degradation of the active substance in aerobic soil	Applicant: Page 36, the Applicant would like to highlight that regardless of the viability of the soils in the study, which remains to be demonstrated, levels of trinexapac-ethyl were very low while NER levels did not go above 6%. This demonstrates that the extraction methods are fit for purpose.	LT: Noted, however RMS is still of the opinion that applicant argumentation is not suitable and not scientifically justified, since during photolysis study microbial biomass was not measured and the slow degradation indicate that soils were not viable. Addressed.	Noted.
4(12)	Vol. 3, B.8 (CA), 8.1.1.1 Degradation of the active substance in aerobic soil, Walther 2008, p 37 List of endpoints, Route of degradation (aerobic) in soil, p 35	EFSA: High percentage of non-extractable fraction detected at early sampling points. Extraction method similar to Mamouni (2001) was used, which was questioned during previous evaluation. More clarification on the extraction method used should be provided.	Applicant: The Applicant would like to highlight that the Walther (2008) aerobic soil degradation study was carried out as an Annex II study and that, at the time, the Mamouni (2001) study was the most up to date experiment available from the DAR published in 2005. Therefore, the same protocol and the same extraction method were used in these two studies. The Task Force recognise that there is uncertainty arising with the levels of non-extractable residues in the Mamouni (2001) study, and therefore the Walther (2008) study. As a result, it was decided in conjunction with the RMS not to use the study for deriving endpoints for trinexapac-ethyl and CGA179500.	Addressed.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			However, the study is still considered fit for purpose in assessing the route of degradation of trinexapac-ethyl and CGA179500. LT: More clarification is provided by the applicant. Addressed.	
4(13)	Vol. 3 – B.8 (A.S), B.8.1.1.1, Degradation of the active substance in aerobic soil	Applicant: Page 37, the Applicant would like to highlight that the extraction methods are fit for purpose, but that high levels of NER were still observed in the 18 Acres and Sarpy soils. These levels could not be explained and therefore the uncertainty with regards to generating reliable DT ₅₀ for parent and metabolite CGA179500 in the 18 Acres and Sarpy soils is unacceptable. However, it is worth pointing out that the DT ₅₀ values obtained for 18 Acres and Sarpy are consistent with the reliable values obtained with other soils, which substantiates the fact that NER do not contain any trinexapac-ethyl nor CGA179500 and therefore do not play a role in determining degradation values for these two compounds.	LT: Noted, however the outcome of the risk assessment is not changed, 18 Acres and Sarpy soils were excluded from the DT₅₀ determination. High level of non-extractable residues were detected at first sampling point for 18 Acres and Sarpy soils, what indicate that extraction method was insufficient for these soils. What means that DT₅₀ values are not reliable and may be underestimated. Therefore DT₅₀ values obtained for 18 Acres and Sarpy were excluded from the risk assessment. Addressed.	Addressed.
4(14)	Vol. 3 – B.8 (PPP), 8.1.1.1, Laboratory	Applicant: Page 6, the Applicant would like to highlight that even though there are high	LT: See RMS comment 4(13).	Addressed. See comment 4(13).

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	studies	levels of NER observed in the 18 Acres and Sarpy soils for the Adam (2014) aerobic degradation study, the half-life values obtained for the two soils are consistent with the reliable values obtained with the other soils from the study, which substantiates the fact that NER do not contain any trinexapac-ethyl nor CGA179500 and therefore do not play a role in determining degradation values for these two compounds in the Adam (2014) aerobic degradation study.	Addressed.	
4(15)	List of endpoints, Rate of degradation in soil (aerobic) laboratory studies active substance, p 36	EFSA: the pH values reported for Loam (Gartenacker) and Sandy Clay Loam (18 Acres) soils from the study by Adam (2014) are not the same as the ones reported in Vol. 3, B.8 (CA) (Table 8.1.1.1-21, p 26). The correct values should be 7.2 and 6.47 respectively. Please, correct the LoEP.	LT: The values have been corrected. Thank you. Addressed.	Open point: RMS to provide an amended LoEP correcting the pH values for Loam (Gartenacker) and Sandy Clay Loam (18 Acres) soils from the study by Adam (2014) in order to be consistent the values reported in Vol. 3, B.8 (CA) (Table 8.1.1.1-21, p 26). The correct values should be 7.2 and 6.47 respectively.
4(16)	Vol. 3 – B.8 (A.S), B.8.1.1.1, Degradation of the active substance in aerobic soil	Applicant: Page 42-43 the Applicant would like to comment that even though DT ₅₀ values originating from the Walther (2008) study are considered unreliable due to the amount of non-extractable residues, the study is considered fit for purpose in assessing the route of degradation of trinexapac-ethyl.	LT: Noted. RMS agrees with the applicant that study can be used for the evaluation of the route of degradation of trinexapac-ethyl. Data from Walther (2008) were used for route of degradation in soil and were included in the LoEP (please see LoEP, p 35).	Addressed.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed.	
4(17)	Vol. 3 – B.8 (A.S), B.8.1.1.2, Anaerobic degradation	Applicant: Page 53 the Applicant would like to comment that the lack of reliable DT ₅₀ values originating for the Volkel (2014) study stems from the protocol of the study where there is an aerobic phase prior to the anaerobic phase, in which most of the parent must have degraded. The extraction method used is the same method that was used in the Adam photolysis study and the Adam aerobic degradation study, which is fit for purpose.	LT: Noted. Addressed.	Noted.
4(18)	Vol. 3 – B.8 (PPP), 8.1.1.1, Laboratory studies	Applicant: Page 6 the Applicant would like to mention that a rate degradation study was carried out for metabolite CGA275537. Results confirm that, as expected and highlighted in the Applicant's dossier, the half-life of CGA275537 is very short and comparable to metabolite CGA300405 (< 0.25 day). The data, alongside a FOCUS kinetics assessment, is available and can be found in the latest version of the Caddy supplied to the EFSA, the RMS and other MSs at the end of April 2017.	LT: Noted. Data requirement: applicant to provide degradation study and FOCUS kinetics for metabolite CGA275537.	Data requirement: Applicant to provide the degradation rate study and the FOCUS kinetic assessment for metabolite CGA275537. Furthermore, applicant to update the exposure assessment for metabolite CGA275537. Open point: RMS to evaluate the degradation rate study, the FOCUS kinetic assessment and the updated exposure assessment for metabolite CGA275537 and to provide an

section 4 – Environmental fate and behaviour

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
				amended RAR and LoEP including all new information.
4(19)	Vol. 3 – B.8 (PPP), 8.1.1.2.1, Soil dissipation studies	Applicant: Page 7 the Applicant would like to mention that a rate degradation study is available for metabolite CGA275537 and it confirms that the half-life values are well below the 60 day threshold to trigger field dissipation studies, therefore no data will be submitted under this section.	LT: Please, see response to 4(18).	Noted.
4(20)	Vol. 3 – B.8 (PPP), 8 Fate and behaviour in the environment	Applicant: Page 8, the Applicant disagrees with the definition of residue for soil and surface water highlighted in Table 8-3. CGA300405 should not be assessed in soil, while CGA275537 should not be assessed in soil or surface water. Please see point (23) of this table more further details.	LT: Please, see response to 4(23).	Addressed. See comment 4(23).
4(21)	LoEP, Residues requiring further assessment	Applicant: Page 47 the Applicant disagrees with the definition of residue for soil and surface water. CGA300405 should not be assessed in soil, while CGA275537 should not be assessed in soil or surface water. Please see point (23) of this table more further details.	LT: Please, see response to 4(23).	Addressed. See comment 4(23).
4(22)	Vol. 3, CP, B.8.1.1.3, Soil photolysis, KCA	DE: We support the classification by the RMS, that CGA275537 and CGA300405 are relevant	Applicant: Noted. The applicant also agrees that levels of CGA300405 will depend on	Addressed.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	7.1.1.3/02	photolysis transformation products according to the data in Adam (2015). Further explanations Both under dry and moist conditions, CGA275537 had lower occurrences in the dark control (max. 2.6 % and 0.8 %, respectively) than under irradiated conditions (max. 10.8 % and 6.5 %, respectively). Hence, CGA275537 can be regarded as a relevant photolysis transformation product. Under dry conditions, CGA300405 had lower occurrences in the dark control (max. 1.2 %) than under irradiated conditions (max. 12.5 %). Hence, CGA300405 can be regarded as a relevant photolysis transformation product. Under moist conditions, CGA300405 had low occurrences both in the dark control (max. 1.5 %) and under irradiated conditions (1.5 %). This might be due to biodegradation of CGA300405 under moist conditions.	the moisture content of the soil. However, please see point 4(23) of this table with regards to the Applicant's opinion on the relevance of CGA3004050 and CGA275537 in soil and the relevance of CGA275537 in surface water. LT: Noted. Addressed.	See comment 4(23).
4(23)	Vol. 3 – B.8 (A.S), B. 8.1.1.3.1, Overall conclusion on soil photolysis	Applicant: Page 69-70 the Applicant agrees with the RMS's comments on the microbial activity of the Gartenacker soil in the soil photolysis experiment. In dark moist conditions, degradation of metabolite CGA179500 should have been observed. Since this did not occur,	LT: Noted, however RMS is still of the opinion that both CGA275537 and CGA300405 are relevant photolysis transformation products and should be included in the definition of residues for the risk assessment. Metabolites	Addressed. Note: metabolites CGA275537 and CGA300405 are relevant soil photolysis transformation products, therefore, according to the new data requirements they should be

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		it is reasonable to assume that the microbial activity was not optimal or indeed maintained during the extent of the study. It is therefore not possible to conclude that metabolite CGA179500 is formed <i>via</i> microbial degradation only. However, page 70 the Applicant does not agree that “risk assessment in soil and groundwater should be provided for both CGA275537 and CGA300405 metabolites”. Since it is likely that the microbial activity is not optimal in the soil photolysis experiment, it substantiates the claim that under realistic conditions, that is to say in moist, aerobic conditions with full microbial capacity, CGA300405 and CGA275537 are unlikely to be formed over 5%, and therefore at levels of concern. The Applicant agrees that the conservative position of assessing CGA300405 and CGA275537 in groundwater might be necessary to reach a high degree of confidence that these won't indeed leach to groundwater – however, due to the very short half-life values of CGA300405 and CGA275537 (all the measured values are <0.25 day in three soils	CGA300405 and CGA275537 were found >10% in soil photolysis study. Addressed.	assessed in soil and surface water and sediment. Therefore, PECsoil and surface water calculations are necessary for these two metabolites.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		for both metabolites), it is reasonable to assume that, if ever formed under realistic conditions, their soil exposure would be negligible. As a result, CGA300405 and CGA275537 are not of concern in soil. Due to its very low half-life, CGA275537 soil exposure and therefore its surface water is negligible. Consequently, CGA275537 is not of concern in surface water. In addition, in the unlikely event that CGA275537 is ever formed under realistic conditions, the metabolite would only reach surface water via run-off or drainage as it was solely observed in the soil photolysis experiment. CGA300405 on the other hand was observed >10% AR in the direct photolysis experiment, and for that reason is assessed in surface water.		
4(24)	Vol. 3 CA, 8.1.2.1.1 Aerobic degradation of the active substance	NL: In Table 8.1.2.1.1-5 (page 75), should SFO be considered acceptable for trinexapac acid ?	Applicant: Noted, although the Applicant would like to point out that SFO could be considered acceptable. LT: The fit for trinexapac acid was considered not acceptable because of poor visual fit. However in respect to comments in points 4(24) and 4(29)	Open point: RMS to provide an amended RAR and LoEP adding persistence endpoint derived using SFO model for metabolite trinexapac (CGA 179500) in the Gartenacker (Adam 2014) soil. See also comment 4(29).

section 4 – Environmental fate and behaviour

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			RMS considered SFO acceptable for trinexapac acid. Data for this soil were included in the List of Endpoints. Addressed.	
4(25)	Vol. 3, B.8 (CA), 8.1.2.1.1 Aerobic degradation of the active substance, Terry 2015, p 76	EFSA: In the figure showing the graphs of the different kinetic models applied for deriving persistence endpoints to the Gartenacker (Adam 2014) soil, the y axis for FOMC seems to have an order of magnitude different from the order graphs.	Applicant: Noted. Day 0 was optimised by Cake to 3630 using the appropriate soil concentrations and the scale was reported as suggested by the program – the fit was rejected during the kinetic evaluation. LT: explanation was provided by applicant, no further explanation is required. Addressed.	Addressed.
4(26)	Vol. 3 CA, 8.1.2.1.1 Aerobic degradation of the active substance	NL: In Table 8.1.2.1.1-8 (page 77), the results of DFOP fitting for trinexapac-ethyl can be removed since FOMC is rejected and SFO is acceptable.	LT: Agree with the comment, DFOP fitting was removed. Addressed.	Addressed. RMS to remove the results of DFOP fitting for trinexapac-ethyl in Table 8.1.2.1.1-8 (page 77) in Vol. 3 (CA). This action is needed according to SANCO/10180/2013-rev.1
4(27)	Vol. 3, CP, B.8.1.2.1.1, Aerobic degradation, KCA 7.1.2.1.1/01 KCA 7.1.2.1.1/02 KCA 7.1.2.1.2/02	DE: The t-test or confidence intervals should not be applied to alpha or beta values of a FOMC fit. Further explanations	Applicant: Noted. LT: Noted. Addressed.	Open point: RMS to provide an amended RAR deleting the t-test or confidence intervals for alpha or beta values of FOMC fit in studies KCA 7.1.2.1.1/01,

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Vol. 3, 8.2.2.3 Water/sediment studies, KCA 7.2.2.3/02	FOCUS Deg. Kin.: <i>"Note that this application of the t-test, while applicable for rate constants, may not be appropriate for all model parameters. For example, with FOMC smaller values of beta indicate more rapid degradation, and alpha only indicates the shape of the curve and has nothing to do with the rate of degradation."</i> Recently, the application of the t-test has also been criticised for other kinetics. See Ranke & Lehmann (2015) (poster on conference in Piacenza; link: chem.uft.uni-bremen.de/ranke/posters/piacenza_2015.pdf)		KCA 7.1.2.1.1/02, KCA 7.1.2.1.2/02, KCA 7.2.2.3/02.
4(28)	LoEP, Section 4, Rate of degradation on soil (photolysis) laboratory active substance	Applicant: Page 40 the Applicant would like to highlight that the two indicative rates reported were obtained in a dry irradiated experiment (DT ₅₀ of 5.7 days) and a moist irradiated experiment (DT ₅₀ of 0.7days).	LT: clarification added. Addressed.	Open point: RMS to provide an amended LoEP specifying that the two indicative rates of degradation on soil photolysis reported for trinexapac-ethyl were obtained in a dry irradiated experiment (DT ₅₀ of 5.7 days) and in a moist irradiated experiment (DT ₅₀ of 0.7days).
4(29)	Vol. 3, B.8 (CA), 8.1.2.1.1 Aerobic degradation of the active substance, Terry 2015, p 76	EFSA: it is not clear why a persistence endpoint was not derived for metabolite trinexapac acid in the Gartenacker (Adam 2014) soil.	Applicant: please see response in point 4(24). LT: please see RMS comment in point	See open point in comment 4(24).

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			4(24). Addressed.	
4(30)	Vol. 3, B.8 (CA), 8.1.1 Route and rate of degradation in soil	EFSA: The molecular structures of trinexapac-ethyl and trinexapac acid could lead to the formation of isomers. Information on whether the different isomers of trinexapac-ethyl and trinexapac acid are degraded in soil at different rates is missing. Clarification on this point needs to be provided.	Applicant: The Applicant would like to highlight that both trinexapac-ethyl and trinexapac acid do not contain chiral centres because their chemical structures have planes of symmetry. As a result, neither molecules have stereoisomers. Both trinexapac-ethyl and trinexapac acid have constitutional and conformational isomers. However, these isomers are by definition in rapid dynamic equilibrium with one another and their ratios will vary with environmental conditions (such as temperature, solvation, pH, etc...) and cannot be considered as separate entities under biological test systems. As a result, the degradations of trinexapac-ethyl and trinexapac acid in soil presented in the submission are a true reflection of the degradations of the dynamic equilibrium of their isomers. LT: RMS agrees with the applicant. Addressed.	Addressed.

Route and rate of degradation in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(31)	List of endpoints, Rate of degradation in soil (aerobic) laboratory studies active substance and transformation products, p 36-38	EFSA: Where the rate of degradation endpoints result from a biphasic fit, the alpha, beta, k ₁ , k ₂ and g values should be reported in the list of endpoints.	Applicant: Noted. The Applicant would like to give the following information, relevant for the bi-phasic fits that were considered reliable by the RMS: - Gartenacker soil (Adam 2014) for persistence endpoints: DFOP fit, k₁ = 17.86, k₂ = 0.973 and g value = 0.9601 - East Anglia soil (Adam 2014) for persistence endpoints: DFOP fit, k₁ = 74.93, k₂ = 3.392 and g value = 0.7917 - East Anglia soil (Adam 2014) for modelling endpoints: FOMC fit, Alpha = 0.6894, Beta = 0.005458 Maryland I (Spare 1992) for persistence endpoints: FOMC fit, Alpha = 2.257, Beta = 0.4003 LT: LoEP updated. Addressed.	Open point: RMS to provide an amended LoEP adding the alpha, beta, k ₁ , k ₂ and g values as needed where the rate of degradation endpoints result from a biphasic fit.

Adsorption, desorption and mobility in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(32)	Vol. 3, CP, B.8.1.2.2.2, Adsorption and desorption of the active substance, KCA 7.1.3.1.1/01	DE: In the previous DAR (2003) it was concluded that sorption is pH dependent. The evaluation with the statistical Kendall Test of the German "Input Decision 3.4" did not confirm this conclusion, maybe due to the small number of data. On the other hand the diagrams of Input Decision suggest that sorption is slightly pH dependent. Further explanations Further adsorption studies with soil pH >7 were required by EFSA in 2003 already. Since such studies are still lacking, EFSA recommends to use the worst case K_{foc} values from the soil pH>7 as modelling endpoints for trinexapac-ethyl and trinexapac (See EFSA Scientific report 82005) 57, 1-70). PEC groundwater modelling is required with K_{foc} values for acidic and alkaline soils, due to pH dependence. However, therefore further adsorption studies with soil pH>7 are required.	Applicant: The Applicant agrees that sorption for trinexapac-ethyl and CGA179500 might be dependent on pH, and that the adsorption is expected to increase in decreasing soil pH. However, in the case of trinexapac-ethyl and CGA179500, an adsorption measurement was made at the pH value of 7.5. Since the pKa value for trinexapac-ethyl is 4.57 and the pKa values for CGA179500 are 3.93 and 5.32, parent and metabolite would be almost completely dissociated at pH = 7.5 and therefore the KFOC values reported in this soil are not going to differ significantly with increasing pH (to a recommended maximum of 8). Consequently, the minimum KFOC values obtained for parent and CGA179500 at pH = 7.5 can be considered worst case and used as such in the risk assessment. This position is more conservative than using a geometric mean obtained from acidic or alkaline soils in two separate assessments. This approach, which was presented in the original Annex 1 submission, was agreed by EFSA and the 2005 RMS. It appears in the EU LoEP for trinexapac-ethyl.	Data requirement: Applicant to provide adsorption studies with soil pH >7 for trinexapac-ethyl and trinexapac.

Adsorption, desorption and mobility in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			LT: RMS agrees with the applicant. Since PEC_{gw} were calculated with worst case K_{foc} value, it is considered by RMS that risk is covered for both acidic and alkaline soils. Addressed.	
4(33)	Vol. 3, B.8 (CA), 8.1.3.1.1 Adsorption and desorption of the active substance	EFSA: the study by Spare (1990) on the adsorption/desorption of trinexapac acid is reported under the paragraph concerning the active substance. However, trinexapac acid is a metabolites, and then it should be moved under paragraph 8.1.3.1.2 concerning the adsorption/desorption of metabolites.	LT: RMS agrees with the comment. Study summary was moved under paragraph 8.1.3.1.2. Addressed.	Open point: RMS to provide an amended RAR moving the study by Spare (1990) on the adsorption/desorption of trinexapac acid under paragraph 8.1.3.1.2.
4(34)	Vol. 3 – B.8 (PPP), 8.1.2.1, Laboratory studies	Applicant: Page 7 the Applicant would like to mention that a mobility study is available for metabolite CGA275537. As the report was only finalised in July 2017, it could not be included in the latest version of the Caddy but can be made available on request. Results confirm that, as expected and highlighted in the Applicant's dossier, the mobility of CGA275537 is high. Reliable K_{FOC} values range from 6 to 78 mL/g.	LT: Noted. Data requirement: applicant to provide adsorption study for metabolite CGA275537.	Data requirement: Applicant to provide the adsorption study for metabolite CGA275537. Furthermore, applicant to update the exposure assessment for metabolite CGA275537. Open point: RMS to evaluate the adsorption study and the updated exposure assessment for metabolite GA275537 and to

section 4 – Environmental fate and behaviour

Adsorption, desorption and mobility in soil

No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
				provide an amended RAR and LoEP including all new information.
4(35)		NL: no comments	-	Noted.
4(36)		LV: Section not reviewed, no comments	-	Noted.

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues

No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(37)	Vol. 3, B.8 (CA), 8.2.1.1 Hydrolytic degradation, Adam 2008, p 129	EFSA: it is reported that the hydrolysis of pure [¹⁴ C]-Trinexapac was studied in Adam (2008). However, the reported IUPAC name is: 4- cyclopropyl(hydroxyl)methylene-3,5- dioxo[3,5-14 C]cyclohexane[¹⁴ C]carboxylate which seems to be trinexapac-ethyl. Could the RMS clarify which was the tested substance?	Applicant: The Applicant would like to highlight that the IUPAC name 4- cyclopropyl(hydroxyl)methylene-3,5- dioxo[3,5-14 C]cyclohexane[¹⁴ C]carboxylate is probably a typo in the study. When checking the batch used in the hydrolysis study and comparing it to the certificate of analysis shown on page 63, it confirms that the correct compound was used in the experiment. LT: Clarification is provided by the applicant. Addressed.	Open point: RMS to provide an amended RAR correction the typo error of name IUPAC name of pure [¹⁴ C]-Trinexapac in the hydrolysis degradation study by Adam (2008).

section 4 – Environmental fate and behaviour

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(38)	Vol. 3 – B.8 (AS), B. 8.2.1.1 Hydrolytic degradation	Applicant: Page 134 the Applicant would like to highlight that the unknown metabolite in the Roulstone (2009) hydrolysis study was only observed >10% at 44°C and 50°C. At a relevant realistic temperature of 20°C, the levels of the unknown metabolite did not go over 6.8% AR.	LT: Noted, the amounts of unknown metabolite observed at all tested temperatures are provided in the summary table. Addressed.	Addressed.
4(39)	Vol. 3– B.8 (AS), B. 8.2.1.1.1 Summary Hydrolysis	Applicant: Page 135 the Applicant would like to highlight that WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	LT: Noted, document updated. Addressed.	See open point in comment 4(2). See also comments 4(40) and 4(41)
4(40)	Vol. 1, 2.8.2 Summary of fate and behaviour in water and sediment	Applicant: Page 119 the Applicant would like to highlight that WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	LT: Noted, document updated. Addressed.	See open point in comment 4(2). See also comments 4(39) and 4(41)
4(41)	LoEP, Section 4, Hydrolytic degradation	Applicant: Page 43 the Applicant would like to highlight that WaterM3Hydrolysis has now been identified as SYN549299 and should be referred as such.	LT: Noted, document updated. Addressed.	See open point in comment 4(2). See also comments 4(39) and 4(41)
4(42)	Vol. 3 – B.8 (AS), 8.2.1.3.1, Summary Photolysis	Applicant: Page 150, the Applicant would like to highlight that the OECD Guidelines for the Testing of Chemicals, Phototransformation of Chemicals in Water- Direct and Indirect Photolysis is a draft guidance and that the guidance in place at the time of submission was the OECD Guideline number 316.	LT: Noted, notification included. Addressed.	Addressed. RMS to clarify in an amended RAR that the guidance in place at the time of submission was the OECD Guideline number 316; this action is needed according to SANCO/10180/2013-rev.1.

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(43)	Vol. 3 – B.8 (AS), 8.2.1.3.1, Summary Photolysis	Applicant: Page 153, the Applicant agrees that both direct and indirect photolysis could happen concomitantly. However, by definition of its protocol, indirect photolysis represents a more realistic experiment than direct photolysis as aqueous sterile water, which is used as medium in aqueous direct photolysis, does not exist in the environment. Nevertheless, due to the uncertainty over the potential formation of direct photolysis metabolites CGA300405, M2 and WaterphotolysisM3, these are assessed in Document CP, Section 8.	LT: Noted. Addressed.	Noted.

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(44)	Vol. 3, B.8 (CA), 8.2.4 Impact on water treatment processes, p 167 Vol. 1, 2.14 Effect of water treatment processes on the nature of residues present in surface water, p 154	EFSA: Article 4 (approval criteria for active substances) 3. (b) of Regulation (EC) No 1107/2009 requires that 'it shall have no immediate or delayed harmful effects on human health, including that of vulnerable groups, or on animal health,....through drinking water (taking into account substances resulting from water treatment)'. Information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water has not been presented or discussed in the RAR.	Applicant: Noted, although the Applicant would like to highlight that there isn't at this time a guidance document on how to provide acceptable information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water. LT: Noted. Data requirement: Applicant to provide information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water.	Data requirement: Applicant to provide information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water. Open point: RMS to provide an amended RAR including information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water.

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(45)	Vol. 3, B.8 (CA), 8.2.1 Route and rate of degradation in aquatic system	EFSA: The molecular structures of trinexapac-ethyl and trinexapac acid could lead to the formation of isomers. Information on whether the different isomers of trinexapac-ethyl and trinexapac acid are degraded in aquatic systems at different rates is missing. Clarification on this point needs to be provided.	Applicant: The Applicant would like to highlight that both trinexapac-ethyl and trinexapac acid do not contain chiral centres because their chemical structures have planes of symmetry. As a result, neither molecules have stereoisomers. Both trinexapac-ethyl and trinexapac acid have constitutional and conformational isomers. However, these isomers are by definition in rapid dynamic equilibrium with one another and their ratios will vary with environmental conditions (such as temperature, solvation, pH, etc...) and cannot be considered as separate entities under biological test systems. As a result, the degradations of trinexapac-ethyl and trinexapac acid in water presented in the submission are a true reflection of the degradations of the dynamic equilibrium of their isomers. LT: RMS agrees with the applicant. Addressed.	Addressed.
4(46)		NL: no comments	-	Noted.
4(47)		LV: Section not reviewed, no comments	-	Noted.

section 4 – Environmental fate and behaviour

Fate and behaviour in air				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(48)		NL: no comments	-	Noted.
4(49)		LV: Section not reviewed, no comments	-	Noted.

PEC in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(50)	Vol. 3, B.8 (CP), 8.1.3 Estimation of concentrations in soil, p 9 List of endpoints, PEC soil, p 48	EFSA: in Table 8.1.3-1 the DT50 vales used in the determination of PECsoil for trinexapac-ethyl and trinexapac acid were 1.2 and 40 days, respectively. However, it is not clear the origin of these values. Furthermore, the worst case endpoint derived in dry conditions at 20°C should be used when calculating the PECsoil.	Applicant: both DT ₅₀ values used in the determination of PECsoil for trinexapac-ethyl and trinexapac acid were selected as the highest value from either normalised or unnormalised laboratory values. In the case of trinexapac-ethyl, 1.2 days was obtained from the 18 Acres soil (Adam (2014) study) by calculating the DT ₅₀ from the k ₂ value (0.5831), as DFOP was deemed the best fit. Given the new position proposed by the RMS, the Applicant now suggests to use the data from the reliable soils only, which means that the highest unnormalised DT ₅₀ value is derived from the Capay soil and is 0.72 days . In the case of CGA179500, the normalised DT ₅₀ value of 40 days obtained in the	Data requirement: Applicant to provide new PECsoil calculations using: - for trinexapac-ethyl the highest not-normalised DT₅₀ value derived from the Capay soil (0.72 days) - for metabolite CGA179500 the DT₅₀ value obtained in the Maryland soil normalized only for the temperature and not for the moisture content - for metabolite CGA275537 the new degradation endpoints (see data requirement and open point in comments 4(18)). Open point: RMS to evaluate the udpated PECsoil calculations and to provide an

PEC in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Maryland soil is higher than the unnormalised DT₅₀ value of 32 days. Therefore, as a conservative approach, the highest value of 40 days was selected as DT₅₀ value used in the determination of PECsoil for CGA179500. LT: PEC values in soil for trinexapac-ethyl were recalculated by RMS with worst case DT₅₀ of 0.72 days from reliable lab soils. PEC values for metabolite trinexapac acid were calculated correctly, worst case DT₅₀ of 40 days (rounded from 39.5 d) were used. Therefore no action is required. Addressed.	amended RAR and LoEP including all new information.
4(51)	Vol. 3 – B.8 (PPP), 8.1.3, Estimation of concentration in soil	Applicant: Page 9 The Applicant does not agree that CGA300405 and CGA275537 should be assessed in soil as under realistic field conditions, these will not form at levels of concern. Please see point (23) of Table Route and rate of degradation in soil for further details.	LT: Applicant opinion and argumentation is presented in the Vol. 3 – B.8 (PPP), 8.1.3. No action is required. Please see RMS comment in point 4(23). Addressed.	Addressed. See also comment 4(23).
4(52)	Vol. 1, 2.8.6 Summary of exposure calculations and	Applicant: Page 123 The Applicant does not agree that CGA300405 and CGA275537	LT: Please see RMS comment in point 4(23).	Addressed.

section 4 – Environmental fate and behaviour

PEC in soil				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	product assessment	should be assessed in soil as under realistic field conditions, these will not form at levels of concern. Please see point (23) of Table Route and rate of degradation in soil for further details.	Addressed.	See also comment 4(23).
4(53)	LoEP, Section 4, PEC soil	Applicant: Page 49 The Applicant does not agree that CGA300405 and CGA275537 should be assessed in soil as under realistic field conditions, these will not form at levels of concern. Therefore, calculations of PECsoil are not necessary for these two metabolites. Please see point (23) of Table Route and rate of degradation in soil for further details.	LT: please see RMS comment in point 4(23). Addressed.	Addressed. See also comment 4(23).
4(54)		NL: no comments	-	Noted.
4(55)		LV: Section not reviewed, no comments	-	Noted.

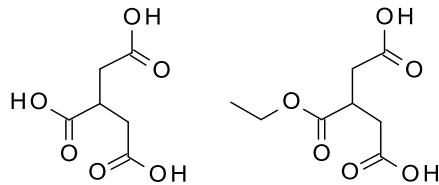
PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(56)	Vol. 3 – B.8 (PPP), 8.1.4, Estimation of concentration in groundwater	Applicant: Page 15-16 the Applicant would like to highlight that the correct endpoint for trinexapac-ethyl is 0.14 days. Please see point (10) of Table Route and rate of degradation in soil for further details.	LT: RMS agrees with the applicant. Correct endpoint is noted in the Table 8.1.4-7. PECgw values were recalculated by RMS. Addressed.	See open point in comment 4(10). See data requirement and open point in comment 4(67).
4(57)	LoEP, Section 4, PEC ground water	Applicant: Page 50 the Applicant disagrees with the modelling soil endpoint derived by the RMS for trinexapac-ethyl. Please refer to point (10) of Table Route and rate of degradation in soil for further details.	LT: RMS agrees with the applicant. Correct endpoint is noted in the LoEP. Addressed.	See open point in comment 4(10). See data requirement and open point in comment 4(67).
4(58)	LoEP, Section 4, PEC ground water	Applicant: Page 51-52 the Applicant does not agree with the crop interception selected by the RMS for groundwater assessment. According to the EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT ₅₀ values of active substances of plant protection products and transformation products of these active substances in soil (2014), the interception for cereals at BBCH 25 should be set to 20% and not 0%, even if this doesn't impact to the outcome of the risk assessment.	LT: RMS agrees with applicant. PECgw values were recalculated taken interception in to account. Addressed.	See data requirement and open point in comment 4(67).
4(59)	Vol. 3 – B.8 (PPP), 8.1.4,	Applicant: Page 15-16 the Applicant agrees	LT: Noted. Table 8.2 updated.	Addressed.

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Estimation of concentration in groundwater	with the latest solubility endpoints selected by the RMS but would like to highlight that the water solubility values of parent and metabolite CGA179500 do not influence the outcome of groundwater models. In addition, Table 8.2 page 5 needs to be updated with these latest solubility endpoints.	Addressed.	RMS to correct Table 8.2 in Vol 3 (CP) using the correct solubility endpoints for parent and metabolite CGA179500; this action is needed according to SANCO/10180/2013-rev.1
4(60)	Vol. 3, B.8 (CP), 8.1.3 Estimation of concentrations in groundwater	EFSA: It is not clear why relative application dates (25 days after emergence) were used when modelling with PEARL in Gabsi (2015) and Bramley (2016).	Applicant: The Applicant would like to clarify that the appropriate version of AppDate was used to determine the dates of applications for the groundwater modelling in Gabsi (2015) and Bramley (2016). Relative application dates of 25 days after emergence were not considered in the Applicant's groundwater modelling. LT: Relative application dates were used by RMS due practical reasons, as more comfortable input parameter for PEARL. Addressed.	Addressed.
4(61)	Vol. 3, B.8 (CP), 8.1.3 Estimation of concentrations in groundwater	EFSA: in Bramley (2016) the application date in Jokioinen scenario was set in October because it reflects more the agricultural practices in the scenario for cereals. However, the same approach was not	Applicant: The Applicant should have made a note of this discrepancy between the two reports in the Top Up submission. The more appropriate application date for winter cereals in the Jokioinen scenario	Open point: RMS to provide an amended RAR addressing the discrepancy between the application date in Jokioinen

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	List of endpoints, PEC groundwater	followed in the study by Gabsi (2015a). Clarifications for using different approaches should be provided.	was only investigated, then reported, when carrying out the specific photolysis modelling, which explains why the two reports (one on microbial degradation and one on photolytic degradation) do not have the same approach. This discrepancy was addressed in modelling report CGA163935_10840, which was included in the most up to date Document M-CP Section 9 supplied with the latest version of the Caddy in April 2017. LT: Clarification is provided by applicant. Addressed.	scenario used in Bramley (2016) and the one used in Gabsi (2015a).
4(62)	Vol. 3, CA, B.8.1.4, Estimation of concentrations in groundwater, KCP 9.1.4/01	DE: It was concluded that the sorption is pH dependent. If this is the case PEC groundwater modelling is required with K_{foc} values for acidic and alkaline soils. Further explanations Due to the small number of values, using minimum K_{foc} as it represents a worst- case is useful. Nevertheless further adsorption studies with soil pH >7 were required by EFSA in 2003 already.	Applicant: The Applicant agrees that sorption for trinexapac-ethyl and CGA179500 might be dependent on pH, and that the adsorption is expected to increase in decreasing soil pH. However, in the case of trinexapac-ethyl and CGA179500, an adsorption measurement was made at the pH value of 7.5. Since the pK_a value for trinexapac-ethyl is 4.57 and the pK_a values for CGA179500 are 3.93 and 5.32, parent and metabolite would be almost completely dissociated at pH = 7.5 and therefore the K_{FOC} values	See data requirement in comment 4(32).

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			reported in this soil are not going to differ significantly with increasing pH (to a recommended maximum of 8). Consequently, the minimum K_{FOC} values obtained for parent and CGA179500 at pH = 7.5 can be considered worst case and used as such in the risk assessment. This position is more conservative than using a geometric mean obtained from acidic or alkaline soils in two separate assessments. This approach, which was presented in the original Annex 1 submission, was agreed by EFSA and the 2005 RMS. It appears in the EU LoEP for trinexapac-ethyl. LT: RMS agrees with the applicant. Addressed.	
4(63)	Vol. 3, CA, B.8.1.4, Estimation of concentrations in groundwater, KCP 9.1.4/02	DE: We appreciate the consideration of photodegradates in the groundwater assessment in Bramley (2016). Further explanations FOCUS-PELMO 5.5.3 can simulate both the biodegradation and the photodegradation of an active substance, along with its	Applicant: Noted. LT: Noted. Addressed.	Noted.

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		metabolites and photodegradates. This is an optional higher tier 2. However, it is important to know that the tiered approach (PEC _{gw,tier1} > PEC _{gw,tier2}), in comparison to the lower tier 1 presented here, is only guaranteed, if in the lower tier a maximum occurrence of 100 % is used. As all concentrations in Bramley (2016) are < 0.001 µg/L, it can be safely assumed, that also maximum occurrences of 100 % would give concentrations < 0.1 µg/L.		
4(64)	Vol. 3, B.8 (CP), 8.1.4 Estimation of concentrations in groundwater, p 20	EFSA: in Table 8.1.4-11 the calculation for CGA179500 in spring cereals does not seem to be correct. The correct number should be 82 instead of 65.6.	Applicant: Noted. The Applicant agrees with the EFSA's comment but would like to highlight that the discrepancy doesn't impact the risk assessment and that the groundwater concentrations for CGA179500 will still be <0.001µg/L. LT: Noted. Correct endpoint is noted in the Table 8.1.4-11. PEC _{gw} values were not used for the risk assessment. Addressed.	Open point: RMS to provide an amended RAR correcting in Table 8.1.4-11 (Vol. 3, B.8 (CP) the application rate of metabolite CGA179500 in spring cereals, being the correct value 82 g/ha.
4(65)	Vol. 3 – B.8 (PPP), 8.1.4, Estimation of concentration in groundwater	Applicant: Page 23 the Applicant agrees with the latest solubility endpoints selected by the RMS but would like to highlight that the water solubility values of metabolites	LT: Noted. Addressed.	Noted.

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		CGA300405 and CGA275537 do not influence the outcome of groundwater models.		
4(66)	Vol. 3, B.8 (CP), 8.1.4 Estimation of concentrations in groundwater List of endpoints, PEC groundwater	EFSA: for metabolite CGA275537 degradation and adsorption endpoints are not available and then endpoints derived for metabolite CGA300405 were used. However, more scientifically based justifications for using values from metabolite CGA300405 as surrogate for metabolite CGA275537 should be provided. Otherwise, worst case or laboratory values should be used.	Applicant: When comparing CGA300405 and CGA275537 (please see Figure 1 below), it is clear that they have a very similar chemical structure. The only difference between the two compounds is the presence of an ethyl ester on CGA300405. On such small moieties, this difference shouldn't impact their physical properties significantly. The Applicant has already advocated this position.  <chem>OC(=O)C1(CCC(=O)O)C(O)C1</chem> CGA275537 <chem>CCOC(=O)C1(CCC(=O)O)C(O)C1</chem> CGA300405 Figure1 To substantiate this argument, the Applicant generated degradation and mobility data for both CGA300405 and CGA275537. The results confirm that the rates of CGA300405 and CGA275537 are almost	See data requirement and open point in comments 4(18) and 4(23). See data requirement in comment 4(67).

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			identical, with a geometric mean of 0.23 and 0.21 days respectively. With regards to their mobility, a reliable K_{FOC} value could not be derived for CGA300405, although it was concluded that it was very mobile. This was also confirmed for CGA275537, as results confirmed reliable mobility values ranging between 6 and 78 g/mL. Because the identity of CGA275537 was only confirmed just before the Top Up submission, data on the metabolite could not be generated in time. However, final reports for its degradation and mobility have now been issued and can be made available upon request (the rate degradation study for CGA275537 is already included in the latest update of the Caddy, which was provided in April 2017. The mobility study can be made available at the Stop-The-Clock period). LT: RMS agrees with applicant. Since provided justification is not sufficient, available studies for metabolite CGA 275537 should be provided.	

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Data requirement: Applicant to provide lab degradation and adsorption studies on metabolite CGA275537.	
4(67)	Vol. 3 – B.8 (PPP), 8.1.4, Estimation of concentration in groundwater	Applicant: Page 24-25 the Applicant does not agree with the crop interception selected by the RMS for groundwater assessment. According to the EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT ₅₀ values of active substances of plant protection products and transformation products of these active substances in soil (2014), the interception for cereals at BBCH 25 should be set to 20% and not 0%, even if this doesn't impact to the outcome of the risk assessment.	LT: RMS agrees with applicant. PECgw values were recalculated with interception taken in to account. Addressed.	Data requirement: Applicant to provide new PECgw calculations using: - the interception for cereals at BBCH 25 set to 20% - for trinexapac-ethyl the geometric mean DT₅₀ value of 0.13 days (see open point in comment 4(10)) - for metabolite CGA275537 the new degradation and adsorption endpoints (see data requirement and open point in comments 4(18) and 4(34)) - application to the soil surface Open point: RMS to evaluate the updated PECgroundwater calculations and to provide an amended RAR and LoEP including all new information. See also open point 4(61).
4(68)	Vol. 3 – B.8 (PPP), 8.2.4, Estimation of	Applicant: Page 30 the Applicant would like to highlight that the correct soil DT ₅₀	LT: Updated.	See open point in comment 4(10). See data requirement in comment

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	concentration in surface water	endpoint for use in modelling for trinexapac-ethyl is 0.14 days. Please see point (10) of Table Route and rate of degradation in soil for further details.	Addressed.	4(67).
4(69)	Vol. 3, B.8 (CP), 8.2.4.1 Estimation of concentrations in surface water for metabolite, p 33	EFSA: in Table 8.2.4.1- 2 the DT ₅₀ in soil reported for trinexapac-ethyl is 1 d. Could the RMS clarify the origin of this value?	Applicant: The Applicant agrees. Please see point 4(70) below for the appropriate DT₅₀ to be used. LT: RMS agrees with the comment. Table updated. PEC_{sw} values recalculated. Addressed.	See open point in comment 4(10).
4(70)	Vol. 3 – B.8 (PPP), 8.2.4.1, Estimation of concentration in surface water for metabolites	Applicant: Page 33 the Applicant would light to highlight that the correct soil DT₅₀ endpoint for use in modelling for trinexapac-ethyl highlighted in Table 8.2.4.1-2 is 0.14 days, not 1 day. Please see point (10) of Table Route and rate of degradation in soil for further details.	LT: RMS agrees with the comment. Table updated. PEC values recalculated with correct endpoint for trinexapac-ethyl. Addressed.	See open point in comment 4(10). See data requirement in comment 4(67).
4(71)	Vol. 3 – B.8 (PPP), 8.2.4.1, Estimation of concentration in surface water for metabolites	Applicant: Page 35 the Applicant does not agree that CGA275537 should be assessed in Surface Water.	LT: Please see RMS comment in point 4(23). Addressed.	Addressed. See also comment 4(23).

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		Please see point (23) of Table Route and rate of degradation in soil for further details.		
4(72)	LoEP, Section 4, PEC surface water and PEC sediment	Applicant: Page 59-60 the Applicant does not agree that CGA275537 should be assessed in Surface Water. Please see point (23) of Table Route and rate of degradation in soil for further details. In addition, the Applicant would like to highlight that CGA275537 was only observed in a soil photolysis study, therefore deriving surface water concentrations from parent is incorrect as any contribution from drift should not be considered for surface water calculations. Please see point (74) of this table for further details.	LT: Please see RMS comment in point 4(23). Addressed.	Addressed. See also comment 4(23).
4(73)	Vol. 3 – B.8 (PPP), 8.2.4.1, Estimation of concentration in surface water for metabolites	Applicant: Page 35 as highlighted in point (16) of Table Route and rate of degradation in soil , CGA275537 is not going to form at levels of concerns in soil, and therefore in surface water.	LT: RMS agrees with applicant suggestion that PEC for CGA275537 should be calculated using "No drift" option. However, since required input parameters for FOCUS Step1 and Step2 simulations are not available, conservative calculation	Data requirement Applicant to provide new PEC_{sw} and sed calculations considering: for trinexapac-ethyl the geometric mean DT₅₀ value of 0.13 days (see open point in comment 4(10))

section 4 – Environmental fate and behaviour

PEC in surface water and ground water				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		In addition, the Applicant would like to highlight that CGA275537 was only observed in a soil photolysis study, therefore deriving surface water concentrations from parent is incorrect as any contribution from drift should not be considered for surface water calculations. Consequently, should the RMS, EFSA or other concerned MSs still wish to calculate concentrations for CGA275537, the Applicant suggests performing Step 1&2 using the "No drift (incorp or seed treatment)" option as the only routes of entry relevant for CGA275537, if ever formed under realistic conditions, could only be <i>via</i> run-off or drainage.	approach for metabolite CGA275537 was used by RMS. Applicant has informed that for metabolite CGA275537 new degradation and adsorption studies are available which should be provided. Consequently applicant can provide new PEC values with "no drift". Addressed.	- for metabolite CGA275537 the new degradation and adsorption endpoints (see data requirement and open point in comments 4(18) and 4(34)) - for metabolite CGA275537 Step 1&2 should be done considering "no drift". Open point: RMS to evaluate the updated new PEC_{sw} and sed calculations and to provide an amended RAR and LoEP including all new information. See also comment 4(23).
4(74)		NL: no comments	-	Noted.
4(75)		LV: Section not reviewed, no comments	-	Noted.

PEC from airborne transport and other routes of exposure				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(76)		NL: no comments	-	Noted.

PEC from airborne transport and other routes of exposure				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(77)		LV: Section not reviewed, no comments	-	Noted.

Definition of the residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(78)	Vol. 1, 2.8.5 Definition of the residues in the environment requiring further assessment, p 122	EFSA: the sediment compartment is missing in the table reporting the residues requiring further assessment.	Applicant: The Applicant would like to highlight that CGA275537 is only to be assessed in groundwater as detailed in point 4(23). In addition, as the K_{FOC} values of CGA275537 are low to very low, it is therefore very unlikely that the metabolite, should it ever reach surface water via run-off or drainage, would partition to the sediment. As a result, CGA275537 should not appear in the Definition of Residue for Sediment. LT: Sediment compartment was added by RMS, table has been updated. RMS considers that argumentation provided by applicant is not sufficient to exclude CGA275537 from the definition of residues for surface and sediment. RMS is of the opinion that metabolite CGA275537 should be included in the definition of residues for surface and sediment since CGA275537 was found >10% in soil photolysis study. Addressed.	Open point: RMS to provide an amended RAR adding the sediment compartment in the table reporting the residues requiring further assessment in Vol. 1. See also comment 4(23).

Definition of the residues				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(79)	List of endpoints, Residues requiring further assessment, p 47	EFSA: in surface water and sediment metabolite CGA275537 is missing.	Applicant: Please consider point 4(78) above. LT: Metabolite CGA275537 was included by RMS. Addressed	Open point: RMS to provide an amended LoEP adding metabolite CGA275537 in surface water and sediment in the list of residues requiring further assessment. See also comment 4(23).
4(80)	Vol. 3 – B.8 (AS), 8.4.1, CGA300405 and CGA275537 are considered to be relevant residues in soil, groundwater and surface water for the risk assessment purposes	Applicant: Page 172 the Applicant does not agree with the RMS to include metabolites CGA300405 and CGA275537 in the definition of residues in soil. In addition, the Applicant does not agree with RMS to include metabolite CGA275537 in the definition of residues in surface water. Please see point (23) of Table Route and rate of degradation in soil	LT: Noted, however RMS is still of the opinion that both photolysis metabolites should be included for the residue definition in soil and surface water. Please see RMS respond in point 4(23). Addressed.	See also comment 4(23).
4(81)		NL: no comments	-	Noted.
4(82)		LV: Section not reviewed, no comments	-	Noted.

Other comments incl. available monitoring data				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(83)		FR: Section not reviewed, no comment	-	Noted.
4(84)	Vol. 3, B.8 (CA), 8.6.1 Literature review, p 173	EFSA: Regulation (EC) No 1107/2009 requires a search of the scientific peer-reviewed open literature. The APPL submitted the search, however the terms used for the search do not consider all the metabolites (possible systematic names, CAS No. etc.) identified in the RAR at levels that trigger assessment (as CGA179500, CGA275537, WaterM3Hydrolysis and M2). Therefore, data or justifications for not providing those data are required. Furthermore, could be confirmed that the EFSA guidance (2011) on open literature search was followed?	Applicant: the Applicant would like to highlight that CGA179500 has been considered during the initial and top up scientific peer-reviewed open literature searches (through its name and its CAS number). Therefore, CGA179500 should not be considered for another search. M2 hasn't been formally identified, as a result the Applicant doesn't recommend performing a scientific peer-reviewed open literature search on such metabolite. As for WaterM3Hydrolysis, even though it has been observed at more than 10% AR in one hydrolysis study, the Applicant believes that under realistic environmental conditions, it will not form at levels of concern and should not be considered further in the risk assessment (please see Document M-CA Section 7 for more details). Consequently, a scientific peer-reviewed open literature search is not appropriate for WaterM3Hydrolysis. On the other hand, CGA275537 is a residue of concern for assessment in groundwater, therefore a scientific peer-reviewed open literature search will be carried out and will be available for the Stop-The-Clock	Data requirement: Applicant to provide an updated literature search including metabolites CGA275537, CGA300405, M2 and. WaterM3Photolysis. Open point: RMS to provide an amended RAR including the updated literature search considering also metabolites CGA275537, CGA300405, M2 and. WaterM3Photolysis.

Other comments incl. available monitoring data				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant period.	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			LT: Provided literature search follows the requirements of EFSA guidance (2011) on open literature search. RMS agrees that for trinexapac acid (CGA179500) additional search is not necessary. RMS agrees with applicant argumentation that search is not required for metabolite WaterM3Hydrolysis since this metabolite will not form in the environment under representative conditions. Metabolite M2 was considered relevant for the definition of the residue for risk assessment in surface water, therefore literature search should be provided for this metabolite. RMS agrees that literature search should be carried for metabolite CGA275537 Data requirement: Applicant to provide literature search on metabolites M2 and CGA275537.	
4(85)	Name of metabolite CGA179500	EFSA: the correct name for metabolite 'trinexapac acid' should be 'trinexapac'. Therefore, the name should be changed to 'trinexapac' or the code CGA179500 should	LT: RMS has referred metabolite CGA179500 as trinexapac acid to maintain uniform name in all sections. For transparency and clarity RMS definition of all substances is	Open point: RMS to provide an amended RAR and LoEP using for metabolite CGA179500

Other comments incl. available monitoring data				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		be used in the whole RAR and LoEP.	provided in the Table 8-1 of Volume B8. In respect to ECHA CGA179500 (CAS:104273-73-6) other name of 'trinexapac-ethyl' is provided. Therefore clarification is required for the name 'trinexapac'. Data requirement: definition of name 'trinexapac' has to be provided.	the code or the name 'trinexapac'. Note: 'trinexapac-ethyl' refers to the active substance.
4(86)		NL: no comments	-	Noted.
4(87)		LV: Section not reviewed, no comments	-	Noted.

5. Ecotoxicology

Birds and other terrestrial vertebrates				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(1)	Vol. 3, (AS) B.9.1.1.3- Sub chronic toxicity and reproduction to birds- Hakin 1991a	EFSA: It is unclear why the reduction the reduction in eggs production at 600 ppm was not considered as biologically significant.	Applicant: As indicated in the original report and the summary there were no statistically significant treatment related effects upon reproductive performance at any of the concentrations tested. The number of eggs produced in the 600 ppm treatment group did not attain the significance level of a difference compared to the control group. RMS (Aug 2017): The reduction in eggs production is biologically relevant. However, this effect was not statistically significant at 600 ppm. Therefore the NOEC for reproduction was set at that level. Addressed	Experts' consultation Experts to discuss the endpoint to be used in the long term risk assessment for birds. In particular, the relevance of the reduction in eggs production at 600 ppm observed in Hakin 1991a should be discussed.
5(2)	Vol. 3, (AS) B.9.1.4 Other data on effects on terrestrial vertebrate wildlife.	EFSA: It is not sufficient to provide the LC50 for the available amphibian test, a summary of this study should be included in the RAR and the study report should be provided in the dossier.	Applicant: The English summary from the Chinese report can be added to the dossier in the stop-the clock period, and a full translation will be requested. RMS (Aug 2017): agrees Data requirement: The applicant should provide the study report and the study summary to include in the RAR.	Data requirement Applicant to provide the study report and a study summary for the available amphibian test.

Birds and other terrestrial vertebrates																																
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)																												
			Open point: the study summary will be included in a revised RAR.																													
5(3)	Vol. 3, (PPP) B.9.2.1 Risk assessment for birds-Secondary poisoning	EFSA: A risk assessment for secondary poisoning is needed for the surface water metabolites, for fish-eating birds and mammals, and for the soil metabolites for earthworm-eating birds and mammals unless the LogKow is lower than 3.	Applicant: The calculated log P_{ow} values of these metabolites are shown below. These were calculated by a physical chemist (A. Pierce, using methodology according to Mannhold, 2009 J Pharm Sci). All the calculated Log P values are below 3 therefore it is not necessary to consider the risk from secondary poisoning. <table><tr><th>Code Number</th><th>Log P values</th></tr><tr><td>Trinexapac-ethyl</td><td>-0.29 at pH 6.9</td></tr><tr><td>CGA179500</td><td>0.019 at pH 5</td></tr><tr><td>CGA275537</td><td>-1.08</td></tr><tr><td>CGA329773</td><td>1.92</td></tr><tr><td>SYN548584</td><td>-1.21</td></tr><tr><td>CGA300405</td><td>0.03</td></tr><tr><td>SYN549229</td><td>-1.85</td></tr><tr><td>CGA351210</td><td>-1.68</td></tr><tr><td>SYN540406</td><td>0.29</td></tr><tr><td>NOA433257</td><td>1.85</td></tr><tr><td>CGA312753</td><td>-0.85</td></tr><tr><td>SYN540405</td><td>-1.09</td></tr><tr><td>SYN549299</td><td>0.54</td></tr></table> RMS (Aug 2017): agrees that is not necessary to consider the risk from secondary	Code Number	Log P values	Trinexapac-ethyl	-0.29 at pH 6.9	CGA179500	0.019 at pH 5	CGA275537	-1.08	CGA329773	1.92	SYN548584	-1.21	CGA300405	0.03	SYN549229	-1.85	CGA351210	-1.68	SYN540406	0.29	NOA433257	1.85	CGA312753	-0.85	SYN540405	-1.09	SYN549299	0.54	Open point RMS to include the information on the calculated LogPow for metabolites in a revised RAR. This should include a study summary detailing how the LogPow values were derived for metabolites. Data requirement Applicant to provide the study report and a detailed study summary of the study at the basis of the LogPow derivation for trinexapac-ethyl metabolites. In addition, from the provided overview in the reporting table it is not clear whether LogPow values are available for the surface water metabolites M2 (3-carboxylic acid ethyl ester-7-hydroxypropyl-5-oxo,7-hydroxyheptanoic acid) and WaterM3Photolysis and these are needed.
Code Number	Log P values																															
Trinexapac-ethyl	-0.29 at pH 6.9																															
CGA179500	0.019 at pH 5																															
CGA275537	-1.08																															
CGA329773	1.92																															
SYN548584	-1.21																															
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Birds and other terrestrial vertebrates																																
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)																												
			poisoning for metabolites as the LogKow is lower than 3. Addressed. Open point: This information will be added in the revised RAR																													
5(4)	Vol. 3, (PPP) B.9.2.1 Risk assessment for birds-Metabolites	EFSA: The extrapolation of the toxicity from mammals to birds is questionable. Further consideration is needed also for metabolites CGA 275537, CGA300405, CGA313458 and CGA 329773. Could a list of plant metabolites relevant for the assessment, possibly in a tabular format be provided?	Applicant: Consideration of metabolites CGA275537, CGA300405, CGA313458 and CGA329773 is given in the previously submitted text (CP 10.1.2 and 10.1.2). A table showing the full list of soil, water and plant metabolites is given below. <table><tr><th>Code Number</th><th>Compound found in:</th></tr><tr><td>Trinexapac-ethyl</td><td>Soil, Water, Plant</td></tr><tr><td>CGA179500</td><td>Soil, Water, Plant</td></tr><tr><td>CGA275537</td><td>Soil, Plant</td></tr><tr><td>CGA329773</td><td>Plant</td></tr><tr><td>SYN548584</td><td>Plant</td></tr><tr><td>Citric acid</td><td>Plant</td></tr><tr><td>CGA312753</td><td>Plant</td></tr><tr><td>CGA300405</td><td>Soil, Water, Plant</td></tr><tr><td>SYN549229</td><td>Soil</td></tr><tr><td>CGA113745</td><td>Water</td></tr><tr><td>CGA351210</td><td>Plant</td></tr><tr><td>SYN540406</td><td>Plant</td></tr><tr><td>NOA433257</td><td>Plant</td></tr></table>	Code Number	Compound found in:	Trinexapac-ethyl	Soil, Water, Plant	CGA179500	Soil, Water, Plant	CGA275537	Soil, Plant	CGA329773	Plant	SYN548584	Plant	Citric acid	Plant	CGA312753	Plant	CGA300405	Soil, Water, Plant	SYN549229	Soil	CGA113745	Water	CGA351210	Plant	SYN540406	Plant	NOA433257	Plant	Data requirement Applicant to provide a list of relevant plant metabolites. Applicant to provide further information to address the risk to birds and mammals for the relevant plants metabolites. See also 5(5).
Code Number	Compound found in:																															
Trinexapac-ethyl	Soil, Water, Plant																															
CGA179500	Soil, Water, Plant																															
CGA275537	Soil, Plant																															
CGA329773	Plant																															
SYN548584	Plant																															
Citric acid	Plant																															
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CGA300405	Soil, Water, Plant																															
SYN549229	Soil																															
CGA113745	Water																															
CGA351210	Plant																															
SYN540406	Plant																															
NOA433257	Plant																															

Birds and other terrestrial vertebrates															
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant		Column 4 Data requirement or Open point (if data point not addressed or fulfilled)										
			<table><tr><td>CGA312753</td><td>Plant</td></tr><tr><td>SYN540405</td><td>Plant</td></tr><tr><td>CGA313458</td><td>Water</td></tr><tr><td>CGA224439</td><td>Water, Plant</td></tr><tr><td>SYN549299</td><td>Water</td></tr></table> RMS (Aug 2017): All information about trinexapac-ethyl plant metabolites provided by applicant has been included in Vol.3, (PPP) B.9.2.1 and B.9.2.2. In the EFSA Birds and mammal guidance 2009 it is indicated possibility to use data from mammals metabolism studies when hen metabolism study is not available, therefore the extrapolation is possible. Data requirement: A list of plant metabolites relevant for the assessment in tabular format and further consideration for metabolites if needed should be provided by applicant.		CGA312753	Plant	SYN540405	Plant	CGA313458	Water	CGA224439	Water, Plant	SYN549299	Water	
CGA312753	Plant														
SYN540405	Plant														
CGA313458	Water														
CGA224439	Water, Plant														
SYN549299	Water														
5(5)	Vol. 3, (PPP) B.9.2.2 Risk assessment for mammals-Metabolites	EFSA: Please could it be clarified if CGA 113745 is a relevant plant metabolite, it is not mentioned as such when relevant plants metabolites are listed e.g. for birds. It is unclear why the metabolite CGA275537 was considered of low toxicological	Applicant: As indicated above a comprehensive list of metabolites will be added to the dossier during the stop-the-clock period. CGA113745 was not found in plants, but was found in a processing study.		See 5(4)										

Birds and other terrestrial vertebrates				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		concern since it is acutely more toxic than the parent compound. Further consideration is needed also for metabolites CGA300405. Could a list of plant metabolites relevant for the assessment, possibly in a tabular format be provided?	For CGA275537 the LD₅₀ is given as >300 mg/kg bw, this compares to an LD₅₀ of 4210 mg a.s./kg bw for trinexapac-ethyl. However this difference is due to CGA275537 not being tested at higher rates, and so its true LD₅₀ has not been determined. These data still suggest that CGA275537 is of low toxicological concern. The acute risk assessment for trinexapac-ethyl gives a TER value of 178 (= 4210/23.7), if the same DDD value is used (an extremely conservative assumption for exposure to CGA275537) the TER value for CGA275537 would be >13 (= >300/23.7) indicating no unacceptable risk. RMS (Aug 2017): CGA113745 metabolite identified in goat tissues is not relevant plant metabolite as it is found in a processing study. The RMS is of the opinion that taking into account all available information and given that exposure levels will be significantly less than for the parent it is considered that the risk to mammals from metabolites will be addressed. Data requirement: A list of plant metabolites relevant for the assessment in tabular format should be provided by	

Birds and other terrestrial vertebrates				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			applicant.	
5(6)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP e.g. acute toxicity study with bobwhite quail.	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated in a revised RAR.	Open point RMS to include all valid endpoints for birds and mammals in the list of endpoints.
5(7)	List of endpoints	EFSA: Could the available toxicity data on metabolites for mammals be included in the LoEP	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated in a revised RAR.	Open point RMS to include all valid endpoints for the metabolites for mammals in the list of endpoints.
5(8)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted
5(9)		NL: no comments.	RMS (Aug 2017): Noted.	Noted

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(10)	Vol. 3 (AS) B9.2; Vol. 3 (PPP) B9.3. Effects on aquatic organisms	EFSA: Please could the results of the analytical verifications of the tested concentrations be included in all the study summaries of the aquatic toxicity studies? In various cases only the overall recovery percentage is reported. Also, it should be specified were relevant whether trinexapac ethyl or trinexapac acid (or both) were measured in the tests with the trinexapac-ethyl technical. In addition, EC10 and EC20, or a justification for not providing those, should be provided for all the available chronic toxicity studies, this was not done for Putt 1991 (reproductive toxicity study for <i>Daphnia magna</i>).	Applicant: Additional data on analytical verification can be added to the dossier during the stop-the-clock period. In these data the studies either analysed for triexapac-ethyl (CGA163935) or trinexapac acid (CGA179500), but not both. The previously submitted dossier also includes additional calculations to show give the EC10 and EC20 values for aquatic studies. However the recalculations for one study (Putt 1991) have been omitted in error. This will be added during the stop-the-clock period. RMS (Aug 2017): agrees. Data requirement: EC10 and EC20, or a justification for not providing those should be provided for chronic toxicity study - Putt 1991 (reproductive toxicity study for <i>Daphnia magna</i>) and the results of the analytical verifications of the tested concentrations should be provided by the applicant. Open point: the results of the analytical verifications of the tested concentrations will be included in all the study summaries of the aquatic toxicity studies in a revised RAR also EC10 and EC20 will be included where relevant.	Data requirement Applicant to provide the EC10 and EC20, or a justification for not providing those, for the study Putt 1991 (reproductive toxicity study for <i>Daphnia magna</i>). Data requirement Applicant to provide the results of the analytical verifications of the tested concentrations for the aquatic toxicity studies. It should be specified were relevant, whether trinexapac ethyl or trinexapac acid were measured.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(11)	Vol. 3, B.9 CA, CA 8.2.1/05, p. 38.	NL: Why 60 mg/L has been chosen as an endpoint? Low effects on survival were observed at 80 and 130 mg/L. In addition, the symbol "<" next to the endpoint seems not to belong there.	RMS (Aug 2017): 60 mg/L was the lowest treatment level tested. Symptoms of toxicity were observed included erratic swimming at concentration of 60 mg/L and above. At 80 mg a.s/L during 96-hours flow-through toxicity test all of the surviving fish exhibited erratic swimming behaviour. Several of the surviving fish exhibited darkened pigmentation. Addressed.	
5(12)	Vol. 3 (AS) B9.2.1- ELS study- Sousa 1991	EFSA: Please include the valid EC10 and EC20 for this study in the LoEP.	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated in a revised RAR.	Open point RMS to include the EC10 and EC20 for Sousa 1991 in the list of endpoints.
5(13)	Vol. 3 (AS) B9.2.2- Bioconcentration in fish- Fackler (1990)	EFSA: Please include an assessment of the validity criteria for this study. In addition, could it be clarified whether the bioconcentration factors as a function of lipid content of the fish was determined?	Applicant: We consider that this study meets all requisite validity and this will be added during the stop-the-clock period. The bioconcentration factors were only measured for edible, non-edible and whole body tissue. RMS (Aug 2017): Agrees with the applicant. The lipid content of fish tissue was not measured. Open point: An assessment of the validity criteria for study (Fackler 1990) will be included in a revised RAR	Open point RMS to include an assessment of the validity criteria for the study from Fackler 1990.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(14)	Vol. 3 (AS) B9.2.2- Bioconcentration in fish- Fackler (1991)	EFSA: Please include an assessment of the validity criteria for this study.	Applicant: We consider this study meets all requisite validity criteria and this will be added during the stop-the-clock period. RMS (Aug 2017): agrees. Open point: An assessment of the validity criteria for study (Fackler 1991) will be included in a revised RAR	Open point RMS to include an assessment of the validity criteria for the study from Fackler 1991. Data requirement In line with the data requirement (Reg. EU No 283/2013), the bioconcentration factors shall be expressed as a function of both total wet weight and of the lipid content of the fish. Applicant to provide further information to address this point. See also 5(13).
5(15)	Vol. 3 (AS) B9.2.4- Acute toxicity to aquatic invertebrates- Smith 1990	EFSA: The mean measured tested concentrations are reported only for 3 concentrations out of 5, where the analytical measurements limited to those three concentrations?	Applicant: This is correct - in this study the analytical measurements were only made for the low, middle and high concentrations. RMS (Aug 2017): analyses were performed only on the lowest, intermediate and highest test concentrations. Addressed.	Addressed
5(16)	Vol. 3 CA, B.9.2, Effect on aquatic organisms	DE: KCA 8.2.4.1/01 The acute toxicity study for aquatic invertebrates by Smith et al. (1990) is considered to be not valid because up to	Applicant: The guidelines limiting the solvent to a maximum of 100 mg/L are been introduced since this study was undertaken. It is unlikely that the	Open point RMS to include in a revised RAR, the additional information concerning the level of solvent used in the study from

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		467 mg acetone/L have been added as solvent. However, this endpoint is not driving the risk for aquatic organisms.	additional solvent used for the high rate treatments will have impacted the results as the study included two controls one with and one without solvent and no differences were seen between the two controls. RMS (Aug 2017): The maximum concentration of acetone solvent used was 0.467ml/L which is less than the 0.5 ml/L limit specified in the study specific protocol. Addressed.	Smith et al. (1990).
5(17)	Vol. 3 (AS) B9.2.4- Acute toxicity to aquatic invertebrates- Mysids- Sousa 1991	EFSA: Could it be indicated whether the drop in the oxygen was observed in all treatments and control?	Applicant: A drop in dissolved oxygen (DO) levels was first measured at 48 hours. At this time the DO for controls was 6.5-7.3 mg/L, but treatments the range was 4.2-6.4 mg/L, and at 96 hours the controls were at 4.2-6.6 mg/L, with treatments at 3.0-3.9 mg/L. Aeration was introduced on day 3 to try to increase DO levels. RMS (Aug 2017): the drop in the oxygen was observed at 72 and 96 hours in all treatments, except in control. Addressed.	Data requirement Applicant to provide further details on the oxygen levels during the acute toxicity test with aquatic invertebrates- Mysids, Sousa (1991). It is noted that according to OPPTS 850.1035 (Mysid Acute Toxicity test guideline) the oxygen level in the test should be maintained within 60 and 105% saturation. In Sousa (1991) a drop in oxygen was observed in all treatment excepts control and this may have an influence on the results of the study.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(18)	Vol. 3 (AS) B9.2.5.3- Sediment dwelling organisms	EFSA: Further information is needed to address the risk to sediment organisms for CGA179500 (trinexapac acid).	Applicant: No toxicity test with the sediment dwelling midge <i>Chironomus</i> spp. was deemed necessary for trinexapac acid (CGA179500). CGA179500 is lower toxicity to aquatic organisms than the parent, but slightly more persistent in the aquatic system than the parent (DT₅₀ in the total system is 14 to 18 days). However CGA179500 is NOT likely to persist in sediments due to its low K_{FOC} (140 mL/g). This is confirmed in the water sediment studies where the quantity of CGA179500 in the sediment phase never reaches more than 6.9% AR. RMS (Aug 2017): agrees with the applicant. Addressed	Data requirement Applicant to provide further information to address the risk to sediment organisms for CGA179500 (trinexapac acid).
5(19)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Taylor and Pickering 2015b,d,e, f	EFSA: The study from Hoberg (1991a), Hoberg (1991b), Hoberg (1991c) were not considered valid; the EC10 and EC20 estimates are not needed and should not be considered valid.	Applicant: See comment 5(20) below. RMS (Aug 2017): agrees. Open point: The irrelevant information will be withdrawn in a revised RAR.	Addressed RMS to amend in a revised RAR. See 5(20)
5(20)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Hoberg (1991a), Hoberg (1991b), and Hoberg (1991c)	EFSA: Please could it be further described why the studies from Hoberg (1991a), Hoberg (1991b), and Hoberg (1991c) were considered not reliable? The level of details in the study summaries is not sufficient for an independent assessment of these studies.	Applicant: Additional data on the analytical analysis in these studies and the validity criteria will be added during the stop-the- clock period. We consider the Hoberg 1991a and 1991b studies to be valid. RMS (Aug 2017): These studies were considered unreliable at	Open point RMS to include additional details on the assessment of the studies from Hoberg (1991a) and Hoberg (1991c). Data requirement

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Annex I. In the study with <i>Pseudokirchneriella subcapitata</i> Hoberg (1991a) the two lowest nominal doses could not be verified after 120 h as these measurements were below the limit of detection (<1.4 mg as/L). Therefore a proper dose-effects relationship could not be established. No calculations were made to generate toxicity values specifically related to area under the growth rate curve. pH increase to 4.7-10.6 at the end of the test also in control from 7.4 (0 h) to 10.5 (120 h). During the recovery the temperature ranged from 24-30°C. Not all validity criteria are met according OECD guideline 201 (2006): biomass increase (x) 98, CV for section by section growth rates (%) - 64.3, CV for average specific growth rates (%) -1.1. In the study with <i>Anabaena flos-aquae</i> Hoberg (1991b) EC values were not calculated for the 24, 48 and 72 h observation intervals because of variable cell counts and lack of a clear concentration-response. No calculations were made to generate toxicity values specifically related to area under the growth rate curve, or growth rate. There is no possibility to check validity criteria as	Applicant to provide additional details from the study Hoberg (1991b), this should include an assessment of the validity criteria.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			not possible to calculate criteria from data report as only rounded, mean values are provided. In the study with <i>Navicula pelliculosa</i> Hoberg (1991c) The 24-h, 48-h, 72-h, 96-h and 120-h EC50 were 15, 14, 11, 26, and 55 mg as/L. There is no explanation for this irregular course. No calculations were made to generate toxicity values specifically related to area under the growth rate curve, or growth rate. pH ranged from 8.3 to 9.0 at the end of the test, while a pH of 5.0 was measured in the 110 mg as/L exposure. During the recovery the temperature ranged from 24-30°C. Not all validity criteria are met according OECD guideline 201 (2006): biomass increase (x) 21, CV for section by section growth rates (%) - 62, CV for average specific growth rates (%) -4.3. The RMS is of the opinion that the three mentioned studies are not considered valid. However, if necessary the additional details of the biological results will be provided. Addressed	
5(21)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Maetzler	EFSA: Please include additional details of the biological finding (biomass/yield/growth	Applicant: An additional summary of these data will be added during the stop-the-	Data requirement Applicant to provide additional details

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	2001	rate in the control and in the treatments) of this study possibly in a tabular format. The endpoints from this study were not included in the LoEP. It is additionally noted that for this study EC10 were not available.	clock period. The previously submitted dossier includes additional calculations to show the recalculated EC10 and EC20 values. RMS (Aug 2017): agrees. EC10 was calculated in the study report ErC10 is 17 mg/L (95% confidence limit 11.8-22.6) Open point: The additional details of the biological finding (biomass/yield/growth rate in the control and in the treatments and EC10 will be provided. The endpoint will be included in the LoEP.	of the biological finding (biomass/yield/growth rate in the control and in the treatments) for the study effects on algal growth- Maetzler 2001. This should include the recalculated EC10 and EC20 values.
5(22)	Vol. 3, B.9 CA, CA 8.2.6/01, p. 96.	NL: <i>A. flos-aquae</i> does not belong to the group of green algae, please amend (conclusion part).	RMS (Aug 2017): agrees. Open point: the conclusion part will be amended accordingly	Addressed RMS to amend in a revised RAR.
5(23)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Grade 2001a,b; 1995b	EFSA: It is not agreed that the validity criteria of OECD 201 does not apply to <i>Anabaena flos-aquae/Navicula pelliculosa</i> since this species is listed between the test species in the same test guideline. Please clarify.	RMS (Aug 2017): OECD 201 guideline is more suitable for fast growing green algae species, the <i>Anabaena</i> is slow growing algae also the old studies were conducted according to prevailing guidelines. Therefore, it is inappropriate to use these criteria in evaluating the regulatory acceptability of studies conducted with non-green species. If this approach is not accepted then all old algae studies except with green algae cannot be considered valid after the	Open point The validity criteria of the OECD 201 apply to <i>Anabaena flos-aquae/Navicula pelliculosa</i> . Please revise the RAR accordingly; the studies with these species not meeting the validity criteria should be invalidated and the risk assessment should be updated as necessary.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			application of the validity criteria as reported in OECD 201. However, there are four new studies with <i>Anabaena flos aquae</i>. Two conducted with trinexapac-ethyl and two conducted with trinexapac acid. These studies indicate less toxicity compared to old ones. Open point.	
5(24)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Grade 1995c	EFSA: The validity criteria in line with OECD 201 (most recent version) are not met. It is, however, noted that this species is not listed between the test species in the guideline. In consideration of the above, it is unclear whether this study should be considered as valid. Please include further details on the results i.e. biological finding (biomass/yield/growth rate in the control and in the treatments).	Applicant: An additional summary of these data will be added during the stop-the-clock period. RMS (Aug 2017): agrees Open point: The additional details of the biological finding (biomass/yield/growth rate in the control and in the treatments will be provided.	Data requirement Applicant to provide further details on the results i.e. biological finding (biomass/yield/growth rate in the control and in the treatments) for the study effects on algal growth- Grade 1995c.
5(25)	Vol. 3 CA, B.9.2, Effect on aquatic organisms	DE: The study on toxicity for algae (<i>Anabaena-flos-aquae</i>) caused by trinexapac (acid) by Grade (2001b; KCA 8.2.6.2/04) with an $ErC_{50} = 17.5$ mg a.s./L is classified as "not valid", because no exponential growth could be observed. The control group has a lag phase of 24h. In addition, biomass has	RMS (Aug 2017): In the study with <i>Anabaena flos-aquae</i> Grade (2001b) cell densities were measured at 24, 48, 72 and 96 hours of exposure using CytoFluor II (a fluorescence multi-Well Plate Reader). Changes in mean density indicated that exponential growth occurred in the negative control replicates.	Open point RMS to invalidate the study from Grade (2001b; KCA 8.2.6.2/04) since the validity criteria according to the most recent version of the OECD 201 are not met.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		been determined by fluorescence, the evaluation in this case is not plausible as the test substance seems to have great influence on fluorescence. In the highest test-concentrations fluorescence is in almost all measurements smaller than fluorescence of control medium. A discussion of these findings was not conducted. In this case an inappropriate method for determination of algae biomass has been used.	According OECD guideline 201 (2006): "alternative techniques for measurements of biomass, e.g. ... fluorescence can be used..." The RMS is of the opinion that study should not be classified as "not valid" for the reasons mentioned in DE comment. However, in this study validity criteria are not met according OECD guideline 201 (2006): biomass increase (x) 9, CV for section by section growth rates (%) - 247, CV for average specific growth rates (%) -48. Therefore, the validity of study is questionable. Also see comments 5 (23). Open point.	
5(26)	Vol. 3 (AS) B9.2.6- Effects on algal growth- Seeland-Fremer & Emnet 2015a	EFSA: Please include further details on the EC10 and EC20 derivation.	Applicant: In this study the NOEC was determined to be 100 mg/L (the highest rate tested). Consequently it is not possible to calculate EC10 or EC20 figures (other than to be >100 mg/L). RMS (Aug 2017): In the study report it is stated that based on calculated cell densities, the corresponding EC20 and EC10 values and where possible their 95%-confidence limits were calculated by Probit analysis. The 96-hour EbC20, ErC20 and EyC20 (mg/L) were determined to be	Open point RMS to include further details on the EC10 and EC20 derivation for Seeland-Fremer & Emnet 2015a.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			1.9 (95% c.l. 0.0-6.6), >100 (95% c.l. 77- >100) and 1.3 (95% c.l. 0.0-4.9) resp. The 96-hour EbC10, ErC10 and EyC10 (mg/L) were determined to be n.d (95% c.l. n.d), 18 (95% c.l. 1.3-67) and n.d (95% c.l. n.d.) resp. Further information if needed should be provided by applicant. Addressed.	
5(27)	Vol. 3 CA, B.9.2, Effect on aquatic organisms	DE: The study by Hoberg (1992, CGA163935/279) on the toxicity for <i>Lemna</i> which has also been evaluated in the DAR reports a NOEC (14 d) of 0.018 mg a.i./L and an EC ₅₀ (14 d) of 0.19 mg a.i./L. However, the toxicity of trinexapax-ethyl towards <i>Lemna gibba</i> does not drive the risk for aquatic organisms as fishes as well as aquatic invertebrates are more sensitive towards the active substance. Also, there is another endpoint (EyC ₅₀ = 0.2 mg a.s./L <i>Myriophyllum spicatum</i>) for the risk assessment of aquatic higher plants.	RMS (Aug 2017): The study from Hoberg (1992) was not considered valid as validity criteria were not met also the initial and final concentrations were not measured. Addressed	Addressed
5(28)	Vol. 3 (AS) B9.2.7- Effects on aquatic Macrophytes- Hoberg (1991), Hoberg (1992),	EFSA: The studies from Hoberg (1991), Hoberg (1992) were not considered valid; the EC10 and EC20 estimates are not needed and should not be considered valid.	RMS (Aug 2017): agrees. Open point: The irrelevant information will be withdrawn in a revised RAR.	Addressed RMS to address in a revised RAR.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(29)	Vol. 3 CA, B.9.2, Effect on aquatic organisms, Table B.9.2-1 to Table B.9.2-3:	DE: Chronic endpoints: EC ₁₀ and EC ₂₀ values have been calculated. Please provide all chronic endpoints (NOEC, EC ₁₀ and EC ₂₀ values) and also a reasoning for the chronic endpoint to be used in risk assessment (NOEC or EC ₁₀).	Applicant: The previously submitted dossier includes the additional calculations to show the EC10 and EC20 values. RMS (Aug 2017): agrees. Open point: The requested information will be provided and revised RAR will be amended accordingly.	Open point RMS to provide in a revised RAR a reasoning for the chronic endpoint to be used in risk assessment (NOEC or EC ₁₀).
5(30)	Vol. 3 CA, B.9.2, Effect on aquatic organisms, Table B.9.2-1 to Table B.9.2-3:	DE: There is a typo in this table since for the study of Hoberg (1992), CGA163935/279 the endpoint is stated as 14 d EC ₅₀ 8-0.19 mg a.s./L. Please correct.	RMS (Aug 2017): agrees. The typo will be corrected. Open point.	Addressed RMS to correct the typo in a revised RAR.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(31)	Vol. 3 (AS) B9.2.7- Effects on aquatic Macrophytes-Grade (2001)- trinexapac ethyl study	EFSA: The test item concentrations were not maintained within 20% with respect to the nominal concentration; therefore the endpoints cannot be expressed in term of nominal concentrations. Please include the details of the biological findings in a tabular format and an assessment of the validity criteria.	Applicant: As stated in the summary the endpoints calculations are based on the measured concentrations (NOT nominal concentrations). The doubling time of the frond numbers in the control was less than 2 days corresponding to a 13-fold increase in biomass in 7 days - so the test is valid. RMS (Aug 2017): 27.4 mg/L ErC50 based on actual mean concentration Open point: The additional details of the biological finding will be provided. An assessment of the validity criteria for study (Grade 2001) will be included in a revised RAR	Open point RMS to include additional details of the biological finding and an assessment of the validity criteria for the study on the effects of trinexapac-ethyl on aquatic macrophytes- Grade (2001) in a revised RAR. RMS to correct in the LoEP the endpoint from the same study; the endpoint is based on mean measured and not on the nominal concentration (as reported in the LoEP).

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(32)	Vol. 3 (AS) B9.2.7- Effects on aquatic Macrophytes- Kirkwood (2015)	EFSA: EC10 and EC20 estimates were not provided for this study.	Applicant: These data have been added to the previously submitted dossier. RMS (Aug 2017): In the study summary in the dossier EC10 and EC20 values were not provided, however, these values were calculated in the study report and were included in the RAR by RMS. However, for clarity, EC10 and EC20 values with confidence intervals (95%) can be included in the revised RAR for Kirkwood 2015. Addressed	Open point RMS to include in the study summary of the study effects on aquatic Macrophytes- Kirkwood (2015) the EC10 and EC20 values with confidence intervals (95%) and their assessment.
5(33)	Vol. 3 (AS) B9.2.7- Effects on aquatic Macrophytes- Grade (2001)- trinexapac acid study	EFSA: Please include additional details of the biological finding of this study possibly in a tabular format.	RMS (Aug 2017): agrees. Open point: The additional details of the biological finding will be provided.	Open point RMS to include additional details of the biological finding possibly in a tabular format for the study - effects on aquatic macrophytes- Grade (2001)- trinexapac acid.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(34)	Vol. 3 (PPP) B9.3.1- Effects on aquatic Macrophytes- Brown and Maynard 2003	EFSA: Since the concentrations were not maintained within 20% of the nominal the endpoints from this study should be expressed in term of mean measured concentrations.	Applicant: The study summary has been corrected in the dossier to show that the mean measured concentrations were in the range from 85.5% to 94.5% of nominal, so the correct endpoints have been used. RMS (Aug 2017): In the study report it is stated the measured concentrations in the test solution at the start of the test ranged from 100 to 106% of the nominal values. The measure concentrations at the end of the test ranged from 71 to 86% of the nominal values. The overall mean measured concentrations ranged from 86 to 96% of the nominal values. Data requirement: The applicant should provide endpoints expressed in term of mean measured concentrations	Data requirement Applicant to provide the endpoints expressed in term of mean measured concentrations for the study effects on aquatic Macrophytes- Brown and Maynard 2003; the tested concentrations were not maintained within 20% of the nominal.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(35)	Vol. 3 CP, B.9.3, Effect on aquatic organisms	DE: Study evaluation K-CP 10.2.1/04 Brown, R. J. & Maynard, S. J., (2003): Please correct the endpoints for <i>Lemna gibba</i> given in the RMS's conclusion. Based on frond number: (7 d ErC ₅₀ = 45 mg A8587F/L. This is the lowest endpoint. Please include this endpoint in the study evaluation and subsequent compilations referring to this study in the other documents. Based on growth rate (7 d ErC ₅₀ >100 mg A8587F/L; corresponding to >27.1 mg a.s./L) Based on biomass (7 d EbC ₅₀ = 85.2 mg A8587F/L; corresponding to 23.1 mg a.s./L).	Applicant: This endpoint was omitted from the OECD summary in error and this will be corrected during the stop-the-clock period. RMS (Aug 2017): agrees. The lowest endpoint based on frond number should be 7 d ErC ₅₀ = 45 mg A8587F/L. Open point: The correct endpoint will be provided where necessary.	Open point RMS to revise the endpoints from the study K-CP 10.2.1/04 Brown, R. J. & Maynard, S. J., (2003) and to correct as necessary in the list of endpoints and in the revised RAR.
5(36)	Vol. 3 (PPP) B9.3.3- Aquatic risk assessment	EFSA: The endpoint expressed in term of growth rate should be used in the aquatic risk assessment for algae.	RMS (Aug 2017): agrees. The endpoint expressed in term of growth rate will be used in the aquatic risk assessment for algae. Open point: The risk assessment will be updated accordingly.	Open point RMS to correct the risk assessment for algae by using the endpoint expressed in term of growth rate.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(37)	Vol. 3 (PPP) B9.3.3- Aquatic risk assessment- metabolites	EFSA: From the available acute toxicity data for trinexapac-ethyl <i>Mysidopsis bahia</i> seems to be the most sensitive species. However, a chronic toxicity test is not available for this species. In addition, a test on this species is not available for trinexapac acid.	Applicant: These additional data on <i>Mysidopsis bahia</i> are not a standard requirement in the EU but are required for the US EPA, and are therefore included here. Trinexapac-ethyl inhibits gibberellin biosynthesis in plants, and this result in stem growth inhibition via inhibition of internodal elongation. Given this mode of action it is likely that the chronic risk assessment will be driven by aquatic plants, and this has been confirmed with the lowest RAC of 20 µg /L being obtained from the study with the rooted aquatic plant <i>Myriophyllum spicatum</i>. The use of the <i>Myriophyllum</i> endpoint ensures an acceptable chronic risk to aquatic organisms. RMS (Aug 2017): agrees with the applicant. Addressed	Data requirement From the available acute toxicity data for trinexapac-ethyl <i>Mysidopsis bahia</i> seems to be the most sensitive species of aquatic invertebrates. However, a chronic toxicity test is not available for this species. The applicant is given the possibility to provide further information to address this point. See also 5(17)
5(38)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP. It seems that only the lowest endpoints were included whilst all valid endpoints should be included.	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated.	Open point RMS to include all valid aquatic toxicity endpoints in the LoEP.

Aquatic organisms				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(39)	List of endpoints	EFSA: Please double check the acute endpoint for <i>Daphnia magna</i> for trinexapac acid it should be >100 mg a.s./L (ref. study from Grade (1995)).	Applicant: In the dRAR this <i>Daphnia</i> acute endpoint for trinexapac acid is listed as 111 mg/L (Table B.9.4.1-1). RMS (Aug 2017): The endpoint should be 111 mg/L Addressed Open point: The LoEP and the RAR will be updated where relevant.	
5(40)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(41)	Vol. 3 (CA), B.9.3.1.1, acute toxicity to adult honeybees, page 179, table B 9.3.1.1-1	DE: According to the header of the second column in table B.9.3.1.1-1 the presented acute oral and contact LD ₅₀ values (> 200 µg a.s./bee) were taken from the EFSA Scientific Report (2005). However, these values were used for the risk assessment in the previous DAR (Netherlands, 2003) but not presented in the cited EFSA document.	Applicant: These data for trinexapac-ethyl technical are from the study by of Barth 2000 "Acute toxicity of CGA 163935 technical to the honeybee <i>Apis mellifera</i> L. under laboratory conditions" File No CGA163935/0672 as shown in Table CA 8.3.1-1 of our previous submission. RMS (Aug 2017): Agree with comment. In the EFSA scientific report (2005) only	Addressed RMS to address in a revised RAR.

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			formulation Moddus 250 EC endpoints were provided: LD50>108 µg a.s./bee (oral) and LD50=69.6 µg a.s./bee (contact). Open point: The header of the table will be corrected.	
5(42)	Vol. 3(AS) B.9.3.1 Effects on bees- Hoxter 1990	EFSA: Please clarify why this study was considered not acceptable. The presented summary does not include enough details for an independent assessment.	Applicant: In this study there was an irregular dose response curve with mortalities up to and including the 22 µg/bee group. This was considered not to be treatment related, since it was confined primarily to one replicate within this dosage groups. There were technical deficiencies in the study with effects observed in the control group, mortalities associated with individual replicates, no toxic standard and no analysis. Because of these technical deficiencies the resulting endpoints from this study are not considered robust and reliable for the risk assessment. The studies used in the risk assessment are all well conducted GLP studies. RMS (Aug 2017): Agree with applicant. Study is not considered acceptable. Addressed	Data requirement Applicant to provide a detailed study summary for effects on bees- Hoxter 1990.
5(43)	Vol. 3 (PPP) B.9.5.1 Effects on bees- Bocksch	EFSA: Please include a summary table of the biological observations for this study.	Applicant: These data can be added during the stop-the-clock period.	Open point RMS to include a summary table of the

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	(2004)		RMS (Aug 2017): agree. Open point: The details of the biological observations will be provided.	biological observations for the study on bees- Bocksch (2004).
5(44)	Vol. 3 (PPP) B.9.5.1 Effects on bees- Ruhland 2014	EFSA: Was the mortality assessed at daily interval in this study? It is additionally noted that an assessment of the sublethal effects e.g. effects on the HPG was not performed. Please clarify how the endpoint is expressed in the results; it is not consistently reported see section B.9.6 and the list of endpoints.	Applicant: As per protocol, mortality was assessed daily. In the original OECD summary the endpoints were expressed wrongly expressed as μg formulation/bee/day and not in terms of active substance. The correct 10-day LD_{50} is $46.6 \mu\text{g a.s./bee/day}$ as stated in the original report RMS (Aug 2017): The mortality, sublethal effects and behavioural abnormalities were recorded daily. The correct endpoints should be adult chronic -10 d NOED $26.9 \mu\text{g a.s./bee/day}$ and 10d LD_{50} $46.6 \mu\text{g a.s./bee/day}$. Open point: The endpoint will be corrected in revised RAR section B.9.6 and in the LoEP.	Open point RMS to make sure that the endpoint from the study effects on bees- Ruhland 2014 is consistently and correctly reported in the revised RAR and in the list of endpoints. In addition, RMS to include additional details on the mortality, sublethal effects and behavioural abnormalities assessment in the revised RAR. Data requirement Applicant to provide additional information on potential sub-lethal effects of trinexapac-ethyl on honeybees (e.g. effects on HPG).
5(45)	Vol. 3 (PPP) B.9.5.1 Effects on bees- Kleebaum (2014)	EFSA: The available larvae test foresee a single dosage and it is therefore not a repeated exposure study, as it is recommended in the EFSA bee guidance.	Applicant: In the honeybee larval study (Kleebaum, 2014) there were 4 days of exposure (days 3, 4, 5 and 6) and so it can be described as a repeated exposure study. Also see comment 5(50) below.	See 5(46)

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			RMS (Aug 2017): Agree with applicant. Also, the new study is available on request. See comment 5(46). Addressed	
5(46)	Vol. 3 – B.9 (PPP), B.9.5.1.2: New data, Kleebaum (2016)	Applicant: Since submission of the Trinexapac supplementary dossier a new chronic toxicity study to honeybee larvae with trinexapac-ethyl a.s. (Kleebaum, 2016; CGA163935_10774) was done by Syngenta for the Canadian regulatory authorities. This new study is available on request. A comparison of the reported 8-day endpoints from this 22-day repeated exposure laboratory study with honeybee larvae using trinexapac-ethyl A.I. (Kleebaum, 2016) with the reported endpoint from a previously submitted 8-d repeated exposure laboratory study with trinexapac-ethyl formulation A8587F (Kleebaum, 2014) indicated differences in the shape of the rate response, the required statistical analysis and in the endpoints. Further statistical evaluation demonstrated that the statistical method used resulted in this difference in reported endpoints. When the same statistical method is used, the endpoints from the two studies are very similar, indicating that there is no biologically significant	Applicant: These data can be added during the stop-the-clock period. In this honeybee larval study (Kleebaum, 2016) there were 4 days of exposure (days 3, 4, 5 and 6) and so it is described as a repeated exposure study. The critical 8 day NOED endpoint in this study is 12.6 µg a.s./larva/development period. RMS (Aug 2017): Noted	Data requirement Applicant to provide the available chronic toxicity study on honeybee larvae. See also 5(45) Open point RMS to assess the additional information on chronic toxicity to larvae, this includes the document 'Comment on trinexapac honeybee', embedded in column 2 of the reporting table.

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		difference between the two studies. A more detailed assessment on the statistical method is provided here:  Comments on Trinexapac Honeybe		
5(47)	Vol. 3 – B.9 (PPP), B.9.6.1, Table B.9.6.1-1: Honeybee adult chronic endpoint and risk assessment.	Applicant: In Tables B.9.6.1-1 and B.9.6.1-2 the endpoints for adult chronic toxicity (Ruhland, 2014; A8587F_10096) are incorrect. The correct values are as given in the OECD summary (table B.9.5.1.2-1): Adult Chronic -10 d NOED 26.9 µg a.s./bee/day and 10d LD50 46.6 µg a.s./bee/day. These revised values should be used in risk assessment. The adult chronic NOED 26.9 µg a.i./bee/day is compared to the total exposure ETE of 0.128 µg a.i./bee/day, to give a TER of 210 indicating acceptable risk.	RMS (Aug 2017): agrees. Also See comments 5(44). Open point: The chronic risk to bees will be updated accordingly.	See 5(44)
5(48)	Vol. 3 (CP), B.9.6.1., Risk assessment for honeybees, page 96, Acute Risk Assessment	DE: The acute endpoints derived from the study by Jeker (2008) (oral LD ₅₀ = >83 µg a.s./bee, oral LD ₅₀ = >100 µg a.s./bee) indicate that the specific	Applicant: Trinexapac-ethyl is not highly toxic to bees and so in these studies we get "greater than" values rather than true LD ₅₀ values. Here the range of endpoints	Addressed

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		endpoints are set above 83 and 100 µg a.s./bee. This is confirmed by the results of the acute study by Barth (2000) with oral and contact LD₅₀ values of >200 µg a.s./bee and the acute study by Schmitzer et al. (2008) with an oral LD₅₀ of >216 µg a.s./bee and a contact LD₅₀ of >200 µg a.s./bee. Please explain why the acute endpoints derived from the study by Jeker (2008) instead of the acute endpoints from the study by Barth (2000) or by Schmitzer et al. (2008) were used in the risk assessment.	from >83 µg a.s./bee to >216 µg a.s./bee) is not critical as all will pass the risk assessment. RMS (Aug 2017): Agrees with the applicant also these endpoints from the study Jeker (2008) were used in the risk assessment as the lowest available endpoints. Addressed	
5(49)	Vol. 3 (CP), B.9.6.1., Risk assessment for honeybees, page 97, Larval assessment	DE: It should be noted that the chronic larval study had a duration of 8 days and the actual exposure took place from day 3 (first application of the test substance) until day 8 (end of study). This sums up to a duration of 6 days, which should be considered for the calculation of the larval TER.	Applicant: See applicant comment under 5(50) below. RMS (Aug 2017): agree that the NOED for the risk assessment should be 13.9 µg a.s./larva/day. Test duration: Application: D3 to D6 Post exposure: D7 to D8, so duration is 6 days. Open point: The risk assessment will be corrected.	Addressed It is noted that the risk assessment as reported on page 97 is not considered suitable. See also 5(51).

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(50)	Vol. 3 – B.9 (PPP), B.9.6.1: Honeybee larval risk assessment	Applicant: When referring to the honeybee larval study on the representative formulation A8587F (Kleebaum, 2014) the NOED of 83.4 µg a.s./larva in the larval risk assessment was converted to an equivalent to 11.9 µg a.s./larva/day for the EPPO risk assessment based on 7 day study duration. However the applicant believes that the conversion should be to divide by 5, based on 4 days exposure and 1 extra day for food consumption. On this basis the NOED for the risk assessment would be 16.7 µg a.s./larva/day.	RMS (Aug 2017): Please refer to the comment above 5(49)	See 5(49) and 5(51).
5(51)	Vol. 3 (PPP) B.9.6- Risk assessment for honeybees	EFSA: A risk assessment according to the EFSA Bee Guidance Document was included in the RAR. However, this does not include an assessment via all the relevant exposure routes; an assessment of the exposure via contaminated water is missing. Although it is acknowledged that the EFSA Bee Guidance Document is yet to be implemented, it was recently agreed at the Pesticides Peer Review Expert Meeting 133 (September, 2015) that it should be used (at least the first tier scheme and the general principles for the higher tier). The previous risk	Applicant: The previously submitted dossier includes all the required data for chronic larval and adult honeybee studies. The adult chronic LC50 is 46.6 µg a.s./bee/day, and the larval endpoint is 83.4 µg a.s./bee/larva/development period. But also see applicants comment 5(46) on the Kleebaum, 2016 study the critical 8 day NOED endpoint in this study is 12.6 µg a.s./larva/development period. Trinexapac-ethyl is not highly toxic to bees, and guttation is not frequent in crops such as wheat and barley so there should be no need for a risk assessment via contaminated water. However a	Data requirement Applicant to provide an updated risk assessment for honeybees according to the EFSA Bee Guidance Document. This should include: i) a risk assessment via exposure to contaminated water ii) information/assessment of the potential for accumulative effects iii) in accordance with Regulation (EU) 283/2013, a consideration of the risk to bees from metabolites. It is suggested that the methodology in the EFSA (2013) Bee guidance is followed to identify which plant metabolites

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		assessment schemes are not able to consider various aspects which are now considered to be important in the risk assessment for bees (e.g. chronic, larvae, additional exposure scenarios). Furthermore, it is now necessary to provide chronic adult and larvae data according to regulation 283/2011. Therefore, in the absence of an alternative risk assessment scheme which is able to address these points, it was agreed that the EFSA Bee Guidance should be used.	revised risk assessment can be added to the dossier during the stop-the-clock period. RMS (Aug 2017): The exposure via contaminated water should be provided. Data requirements: to be addressed by the Applicant.	should be assessed. See also 5(46), 5(52) and 5(53)
5(52)	Vol. 3 (PPP) Risk assessment for honeybees	EFSA: In addressing the risk assessment for bees according to the EFSA guidance document information/assessment is needed of the potential for accumulative effects.	Applicant: Trinexapac-ethyl is essentially of low toxicity to bees and there is no suggestion that of accumulative effects, neither is there agree guidance for such a risk assessment. RMS (Aug 2017): Consideration of accumulative effects should be provided. Data requirements: to be addressed by the Applicant.	See 5(51)
5(53)	Vol. 3 (PPP) Risk assessment for honeybees	EFSA: In accordance with Regulation (EU) 283/2013, a consideration of the risk to bees from metabolites is needed. It is suggested that the methodology in the EFSA (2013) Bee guidance is followed to	Applicant: A8587F is only used on wheat and barley crops, and these crops are not attractive to bees. However bees could be exposed via flowering weeds in the crop. We have no data on the	See 5(51)

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		identify which plant metabolites should be assessed.	occurrence of metabolites in such pollen and nectar, but a risk assessment can be done based on the conservative assumption that the metabolites are 10 times more toxic than the parent. When one considers the mode of action of trinexapac-ethyl it is very unlikely that its metabolites would be toxic to bees. RMS (Aug 2017): Consideration of the risk to bees from metabolites should be provided. Data requirements: to be addressed by the Applicant.	
5(54)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP. It seems that only the part of the endpoints was included whilst all valid endpoints should be included.	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated.	Open point RMS to include all valid bee toxicity endpoints in the LoEP.
5(55)	List of endpoints	EFSA: The risk assessment for bees in line with EFSA (2013) should be included in the LoEP.	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated.	Open point RMS to include the risk assessment for bees in line with EFSA (2013) in the LoEP. See also 5(51)

Bees and non-target arthropods				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(56)	LoEP, Effects on other arthropod species, Extended laboratory tests, aged residue tests	DE: Please indicate substrate used in the tests 3 rd column).	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated.	Open point RMS to report in the list of endpoints the substrate used in the tests on other arthropod species, extended laboratory tests, aged residue tests.
5(57)		NL: no comments.	RMS (Aug 2017): Noted.	Noted
5(58)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted

Earthworms and other non-target soil macro- and mesofauna				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(59)	Vol. 3 (AS) B.9.4 Earthworms and other non-target soil macro- and mesofauna	EFSA: No chronic studies performed with the active substance are available for earthworms and other non-target soil macro- and mesofauna.	Applicant: The chronic studies submitted are done with the representative formulation of trinexapac-ethyl and we consider that, as has been done previously, this requirement for active substance data for a solo formulation can be bridged from the studies with the A8587F 250 g/L formulation of trinexapac-ethyl. RMS (Aug 2017): Three new studies on <i>Eisenia fetida</i>, <i>Hypoaspis aculeifer</i> and on <i>Falsomia candida</i> have been carried out with the representative formulation, A8587F, <i>in lieu</i> of the technical active substance. The data requirements are fulfilled. Addressed.	Data requirement No chronic studies performed with the active substance are available for earthworms and other non-target soil macro- and mesofauna. Applicant to provide further information/a case in support of the bridging of the chronic toxicity data on earthworms and other non-target soil macro- and mesofauna from the formulation to the active substance.

Earthworms and other non-target soil macro- and mesofauna				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(60)	Vol. 3 (PPP) B.9.7 Effects on on-target soil meso- and macrofauna- Friedrich 2015	EFSA: The NOEC for reproduction was set at 309 mg test item /kg soil dw, however, at that level a reduction in the number of juveniles with respect to the control was observed. Please clarify why this effect was not considered as biologically significant.	Applicant: As indicated in the original report the only statistically significant effects were seen at the 556 and 1000 mg test item/kg soil dw, and so the NOEC is 309 mg test item/kg soil dw. RMS (Aug 2017): The reduction in the number of juveniles is biologically relevant. However, this effect was not statistically significant at 309 mg test item /kg soil dw. Therefore the NOEC for reproduction was set at that level. Addressed.	Addressed
5(61)	Vol. 3 – B.9 (PPP), B.9.7.1: New earthworm data for CGA300405, Luhurs (2015)	Applicant: CGA300405 - Chronic toxicity to earthworms: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC was found to be 1000 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil organisms.	RMS (Aug 2017): noted. RMS is of the opinion that this study can be included in RAR for transparency and data completeness	Data requirement Applicant to provide the new earthworm data for CGA300405, Luhurs (2015).

Earthworms and other non-target soil macro- and mesofauna				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(62)	Vol. 3 – B.9 (PPP), B.9.7.1: New Collembola data for CGA300405, Luhurs (2015)	Applicant: CGA300405 - Toxicity to collembolan: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC was found to be 1000 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil organisms.	RMS (Aug 2017): please refer to 5(61).	Data requirement Applicant to provide the new Collembola data for CGA300405, Luhurs (2015).
5(63)	Vol. 3 – B.9 (PPP), B.9.7.1: New Hypoaspsis for CGA300405, Luhurs (2015)	Applicant: CGA300405 - Chronic toxicity to Hypoaspsis: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC was found to be 1000 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil organisms.	RMS (Aug 2017): please refer to 5(61).	Data requirement Applicant to provide the new toxicity study on Hypoaspsis for CGA300405, Luhurs (2015).
5(64)		NL: no comments.	RMS (Aug 2017): Noted.	Noted
5(65)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted

Soil nitrogen transformation				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(66)	Vol. 3 (AS) B.9.5 Effects on soil nitrogen transformation	EFSA: Further information may be needed to address the risk to soil microorganisms for trinexapac acid.	Applicant: In the aerobic soil degradation studies trinexapac acid was the major transformation product, with formation rates up to 98% after 1 day. This rapid transformation from the parent to trinexapac acid is expected to be similarly fast in this soil micro-organism study. On this basis a separate SMO study for trinexapac acid is not considered necessary, since it can be assumed that the soil organisms will have been exposed to trinexapac acid in the test with the parent. RMS (Aug 2017): agrees with the applicant. Trinexapac acid is major soil metabolite and its effects are covered by the test with the parent compound due to rapid conversation of trinexapac ethyl into trinexapac acid in soils. Addressed.	Data requirement A case/further information may be needed to address the risk to soil microorganisms for trinexapac acid.

Soil nitrogen transformation				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(67)	Vol. 3 – B.9 (PPP), B.9.7.1: New SMO data for CGA300405, Hammesfahr (2015)	Applicant: CGA300405 – Effects on carbon and Nitrogen transformation: Since submission a new study with the metabolite CGA300405 has been completed. The new study is available on request. In the new study the NOEC for both Carbon and Nitrogen transformation was found to be 200 mg CGA300405/kg soil, confirming that this metabolite does not present a risk to soil micro-organisms.	RMS (Aug 2017): Noted Also please refer to 5(61).	Data requirement Applicant to provide the new study on the effects on carbon and nitrogen transformation with the metabolite CGA300405.
5(68)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted
5(69)		NL: no comments.	RMS (Aug 2017): Noted.	Noted

Terrestrial non-target higher plants				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(70)	Vol. 3 (CP) B.9.7 Effects on other terrestrial organisms	EFSA: It is reported that in the study Chetram 1991 an inverse dose response in the radicle elongation was observed. Could additional details on these findings be included?	Applicant: This 1991 study to evaluate seed germination on petri dishes is not relevant to the potential exposure under field conditions from a spray or in the soil. RMS (Aug 2017): no new information on radicle elongation was provided since the first inclusion of a.s. and it was agreed that the radicle elongation in the seed germination test at lower test rates is not of ecological significance for the non-target plant communities. RMS is in opinion that no further consideration on the radicle elongation is required. Addressed.	Experts' consultation Experts to discuss the ecotoxicological relevance of the effects on radicle elongation observed in the study Chetram 1991. Data requirement Applicant to provide a detailed study summary for the study on the effects on non target terrestrial plants from Chetram (1991).
5(71)	List of endpoints	EFSA: For completeness it should be indicated that the studies from Wardle (2003) were neither performed under GLP nor according nor were guideline studies. This makes it difficult to assess their validity.	Applicant: The Walder 2003 studies are plant screening studies and were not performed under GLP. RMS (Aug 2017): Agrees. Open point: The LoEP will be updated.	Open point RMS to indicate in the list of endpoints that Walder (2003) were neither performed under GLP nor according nor were guideline studies.
5(72)		NL: no comments.	RMS (Aug 2017): Noted.	Noted
5(73)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted

section 5 – Ecotoxicology

Other non-target terrestrial organisms (flora and fauna)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(74)		NL: no comments.	RMS (Aug 2017): Noted.	Noted
5(75)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted

Biological methods for sewage treatment				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(76)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted

Other comments incl. available monitoring data				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(77)	Vol. 4 Batches used in the ecotoxicological test	EFSA: The equivalence between technical materials should be reconsidered once the technical specification is agreed. Pending on the above, it should be also assessed whether the batches used in the ecotoxicological testing are compliant with the technical specifications of the first approval.	Applicant: The details of technical materials have been submitted previously in Document J. RMS (Aug 2017): Noted. Open point: Vol 4 will be updated if necessary.	Open point RMS to provide further consideration in Vol.4 on whether the batches used in the ecotoxicological testing are compliant with the technical specifications.

Other comments incl. available monitoring data				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(78)	Vol. 3 (CA) B.911 Literature review	EFSA: Please include additional details on how the literature search was performed e.g. identifiers used in the search for the active substance and the metabolites. In addition the criteria for assessing the reliability and relevance of the studies should be included. Could be confirmed that the EFSA guidance (2011) on open literature search was followed?	Applicant: The submitted literature search from 2015 was completed according to the guidelines and included trinexapac-ethyl, trinexapac acid, CGA300405, CGA113745 and CGA224439. A new search with an updated list of metabolites is not yet available, but will be submitted during the stop-the-clock period. RMS (Aug 2017): Agrees. The literature search will be reported more completely. It can be confirmed that the EFSA guidance (2011) on open literature search was followed. Data requirement: Applicant to provide new literature search on metabolites. Open point: The additional details on literature search will be included in the revised RAR.	Data requirement Applicant to provide an updated literature search in line with the EFSA guidance (2011) on open literature search covering the trinexapac-methyl metabolites relevant for the environmental risk assessment. Open point RMS to include additional details on how the literature search was performed e.g. identifiers used in the search for the active substance and the metabolites. In addition the criteria for assessing the reliability and relevance of the studies should be included.

Other comments incl. available monitoring data				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(79)	Classification and labelling	EFSA: It is noted that the classification and labelling is included in the harmonised C&L section, please move it in the Peer Review proposal section. The C&L of trinexapac-ethyl was not yet harmonised.	RMS (Aug 2017): Agrees. Open point: The C&L section will be updated.	Open point RMS to update the classification and labelling section in the list of endpoints considering that the C&L of trinexapac-ethyl was not yet harmonised. The precautionary statements are not needed and should be removed, the acute and chronic classification and the related M-Factor should be reported, as necessary.
5(80)	Endocrine disruption	EFSA: The ecotoxicity data available for trinexapac-ethyl may not be sufficient to conclude on endocrine disruption in non-target organisms.	Applicant: We have submitted a complete set of the required ecotoxicity studies with reproductive studies on birds, fish and aquatic invertebrates. No suggestions of endocrine disruption were seen in these studies. Also note the earlier comments on endocrine disruption 2(31) and 2(36). RMS (Aug 2017): It was not found any indication of endocrine –disruptive effects from existing database for trinexapac-ethyl. Therefore further special testing for endocrine disrupting behaviour is not warranted. Addressed.	Data requirement The applicant is given the possibility to submit further data to address the endocrine disruption in non target organisms. The ecotoxicity data available for trinexapac-ethyl are not be sufficient to conclude on endocrine disruption in non-target organisms. See also 2(31) and 2(36).

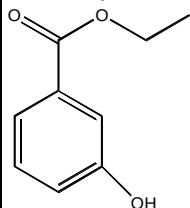
Other comments incl. available monitoring data				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(81)	Formulations tested	EFSA: It is noted in the ecotoxicological section a different formulation that the representative one was tested. It should be ensured that the additional formulation tested is comparable to the representative one.	Applicant: The formulation A8587F is a water based (ME) formulation and the submission includes a full set of studies with this formulation. RMS (Aug 2017): this information is provided in Volume 4. It is ensured that the additional formulation tested is comparable to the representative one. Addressed.	Addressed
5(82)	List of endpoints	EFSA: Please include all valid endpoints in the LoEP. It seems that only the part of the endpoints was included whilst all valid endpoints should be included.	RMS (Aug 2017): Agrees. Open point: The LoEP will be updated.	Open point RMS to include all valid endpoints in the LoEP. It seems that only the part of the endpoints was included whilst all valid endpoints should be included.
5(83)		NL: no comments.	RMS (Aug 2017): Noted.	Noted
5(84)		FR: Section not reviewed, no comment	RMS (Aug 2017): Noted.	Noted
5(85)		LV: Section not reviewed, no comments	RMS (Aug 2017): Noted.	Noted

1. Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(1)	Vol4 C.1.2.2 (Syngenta)	FR: Please specify and report clearly that old specifications of the first inclusion are not any more covered by new toxicological evaluation. Technical specification of the reference proposed for renewal of the active substance should be covered by batches used in key (eco)toxicity studies.	Applicant (August 2017): Noted – RMS to clarify. RMS (August 2017): Noted. At the time of specifications assessment, and in particular toxicological evaluation of all the data and information available thereon this information could not be finalised and further response of the notifier was important. The RMS acknowledge the importance to have this fully clarified in the revised Vol.4 C.1.2.2 with reference to toxicological part of assessment. (Open point: RMS to revise Vol.4 C.1.2.2 accordingly)	Addressed: See comment 1(5)

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(2)	Vol. 4 Syngenta, C.1.2.2, Manufacturing process, impurities, p.20	EFSA: small note: impurity 9 has two chiral centres	Applicant (August 2017): Noted – RMS to clarify. RMS (August 2017): Agreed. That is correct, impurity 9 (CGA252938, i.e. 2'-hydroxy-5,6'-dioxo-bicyclohexyl-6,1'-diene-3,4'-dicarboxylic acid diethyl ester) has two chiral centres. (Open point: RMS to update the revised Vol.4 C.1.2.2 by information on the chiral centres).	Open point: RMS to update the revised Vol.4 C.1.2.2 by information on the chiral centres
1(3)	Vol. 4 Syngenta, C.1.2.2, Manufacturing process, impurities, p.22	EFSA: small note: impurity 12 has two chiral centres	Applicant (August 2017): acknowledges EFSA note. RMS (August 2017): Agreed. That is correct, impurity 12 (NOA427417, i.e. 4,6-bis-cyclopropanecarbonyl-3-hydroxy-5-oxo-cyclohex-3-enecarboxylic acid ethyl ester) has two chiral centres. (Open point: RMS to update the revised Vol.4 C.1.2.2 by information on the chiral centres).	See open point 1(2)

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(4)	Vol. 4 All notifiers, C.1.2.2, Identity of impurities	EFSA: clarification is needed on the assignment of CAS numbers: 95266-40-3, 104273-73-6, 143294-89-7	Applicant (August 2017): Noted – RMS to clarify. RMS (August 2017): Noted. <u>CAS numbers assignment:</u> 95266-40-3: trinexapac-ethyl (enol form) 104273-73-6: is trinexapac acid (keto form), 143294-89-7: trinexapac acid (enol form). (Open point: RMS to add the information in the revised Vol.4 C.1.2.2).	Open point: RMS to amend the Vol.4s with the proper CAS numbers
1(5)	Vol. 4 Syngenta, C.1.2.3, Specification, RMS conclusion, p. 34	EFSA agrees with the RMS on the conclusion on the proposed specification, i.e. the proposed renewal specification should be considered the reference specification. Also agrees with the conclusion on impurity 2.	Applicant (August 2017): Syngenta agrees with EFSA note. RMS (August 2017): the comments are acknowledged. (Addressed)	Addressed: The proposed renewal specification should be considered the reference specification. See also comment 1(7)

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(6)	Vol. 4 Syngenta, C.1.2.2, Manufacturing process, impurities, p.16 -21	EFSA: small note: impurities 1,2,5,6,10,11 have also one or more chirality centres	Applicant (August 2017): acknowledges EFSA note. RMS (August 2017): The RMS agree on the chiral centres present in the impurities (2,5,6,10 and 11) and this information could be added in the revised Vol. 4 C.1.2.2. In regards to presence of chiral centre in the impurity 1 (CGA264324, 3-hydroxy-benzoic acid ethyl ester, chemical structure below)  clarification would be appreciated; unless the impact of hydroxy-group attached to benzene ring could somehow be reasoning this. (Data requirement: to clarify the presence of chiral centre in impurity 1). (Open point: RMS to update the revised Vol.4 C.1.2.2 accordingly).	Addressed: RMS has right, impurity 1 is mentioned by mistake.

Identity				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(7)	Vol. 4, Table C.1.2.3-6 : Comparison of trinexapac-ethyl of Monthey source specifications (Annex I inclusion, provisional specification and the new reference specification), p.33-34.	NL: Agree with the new reference specification of the source.	Applicant (August 2017): Syngenta agrees with NL note. RMS (August 2017): the comments have been acknowledged. (Addressed)	Addressed: See also comment 1(5)

Reasonable steps undertaken to form Task Force				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(8)	Vol. 4, All sources, C.1.9 Steps to form a task force, p. 74	EFSA: if a TF is formed is there the intention to propose also a common minimum purity for all TF members?	Applicant (August 2017): Syngenta confirms that no common minimum purity was proposed within the Trinexapac Task Force (TF). RMS (August 2017): Noted. The specifications of Syngenta source have been supported by their method of manufacture and therefore the analytical profile of batches thereon. (Addressed)	Open point: EFSA to note in the conclusion that no agreement on a common specification was reached

2. Effects on human and animal health

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(1)	Vol. 4, C.1.4.2.2 Syngenta	NL: In Table C.1.4.2.2 when the RMS states that further evaluation on carcinogenicity, reproductive toxicity, immunotoxicity, phototoxicity and neurotoxicity is needed we assume they mean additional QSAR analysis and not actual in vivo studies? Considering the low levels of the impurities we do not consider that additional animal studies are justified. Please clarify in the table.	Applicant: Please see 2(2). RMS (August 2017): When it is stated that 'further data required' and 'additional analysis' needed (e.g. Table C.1.4.2.2-2, Table C.1.4.2.2-3 and Table C.1.4.2.2-4) the following definition is used by the RMS LT (see confidential Vol 4 Syngenta, C.1.4.2.2., 77 pp. and 90 pp.): <i>Taking into account the fact that from a toxicological point of view the proposed technical specification is not supported by the specification of the material used in CMR, critical (basis for the derivation of reference values), skin sensitisation, immunotoxicity, phototoxicity and neurotoxicity studies regarding most of the impurities levels the RMS LT is of the opinion that there is need for additional and comprehensive structural activity relationship analysis (referred to as 'additional analysis') based on additional relevant model (e.g. OECD Toolbox) and open literature search on these specific impurities to see whether they raise any concerns for the above mentioned endpoints.</i>	Data requirement (Syngenta) Additional and comprehensive structural activity relationship analysis (referred to as 'additional analysis') based on additional relevant model (e.g. OECD Toolbox) and open literature search on impurities to see whether they raise any concerns for carcinogenicity, reproductive toxicity, immunotoxicity, phototoxicity and neurotoxicity endpoints.

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			Addressed	
2(2)	Vol. 4, C.1.4.2 Assessment of the toxicological profile of impurities	Applicant Syngenta: At the request of the RMS Lithuania further work has been conducted to address the relevance and safety of impurities in the Syngenta technical specification, although it is not complete. A literature search is in progress, which will be submitted during the stop-the-clock period along with an updated document J. This is intended to aid in fully characterising the impurities if further information is available in the scientific literature. At the suggestion of the RMS, a further QSAR tool is being used to predict the toxicological properties of the impurities. The Applicant Syngenta will submit this information during the stop-the-clock period and combine it with the DEREK predictions in an overall weight-of-evidence assessment. The Applicant Syngenta agrees with the RMS opinion that CGA158377 should be considered to be relevant based on its demonstrated skin sensitisation properties.	RMS (August 2017): Noted. Regarding skin sensitisation potential of technical active substance and/or the representative formulation (A8587F) it should be noted that the different OECD TG were used: Buehler assay (<i>Simon C, 2009</i>) and Maximisation test (<i>Ruddock, 2001</i>) according to OECD TG 406 (1992) and a Local Lymph Node Assay (new study in the reporting phase) according to OECD TG 429. The LLNA is preferred to the M&K-test and clearly preferred Buehler-test according to the current state of knowledge due to different sensitivity and reliability. It means that in some cases a substance itself could show a negative result or weak response in Buehler / M&K studies, however, it could show a positive response in the LLNA test. It should be noted that a Buehler assay with 9 induction applications on the representative formulation (A8587F) was limited and showed a weak response: the sensitisation rate of 10% (below the threshold of significance 15%) (please see Vol 3CP, B.6.1.6). Hence, the	Open point RMS to reconsider the skin sensitisation potential of trinexapac-ethyl technical material based on the content of a relevant impurity (i.e. CGA158377) and potentially relevant impurities (i.e. CGA267934, CGA190042, CGA252938 and NOA42741). Should trinexapac-ethyl be considered skin sensitizer (as proposed by Syngenta) the maximum content of (potentially) relevant impurities might set at the level proposed in the technical specification. Data requirement (Syngenta) Applicant (Syngenta) to present a robust scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of relevant impurity CGA158377. Local lymph node assay with spiked batch material to address skin sensitisation potential.

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		The Applicant Syngenta proposed further testing of technical material spiked with several impurities up to the maximum level they are proposed for inclusion in the Syngenta specification. This was to address potential concerns about inclusion levels of the impurities in batches used for bacterial and mammalian gene mutation assays, and address structural alerts for skin sensitisation. These studies are in the reporting phase although the overall outcomes are available. Both bacterial reverse mutation (Ames) and HPRT mammalian gene mutation assays were negative with this spiked batch of technical material, demonstrating that inclusion of these impurities up to their maximum level in the specification does not result in mutagenicity. The Applicant Syngenta will submit final reports for both of these studies in the stop-clock window. A local lymph node assay was conducted with spiked batch material to address skin sensitisation potential following structural alerts. This study was positive, with an EC3 value of 95.4%. An older local lymph node study with a batch of non-spiked	conclusion regarding the skin sensitisation potential of the representative formulation (negative) might be considered equivocal based on new information provided by the Applicant. It should be noted that an older local lymph node study (<i>Betts C J, 2006</i>) with a batch of non-spiked trinexapac-ethyl Syngenta technical material (Batch No SMO5D180) was not submitted for the purpose of renewal on 28th October 2015 and therefore was not evaluated by the RMS LT. However, this study and its summary in word format should be submitted for the purpose of renewal due to the reasons mentioned above and should be evaluated by the RMS LT in the revised RAR Vol 3. In addition, the Batch No SMO5D180 used in this study should be compared with the proposed technical specification and some levels of the specific impurities might be covered by this study. Data requirement Open point	Additional and comprehensive structural activity relationship analysis based on additional relevant model (e.g. OECD Toolbox) and open literature search on these four specific impurities (CGA267934, CGA190042, CGA252938 and NOA427417) to see whether they raise any concerns for the skin sensitisation. Robust summary reports of the local lymph node study (<i>Betts C J, 2006</i>) with a batch of non-spiked trinexapac-ethyl Syngenta technical material (Batch No SMO5D180). Batch No SMO5D180 used in this study should be compared with the proposed technical specification.

Other comments, incl comments on volume 4 (impurities, batches)				
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		trinexapac-ethyl Syngenta technical material is also available and was negative. The alterations in impurity profile is considered likely to be the reason for the difference in the results of these two studies. Therefore, due to potential for skin sensitisation properties (and not being able to be certain which impurity(s) is responsible), impurities CGA158377, CGA267934, CGA190042, CGA252938 and NOA42741 are considered to be potentially relevant. Given that it has already been demonstrated to be an <i>in vivo</i> skin sensitiser, it is likely that CGA158377 is responsible for the positive response with spiked Syngenta trinexapac-ethyl technical material. The weak skin sensitising potential of Syngenta trinexapac-ethyl technical material is not considered to be of concern for human health, but Syngenta technical material should be labelled as a skin sensitiser. Trinexapac-ethyl technical (when not spiked with impurities) is not considered to be skin sensitising based on the existing studies. Due to the weak response of the Syngenta technical material in the local lymph node assay, a classification for the technical material is not considered to impact the		

Other comments, incl comments on volume 4 (impurities, batches)				
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		representative formulation, A8587F as it contains trinexapac-ethyl at a lower concentration than the technical's EC3 value (i.e. less than 95.4%). A8587F contains 25% trinexapac-ethyl technical. A8587F was non-sensitising when tested previously. The applicant intends to submit final reports for both of these local lymph node studies in the stop-the-clock window.		
2(3)	Vol. 4 Annex C Representativeness of the toxicological studies to the technical specification. Syngenta	EFSA: from the analysis done by the RMS EFSA would consider that at least genotoxicity studies are covered by the Syngenta technical specification. Considering other endpoints, one of the main concerns is the skin sensitisation potential of some impurities as predicted by QSAR analysis. Did trinexapac-ethyl share the same alerts as the impurities?. A read-across analysis using OECD QSAR toolbox might be useful to address this point. The impurities showing a skin sensitisation potential might be considered relevant impurities and maximum content according to classification and labelling of mixtures for skin sensitisation potential might be set from a toxicological point of view.	Applicant: Please see 2(2). RMS (August 2017): 1. The RMS disagrees with EFSA regarding genotoxicity studies: the proposed technical specification is not comparable to the material used in genotoxicity studies regarding four impurities (CGA190042, CGA252938, NOA427417 and Toluene). Please see confidential Vol 4 Syngenta, C.1.4.2.1., 68-73 pp. and Table C.1.4.2.1-1, Table C.1.4.2.2-1, Table C.1.4.2.2-2, Table C.1.4.2.2-3 and Table C.1.4.2.2-4. - CGA190042 was not detected in the technical material used for two genotoxicity studies (gene mutation <i>in vitro</i> and micronucleus <i>in vivo</i>) on the batches P.001010 (n.d.), P.705002/FL	Data requirement (Syngenta) Bacterial reverse mutation (Ames) and HPRT mammalian gene mutation assays with spiked batch material to support the technical specification.

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			872026/FL 881224 (n.d.); - The proposed specification for CGA252938 was above the value found in the technical material used in Ames test (even taking into account acceptable limit 3 g/kg) on a batch P.306042 (0.1%); - The proposed specification for NOA427417 was above the values found in the technical material used in two genotoxicity (gene mutation <i>in vitro</i> and micronucleus <i>in vivo</i>) studies (even taking into account acceptable limit 50%) on the batches P.001010 (0.3%), P.705002/FL 872026/FL 881224 (0.7%); - Taking into account that there are not the acceptable variations for relevant impurities, the proposed specification for toluene was above the values found in the technical material used in two genotoxicity studies (Ames and chromosome aberration <i>in vitro</i>) on the batches SMO7J020 (0.17%) and SMO5D1422 (0.22%). However, it should be noted that toluene was not harmonised classified according to Regulation (EC) 1272/2008 as mutagenic substance due to conclusive but not sufficient data for classification. In addition, two of these impurities	

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			(CGA190042 and CGA252938) triggered EQUIVOCAL Derek Nexus alert for chromosome damage <i>in vitro</i> in mammals due to an alpha, beta-Unsaturated ketone moiety. However, it should be noted that CGA190042 and CGA252938 were tested at 60% and at 74% of the proposed specification (5.0 g/kg) respectively in Chromosome Aberration <i>in vitro</i> test (Human lymphocytes) (Sokolowski A., 2015) on a batch SMO5D1422 and therefore the RMS considers that this study covers the technical specification (taking into account acceptable limit 3 g/kg). Hence, it was concluded by the RMS LT that at least two impurities (CGA252938 and NOA427417) levels in proposed specification are not covered by genotoxicity studies: a further Ames test and gene mutation <i>in vitro</i> test should be considered for CGA252938 and NOA427417, respectively (see Tables C.1.4.2.2-3 and C.1.4.2.2-4 in confidential Vol 4 Syngenta) . 2. Considering the skin sensitisation potential four impurities triggered PLAUSIBLE Derek Nexus alert for skin sensitisation in mammal: three impurities	

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			(CGA158377, CGA252938 and NOA427417) due to the presence of a diketone moiety and one impurity (CGA267934) due to the presence of a phenyl ester moiety. These alerts cannot be disregarded and the potential for skin sensitisation is considered justified for these impurities, moreover, CGA158377 (CAS No 88805-65-6) is a skin sensitiser (Skin Sens. 1, H317) based on harmonised classification according to Annex VI of Regulation (EC) 1272/2008. Furthermore, it was concluded that the Skin sensitization study did not cover the technical specification proposed by the RMS regarding these four impurities (CGA158377, CGA267934, CGA252938 and NOA427417) due to these impurities were not tested at sufficiently high level or were not detected in the Skin sensitization study. In addition, the Skin sensitization study did not cover the technical specification proposed by the RMS regarding CGA190042 too. Trinexapac-ethyl CGA163935 triggered PLAUSIBLE Derek Nexus alert for skin sensitisation in mammal due to the presence of a diketone moiety too. Due to the reasons mentioned above a	

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			further skin sensitisation study should be considered according to the RMS (see Table C.1.4.2.2-3. in confidential Vol 4 Syngenta). The RMS LT is of the opinion that there is need for additional and comprehensive structural activity relationship analysis (referred to as 'additional analysis' in the text of the RAR) based on additional relevant model (e.g. OECD Toolbox) and open literature search on these four specific impurities (CGA267934, CGA190042, CGA252938 and NOA427417) to see whether they raise any concerns for the above mentioned endpoint (skin sensitisation). 3. The RMS is not convinced that generic concentration limits 1.0% for skin sensitiser according to Regulation (EC) 1272/2008, are applicable to these specific impurities. - From a toxicological point of view the impurity CGA158377 is considered toxicologically relevant due to classification as skin sensitiser according to Annex VI of Regulation (EC) 1272/2008. However, this impurity was	

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			not tested at sufficiently high level in the skin sensitization study. Thus in the absence of data or other information permitting a more refined approach this impurity needs to be below 0.1% to ensure it will not increase the toxicological hazard of the active substance (please see confidential Vol 4 Syngenta, C.1.4.2.2., 78 pp.). This default maximum acceptable limit 1 g/kg for relevant impurities (sensitizing chemicals) was indicated in <i>"Manual on development and use of FAO and WHO specifications for pesticides. Series FAO Plant Production and Protection Papers, Rome, 2016, 25 pp."</i>. - The setting maximum content 1.0% for other three impurities (CGA267934, CGA252938 and NOA427417) would be controversial due to the fact that these impurities weren't tested at sufficiently high level or weren't detected in the technical material used in the Skin sensitization study. Hence, additional and comprehensive structural activity relationship analysis would be useful. Data requirement: Applicant (Syngenta) to present a robust	

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of impurity CGA158377. Applicant (Syngenta) to consider a further Ames test and gene mutation <i>in vitro</i> test for CGA252938 and NOA427417, respectively. Applicant (Syngenta) to submit additional and comprehensive structural activity relationship analysis based on additional relevant model (e.g. OECD Toolbox) and open literature search on these four specific impurities (CGA267934, CGA190042, CGA252938 and NOA427417) to see whether they raise any concerns for the skin sensitisation.	
2(4)	Vol. 4 Annex C Representativeness of the toxicological studies to the technical specification. Syngenta Toluene	EFSA: the RMS' view to consider toluene as relevant impurity is supported. In the past, maximum content of toluene (from the toxicological point of view) was established based on classification and labelling of mixtures considering the reproductive toxicity potential of toluene. This approach might be applicable to toluene as a relevant impurity in trinexapac-ethyl technical specification.	Applicant: The applicant notes EFSA's suggested approach and will include it in a revised Document J during the stop-the-clock period. RMS (August 2017): Noted. The setting maximum content 3.0% for toluene (from the toxicological point of view) would be controversial due to the fact that toluene was not detected in the technical material used in two developmental toxicity studies in rats and rabbits on the batches P.705002/FL	Data requirement: Applicant (Syngenta) to present a robust scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of impurity toluene.

Other comments, incl comments on volume 4 (impurities, batches)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur / response from the Notifier/applicant	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			872026/FL 881224 (<0.1%). Thus in the absence of data or other information permitting a more refined approach this impurity needs to be below 0.1% to ensure it will not increase the toxicological hazard of the active substance (please see confidential Vol 4 Syngenta, C.1.4.2.2., 84 pp.). This default maximum acceptable limit 1 g/kg for relevant impurities (reproductive toxicants) was indicated in <i>"Manual on development and use of FAO and WHO specifications for pesticides. Series FAO Plant Production and Protection Papers, Rome, 2016, 25 pp."</i>. Data requirement: Applicant (Syngenta) to present a robust scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of impurity toluene.	

TABLE OF CONTENTS

	Document
00	Cover page
01	Comments on the assessment report
02	Reporting table
03	Pesticides peer review meeting reports
04	Evaluation table
05	Comments on the additional information assessment
06	Comments on the draft EFSA conclusion

List of all reports from Pesticides Peer Review Meetings

Date		Section
08.12.2017	Pesticides Peer Review expert teleconference 160	Ecotoxicology
14.12.2017	Pesticides Peer Review expert meeting 170	Mammalian Toxicology
15.12.2017	Pesticides Peer Review expert meeting 171	Residues

REPORT OF PESTICIDES PEER REVIEW MEETING TC 160

TRINEXAPAC-ETHYL

Rapporteur Member State: LT

Specific comments on the active substance in the section

5. Ecotoxicology

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	Supplier	File Name
None		

2. Documents submitted for meeting:

Date	Supplier	File Name
01 September 2009	RMS/EFSA	Reporting tables on conf and non-conf parts
04 December 2017	RMS	Trinexapac-ethyl evaluation table_section 5_2017-12-04.doc
04 December 2017	RMS	Trinexapac-ethyl_RAR_01_Volume_1_2017-12-04.pdf
04 December 2017	RMS	Trinexapac-ethyl_RAR_11_Volume_3CA_B-9_2017-12-04.pdf
04 December 2017	RMS	Trinexapac-ethyl_RAR_20_Volume_3CP_B-9_2017-12-04.pdf
04 December 2017	RMS	Trinexapac-ethyl_RAR_27_LOEP_2017-12-04.pdf

3. Documents tabled at the meeting:

Date	Supplier	File Name
None		

Appendix 1: Discussion table: TRINEXAPAC-ETHYL

Appendix 1: Discussion Table, Trinexapac-ethyl

5. Ecotoxicology

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
Experts' consultation 5.1 Experts to discuss the endpoint to be used in the long term risk assessment for birds. In particular, the relevance of the reduction in eggs production at 600 ppm observed in Hakin 1991a should be discussed. See reporting table 5(1)	The NOAEL was set at 600 ppm. However, a trend of effects was observed in the number of total eggs laid (20%) even if there was not statistical significant difference. This effect was considered biological relevant. It was suggested to exclude the first 2 weeks as the peak in egg laying was between week 13 and 22. When doing a statistical re-evaluation only considering those weeks, a statistical significant difference is observed in that parameter. Therefore, the NOAEL of 200 ppm is proposed. The total egg laid is considered an ecotoxicologically relevant parameter in order to assess effects on population and therefore the effects are considered biologically relevant. Overall the experts agreed on the NOAEL of 200 ppm. Open point RMS to amend the long term risk assessment for birds by using the NOAEL of 200 ppm both in the RAR and LoEP.	Open point RMS to amend the Risk assessment for birds by using the NOAEL of 200 ppm both in the RAR and LoEP.
Experts' consultation 5.2 Experts to discuss the ecotoxicological relevance of the effects on radicle elongation observed in the study Chetram 1991.	Effects on radical elongation were observed at the lowest concentration and not at the 2 highest doses. The RMS considered this effect as not ecotoxicological relevant. However, the effects at the dose of 0.0645ppm to 0.516ppm were very high. The study is, however, not a standard study and it was performed in petri dishes. The standard study on seedling emergence (White 1991) is available where no effects were observed in the aboveground parameters. However, the belowground parameters are not fully investigated in the standard test on seedling emergence. Although, it is uncertain what could happen in the field, as radical elongation could be relevant from an ecological point of view, considering the evidence from standard seedling emergence test, the experts agreed that those effects should not be considered further.	No action for the RMS.

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
See reporting table 5(70)	Overall, the experts agreed with the RMS' assessment of the study by Chetram, 1991.	

REPORT OF PESTICIDES PEER REVIEW MEETING 170

TRINEXAPAC-ETHYL

Rapporteur Member State: LT

Specific comments on the active substance in the section

2. Mammalian Toxicology

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	Supplier	File Name
8 December 2017	EL	Comments are entered in the discussion table below.
11 December 2017	LV	Comments are entered in the discussion table below.
7 December 2017	AT	Comments are entered in the discussion table below.
7 December 2017	NO	Comments are entered in the discussion table below.
8 December 2017	DE	Comments are entered in the discussion table below.

2. Documents submitted for meeting:

Date	Supplier	File Name
4 December 2017	LV	Trinexapac-ethyl evaluation table_section 2_2017-12-04.doc
4 December 2017	LV	Trinexapac-ethyl_RAR_01_Volume_1_2017-12-04.pdf
4 December 2017	LV	Trinexapac-ethyl_RAR_08_Volume_3CA_B-6_2017-12-04.pdf
4 December 2017	LV	Trinexapac-ethyl_RAR_17_Volume_3CP_B-6_2017-12-04.pdf
4 December 2017	LV	Trinexapac-ethyl_RAR_27_LOEP_2017-12-04.pdf
01 September 2017	UK/EFSA	Reporting tables Conf-Non confidential

3. Documents tabled at the meeting:

Date	Supplier	File Name
xx Month xxxx	Name	

Appendix 1: Discussion table: TRINEXAPAC-ETHYL

Appendix 1: Discussion Table, Trinexapac-ethyl

2. Mammalian Toxicology

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.1 Experts to discuss the toxicological endpoints in the dog studies, including changes in brain and reproductive organs. See also data requirement in 2(13). See also comments 2(15), 2(16) and 2(17). See reporting table 2(14)	Background Pilot 7-week oral dog study (submitted after data requirement): 0, 500, 5000, 15000 and 15000 (1-3 d) →30000 (4-28 d) 50000 (29 onwards) ppm Equal to 0, 22.2, 218.7, 685.8, and 685.8→956.2→733.6 (~861) mg/kg bw/d for males and 0, 23.1, 214.3, 679.9 and 679.9→1373.3→ 964.7 (~1198) mg/kg bw/d for females. NOAEL = 679.9 mg/kg bw /d 13-week dog study: 0, 50, 1000, 15000, 30000 ppm corresponding to 0, 2, 35, 516, 930 mg/kg bw per day for males and 0, 1.9, 40, 582, 890 mg/kg bw per day for females. NOAEL = 516 mg/kg bw /d (M & F) 1-year dog study: 0 (control), 40, 1000, 10000 or 20000 ppm corresponding to 0, 1.56, 31.6, 366 and 727 mg/kg bw per day for males and 0, 1.37, 39.5, 357 and 784 mg/kg bw per day for females. The RMS proposed a NOAEL of 31.6 mg/kg bw /d (M & F). LOAEL= 357.1 mg/kg bw /d, based on clinical signs (faeces mucoid/bloody, M & F), ↓body weight gain (M), haematological changes (↓RBC, ↓HCT, ↓HGB) (F), possible effect on the oestrus cycle & decreased absolute uterus weight, brain histopathology (vacuolation) (M & F). DE commented that a significant reduction of absolute and relative uterus weight was observed at 1000, 10000 and 20000 ppm. Concurrently it could be observed that in these dose groups more or all females were in the middle/late metoestrus cycle. Historical control data for the uterus weight was not available. The explanation of synchronisation of oestrus cycle stages of females in the highest dose groups due to housing conditions is not sufficient as this should also affect the control group. Even though the data on oestrus cycle might explain the alterations in uterus weight, it cannot be excluded that the alterations in oestrus cycle are substance related. In addition a significant decrease of testes weight could be observed at dose levels 1000, 10000 and 20000 ppm and the weight of ovary was also reduced at these dose levels. Altogether these effects are considered as adverse. Due to the effects seen in on the uterus, ovary and testes weight as well as on the	Experts' consultation fulfilled. Majority of experts agreed that appropriate NOAEL for the 1-year dog study should be set NOAEL at 31.6 mg/kg bw per day (1000 ppm) based on changes in uterus weight, changes in oestrous cycle, changes in brain, on clinical signs (faeces mucoid/bloody, M & F), ↓ terminal body weight (M), haematological changes (↓RBC, ↓HCT, ↓HGB) (F).

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	oestrus cycle DE is of the opinion that the dose of 31.6 mg/kg bw/d should be regarded as a LOAEL and the dose of 1.4 mg/kg bw/d as NOAEL This should be taken into account for the establishment of the ADI. LV: A significant reduction of absolute and relative uterus weight was seen in mid-doses and at the highest dose. HCD for the uterus weight is not available. The explanation of synchronisation of oestrus cycle stages of females in the highest dose groups due to housing conditions is not sufficient. It cannot be ruled out that alterations in oestrus cycle are substance related. Overall these effects should be considered as treatment related and should be taken into account for ADI setting. Overall LV is on the opinion that for this study NOAEL should be set as 40 ppm (1.4 mg/kg bw/d) based on effects seen on uterus and ovary. EFSA: the analysis of biological relevance of the findings described that compounds disturbing metabolism of glucose induced similar swelling of astrocytes and oligodendroglia. It is noted that according to literature on metabolites, cyclopropane carboxylic acid is considered a hypoglycemic agent (Buxton D et al, 1983) and tricarballic acid is an inhibitor of the enzyme aconitase and interferes with the Krebs cycle. The role of metabolites and interspecies differences might be further investigated to support applicant's statement on the non-relevance for humans. However, on the basis of current available information EFSA supported the RMS' view that in the absence of mechanistic studies and/or any human data, cerebral vacuolation observed in dogs should be considered relevant for human. Preliminary comments from MS submitted before the meeting: LV comment: A high inter-individual variability in the control group and in the low-dose regarding absolute and also relative uterus was noted. In the control group inter-variability was from 4.19 g till 16.45 g. In the historical control study (even though only one study available with limitations) suggest that there is quite a high variability of uterus weight in the population (2.59 – 13.09 g). Effects on uterus were not seen in 90-day. In both studies (90-day and 1 yr) histopathological changes were not obtained. Taking into account low number of animals and high inter-individual variability statistical significance should be taking into account with precaution. Latvia agrees with RMS conclusion that an effect on uterus weight should be considered as toxicologically relevant at 10000 ppm (357.1 mg/kg bw/d for female) due to possible adverse effect of trinexapac-ethyl on the oestrus cycle via a hormonally mediated mechanism.	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	With respect to the changes in the brain LV agrees with the conclusion of RMS that in the absence of mechanistic studies and/or any human data, cerebral vacuolation observed in dogs should be considered relevant for human Overall taking into account high variability of uterus weight between animals and the absence of any histopathological findings and supported by the conclusion that cerebral vacuolation observed in dogs should be considered relevant for human, LV agrees to set NOAEL at 31.6 mg/kg bw/d AT: RMS prepared a well elaborated evaluation of effects on reproductive organs in males and females as well as on brain of both sexes in the 1 year dog study. The effect under consideration were not observed in the 90 days study, however, this might be well explained by the age of the animals. It is recognised that regarding cerebral vacuolation 1000 ppm can be considered as NOAEL since at this dose no effects were observed. Regarding effects on uterus and ovaries (decreased organ weight) without accompanying histopathological findings the explanation has been given by the notifier that the observed effects derive from different oestrus cycle of animals at the time point of sacrifice rather than from treatment relation. While it is certainly recognised that pheromone exchange may stimulate females to be in the same oestrus cycle stage, this can be questioned here (two females from every dose group were caged in the same room). All treated females suffered decreased weight of uterus and ovaries, however, without clear dose-response. Statistically significant decrease in uterus weight occurred at 1000 ppm and above. At 10000 and 20000 ppm all females were in the middle/late oestrus cycle stage. No other comparable study is available in the dossier for comparison and the information on % oestrus cycle stage for 1 year dog studies from historical database does not reflect the % in the study under consideration. As preliminary opinion AT could support RMS that 1000 ppm (31.6 mg/kg bw/d) can be set as NOAEL, based on the combination of statistically significant decrease in uterus weight and observed physiological changes (middle/late oestrus cycle stage). DE: Reproductive organs: The lack of histopathological findings in the uterus, ovary and testes cannot rule out a treatment and/or potential endocrine mediated effect because no morphometry of the endocrine organs was conducted (i.e. uterine tissue height, ovary follicle count, sperm morphology, seminiferous tubule diameter, etc).	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	The estrous cycle disruption is also an important parameter to be considered in the weight of evidence. Even though not checked before the final sacrifice, this parameter can be used in this study because the animals were in the pre-pubertal age when starting treatment (~ 5 months) up to puberty (8-18 months age) with this one year exposure. The animals were also not mechanically induced to pregnancy (e.g. daily use of swabs to collect vaginal smears) and the final sacrifice of all animals at the same day is better to evaluate when they stopped cycling (which seems to be case of this study with trinexapac-ethyl). These are some of the same principles used by the Female Pubertal Rats Assay OCSPP Guideline 890.1450. Therefore, due to the effects seen in on the uterus, ovary and testes weight as well as on the estrus cycle DE is of the opinion that the dose of 31.6 mg/kg bw/d should be regarded as a LOAEL and the dose of 1.4 mg/kg bw/d as NOAEL; however, if trinexapac-ethyl would be considered an endocrine disruptor then no NOAEL is be possible for this study. Brain: The vacuolation of astrocytes and oligodendroglia were treatment related, age and dose dependent and can be considered a result of the hypoglycemic/metabolic disturbance induced by the active substance and/ or its metabolites. Not only the kidneys, but also the brain could be expected to be affected with the lack of energy and pyruvate metabolism disruption. Therefore, DE supports the RMS and the cerebral vacuolation observed in dogs should be considered and adverse effect and relevant for humans. The NOAEL for cerebral vacuolation could be considered at 1000ppm. Meeting The following deficiencies in the 1-year dog study were noted: use of a single time point and low number of animals. Statistical analysis approach in assessment of organ weights was questioned by one of the experts, suggesting that one-sided rather than two-sided test should have been used as this would increase the power of the test. <u>Brain findings:</u> RMS proposes to set NOAEL at 31.6 mg/kg bw per day (1000 ppm) in the 1-year dog study. Adversity of changes in brain were discussed by experts and it was agreed by all experts that the observed effect was indeed adverse. The agreed NOAEL for changes in brain was set at NOAEL of 31.6 mg/kg bw per day (1000 ppm). The relevance of these effects for humans cannot be excluded based on available information.	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	<u>Reproductive organ findings:</u> Changes in reproductive organs were discussed. RMS considered that possible effect on oestrus cycle and reduction in absolute uterus weight were adverse and suggested to establish the NOAEL at 31.6 mg/kg bw per day (1000 ppm). Some MS proposed lower NOAEL based on changes in organ weights, suggesting that effects were independent of changes in body weight and morphometry, which is more sensitive than histology, was not conducted. Availability of HCD was questioned by one of the experts; only one study was submitted as a HCD by applicant and was not considered acceptable by RMS. Limitations of dog model for investigation of oestrous cycle was noted by one of the experts (i.e. seldom oestrous cycle). It was mentioned that in the absence of the effects in other studies (e.g. 90 day study) it is difficult to consider effects on organs' weight as biologically relevant, however age of animals might be important factor explaining differences in findings between studies. <u>Body weight changes:</u> Changes in body weight of animals was discussed as well. It was noted by one of the experts that body weight gain has changed starting from low dose. Palatability was only considered related to the top dose level. Of note, the top dose for this study was selected based on the effects on palatability observed in the range-finding study. Some experts considered setting NOAEL at 40 ppm based on body weight gain changes. <u>Overall conclusion on the relevant NOAEL in the 1-year dog study:</u> Majority of experts agreed that appropriate NOAEL for this study should be set NOAEL at 31.6 mg/kg bw per day (1000 ppm) based on changes in uterus weight, changes in oestrous cycle, changes in brain, on clinical signs (faeces mucoid/bloody, M & F), ↓ terminal body weight (M), haematological changes (↓RBC, ↓HCT, ↓HGB) (F). Experts' consultation fulfilled.	
Experts' consultation 2.2 Experts to discuss the amended results of	Background During the previous peer review trinexapac-ethyl was considered unlikely to be genotoxic. The RMS assessed new genotoxicity studies submitted during the renewal and considered that the new new genotoxicity studies are in agreement with previously conclusion that trinexapac-ethyl technical (Syngenta) is unlikely to be genotoxic.	Experts' consultation fulfilled. The weight of evidence suggests that trinexapac-ethyl is unlikely to be

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
the genotoxicity studies with trinexapac-ethyl. See data requirements in 2(18) and 2(69). See also open point in 2(22). See reporting table 2(18)	Further details of existing genotoxicity studies (Syngeta) and assessment of further genotoxicity studies provided by other applicants were requested during the commenting phase. The summary of all genotoxicity studies is available on page 46 (volume 1, RAR 2017-12-04). Preliminary comments from MS submitted before the meeting: LV: LV supports conclusion of RMS that trinexapac-ethyl is not genotoxic in-vivo. AT: RMS/notifiers re-evaluated the whole genotoxicity package and presented the results in detail – this is very much appreciated. There is agreement with the RMS that based on all available data trinexapac is unlikely to be genotoxic. NO: We agree with the RMS that trinexapac-ethyl is unlikely to be genotoxic. DE: Considering that new studies with the active substance and with metabolites were included, the in vivo transgenic rodent assay in combination with the Comet assay would be important to disregard possible forward mutations not covered by the micronucleus in vivo test. This information would also help to better evaluate the in vitro positive/equivocal results. Meeting On request from EFSA genotox studies were represented in Vol 3, not in Vol.4. The key difference between studies is different specifications used due to the fact that studies were performed by different producers. <u>Evidence for gene mutation:</u> Gene mutation in mammalian cells (p. 96, Study 3; Gilby, 2017): RMS concluded that the study results were contradictory. The first experiment (4 hour treatment, without S9) showed a weak positive response whereas in the second experiment, although negative the dose level were the same than the first experiment. The RMS indicated that the selection of the doses for the second experiment was not done appropriately. Therefore, the RMS considered the study equivocal. Gene mutation in mammalian cells (p.205, Study 4, Stone 2009) was further discussed. One of the experts noted that observed effect on the mutation frequency in second experiment was observed under conditions of cytotoxicity (with metabolic activation). However, due to the observed increase in mutant frequency it is not possible to conclude that the experiment is clearly negative. Some experts pointed on observed precipitation starting from 1500 ug/ml and they would consider the study as negative because of cytotoxicity observed. Other gene mutation assays in mammalian cells were negative.	genotoxic <i>in vivo</i>.

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	All experts agreed that AMES tests were negative. Some experts expressed opinion that study of Stone, 2009 and Gilby 2017 to be considered equivocal and suggested to request <i>in vivo</i> tests (e.g. transgenic rodent assay). Overall, considering available data on AMES test and mammalian gene mutation, majority of experts expressed opinion that the compound is unlikely to be of gene mutation concern and further <i>in vivo</i> studies are not justified. <u>Evidence for chromosome aberrations:</u> One of the MS suggested to discussion <i>vitro</i> CA test. For In <i>vitro</i> CA test (summary table p.169) one of the expert mentioned 3 fold increase in number of chromosomal aberrations, but it was pointed out that the dose-related increase was not observed, and that was one of the reasons for RMS to conclude that the study was negative. Acceptance of the study on chromosomal aberration with human lymphocytes (p.170) was questioned by one of the experts, indicating that 22 hours is shorter than 1,5 cell cycle and the minimum should be set at 30 hours. EFSA commented that 22 hours have been considered appropriate in the past to cover 1.5 cell cycle for human lymphocytes. Experts as well invited the EFSA Scientific Committee Genotoxicity Working Group to comment on the suitable length of the treatment period for human lymphocytes in relation to their cell cycle. Discussion of <i>in vivo</i> micronucleus tests took place focusing on evidence of bone marrow exposure. The assessment by RMS relied on a negative <i>in vivo</i> micronucleus test (Whitwell 2010). The RMS indicated that there is sufficient evidence of bone marrow exposure from available toxicokinetic data. The experts agreed. Taking into account the results of the <i>in vivo</i> MN test the experts agreed that there is no concern for chromosome aberration <i>in vivo</i>. Overall, experts concluded that the substance does not pose genotoxic concern <i>in vivo</i>. Experts' consultation fulfilled.	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2.3 Experts to discuss the developmental toxicity studies with trinexapac-ethyl. See also comment 2(28). See reporting table 2(27)	Background Rat developmental toxicity: 0, 20, 200, 1000 mg/kg bw per day. EFSA: asymmetrically shaped sternebrae is described as anomalies. Can the RMS/applicant clarify if the anomaly should be considered malformation, variation or a grey zone anomaly according to current state of art?. Based on litter incidence of asymmetrically shaped sternebrae and historical control data its biological relevance might not be excluded. Please also considered whether the incidence of asymmetrically shaped sternebrae and still absent ossification should be considered together. Could the RMS/applicant clarify if trinexapac-ethyl has been discussed by ECB or ECHA?. Is there any intention to submit the CLH report to ECHA?. EFSA: All developmental toxicity studies have been performed with a shorter administration period. Data requirement 2.5. More detailed historical control data for the rat developmental toxicity study. Preliminary comments from MS submitted before the meeting: LV comment: The RMS proposal to maintain the previously agreed developmental NOAEL is supported. AT: General comment: Historical control data should be primarily used to check the validity of the concurrent control. Especially where dose-response is observed HCD should be used with caution. In rat developmental study under consideration, 7 litters (29.2%) were affected regarding asymmetrically shaped sternebrae, comparing to 2 litters (9.1%) in the control group. Observations in control group reflect well the HCD so that the concurrent control can be considered as representative. In the low and the mid dose group each, 4 litters (16.7%) were affected. The occurrence of the finding in the treated groups was not statistically significantly different from those in control group. By balancing all the available information and general profile of the active substance, both developmental NOAEL (200 and 1000 mg/kg bw) could be supported. Based on lack of statistical significance and rather a shallow dose-response, the apparent increase in asymmetrically shaped sternebrae could be considered to be an incidental finding. In this case 1000 mg/kg bw/d would be seen as NOAEL. On the other hand there was a dose-response and the incidences in the highest dose are not covered by historical control data. This would explain setting the developmental NOAEL at 200 mg/kg bw/d. If developmental NOAEL is set the mid dose of 200 mg/kg bw/d (which is below the maternal NOAEL), no proposal for classification for developmental toxicity is supported.	Experts' consultation fulfilled. The agreed rat developmental NOAEL is 200 mg/kg bw per day. No consensus was achieved by experts regarding the proposal for classification of the substance based on the observed findings of asymmetrically shaped sternebra, with 8 experts out of 16 supporting classification. Thus in EFSA conclusion no proposition for classification will be suggested as proposed by RMS.

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	NO: In the teratology study in the rat, the asymmetric sternebrae was within the HCD. NOAEL maternal and developmental > 1000 mg/kg bw/day. In the teratology study in the rabbit, there was a significant trend for post-implantation loss and for reduced litter size in the treated groups compared to the control. There were large variations within the groups. Maternal NOAEL could be set to 10 mg/kg based on reduced weight gain in parts of the treatment period, but a higher NOAEL could also be discussed. Developmental NOAEL could also be set 200 mg/kg bw /day, but lower NOAEL could also be discussed. There seems to be no need for classification as a teratogen. DE: As the incidences of asymmetrically shaped sternebrae and still absent ossification are different anomalies and the asymmetrically shaped sternebrae incidences were dose-response and above the historical control data when considering the affected litters and also the foetuses. Therefore, these findings can be considered treatment related and a NOAEL could be set at 20 mg/kg bw per day. Meeting RMS expressed position to set NOAEL at the highest dose, i.e. 1000 mg/kg bw per day in rat study (Schoch 1988), with observed asymmetric sternebra considered as "grey zone anomaly". Experts discussed if observed asymmetric shaped sternebra should be taken into consideration when setting NOAEL for this study. Experts quoted ECETOC Guidance, 2002 and Moore et al. 2013 where asymmetric sternebra considered as an anomaly or malformation of high concern. The incidences were above the HCD (1985-1987) and equal to maximum observed in the HCD (1987-1993) at the top dose level. Experts agreed to set NOAEL at the level of 200 mg/kg bw per day; RMS supported suggested NOAEL. Experts discussed a need to propose classification of the substance based on the observed effect on asymmetrically shaped sternebra and discussed the adversity of observed effects. According with the description of the effects in the study report it is not clear if the observed effect is malformation or delayed ossification. Some experts questioned if the re-evaluation of data is possible by the pathologist. Additionally, there was an effect on body weight gain in dams observed (6%), treatment-related, but not adverse and it was suggested that this might have affected the litters in which asymmetrically shaped sternebrae were observed, but no evaluation of correlation was conducted. No consensus was achieved by experts regarding the proposal for classification of the substance based on the	

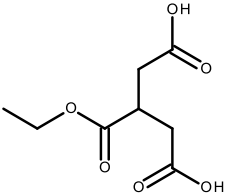
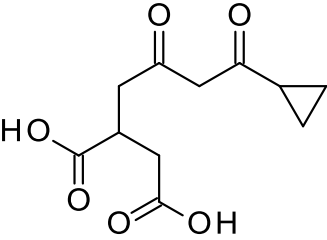
Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	observed findings of assymmetrically shaped sternebra, with 8 experts out of 16 supporting classification. Thus in EFSA conclusion no proposition for classification will be suggested as proposed by RMS. EFSA encouraged the RMS to revise the CHL report to include further discussion on the relevance of this finding for classification and labelling by ECHA. References quoted during the meeting: Crit Rev Toxicol. 2013 Nov;43(10):850-91. doi: 10.3109/10408444.2013.854734.Guidance on classification for reproductive toxicity under the globally harmonized system of classification and labelling of chemicals (GHS).Moore NP, Boogaard PJ, Bremer S, Buesen R, Edwards J, Fraysse B, Hallmark N, Hemming H, Langrand-Lerche C, McKee RH, Meisters ML, Parsons P, Politano V, Reader S, Ridgway P, Hennes C. ECETOC 2012. Guidance on Evaluation of Reproductive Toxicity Data. Monograph N 31. ISSN-0773-6347-31. Experts' consultation fulfilled.	
Experts' consultation 2.4 Potential for endocrine disruption of trinexapac-ethyl to be discussed by the experts. See data requirements in 2(31) and 2(33). See also comments 2(32), 2(34), 2(35),	Background Applicant to submit further detailed information on ToxCast results regarding endocrine-disruption potential of trinexapac-ethyl. DE: DE supports the opinion of the RMS that in the absence of further data on the effect of trinexapac-ethyl on the oestrus cycle and weight of reproductive organs an endocrine disrupting potential cannot be excluded. Further data are needed (e.g. suitable studies from the OECD Endocrine Disruptor Screening Program). NL: Could the RMS provide a more detailed summary of the Böhmeler et al. 2006 study. NL: Based on the available information it does seem likely that the effects on uterus weight in the 1-year dog study are due to differences in oestrus cycle stage between the dose groups and not by a specific endocrine effect. However, the ToxCast data should be submitted to support this. We therefore agree with the RMS that further clarification is needed. LV: Agree with the RMS that further investigation is needed (at least Tox Cast data further and further investigation according OECD framework). Applicant: The applicant agrees with the rapporteur's conclusion that trinexapac-ethyl does not meet the interim criteria for endocrine disruption specified in EC 1107/2009.	Experts' consultation fulfilled. The majority of experts (slight, 9 vs 7) could not conclude on the ED-properties based on available information of the substance and suggested to provide <i>in vitro</i> assays (e.g. steroidogenesis assay OECD TG456) and comparative metabolism study between dog and human. A data gap will be included in the EFSA

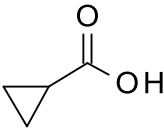
Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
2(36), 2(37), 2(38) and 2(39). See reporting table 2(31)	The applicant notes that on the 4th of July 2017 The Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) voted to adopt a definition of endocrine disruption derived from the internationally recognized WHO/IPCS definition. It is considered that the interim criteria for identification of endocrine disruptors described in regulation EC 1107/2009 were a regulatory construct that do not constitute a best scientific approach to endocrine identification, and are therefore not appropriate. The applicant therefore acknowledges that the most suitable and scientifically valid approach would be for the final criteria for identification of endocrine disruptors agreed by the SCoPAFF to be used in the evaluation of trinexapac-ethyl. Applicant: The differences in oestrus cycle stage between treated and control animals in the 52 week dog study with trinexapac-ethyl are not the result of treatment with trinexapac but are instead reflective of a combination of methodological deficiencies in study design and normal dog reproductive biology. To provide additional critique of the relevant data, an expert technical review of this study illustrating the deficiencies in methodology and providing a comparison with established knowledge of oestrus cyclicity in dogs has been provided to the rapporteur. Applicant: Whilst the applicant does not share the rapporteur's concerns around the one year dog study with trinexapac-ethyl the applicant notes that assessment of endocrine disruption should be conducted through a weight of evidence evaluation and that all studies with trinexapac-ethyl should be evaluated holistically with both positive and negative evidence considered together. The applicant does not believe that a single isolated data point that is inconsistent with all other OECD conceptual framework level 4 and 5 studies in the database should be considered to constitute evidence of endocrine disruption, particularly in the presence of a comprehensive battery of endocrine related assays indicating that trinexapac-ethyl does not have the potential to interact with components of the endocrine system. The applicant draws particular attention to the fact that no effects were seen on end-points relating to oestrogenic, androgenic and/or steroidogenic processes. A lack of effects in this set of assays provides further evidence that any inter-group differences noted in the one-year dog study oestrus cyclicity data were without relationship to treatment with Trinexapac-ethyl and therefore incidental in nature. Applicant: The rapporteur noted that whilst a battery of assays designed to assess the potential for interaction with components of the endocrine system as part of the US EPA's ToxCast data had been supplied by the applicant the level of methodological information provided alongside these data was limited. The applicant	conclusion to reflect the view of the majority of experts.

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	has provided a review containing additional methodological information for the endocrine system related assays conducted with trinexpac-ethyl as part of the US EPA ToxCast program. Trinexpac-ethyl was negative in all of these assays, providing comprehensive evidence that trinexpac-ethyl does not interact with isolated components of the endocrine system. Preliminary comments from MS submitted before the meeting: LV comment: LV agrees that according interim criteria trinexpac-ethyl is not considered as endocrine disruptor. However, taking into account limited and inconclusive evidence from the tox-cast data and 1 yr dog studies, further information would be needed. AT: No clear evidence for potential ED properties of trinexpac is given by the majority of results of the studies provided in the dossier and by evaluation of the ToxCast data. If decrease in reproductive organ weight observed in 1 year dog study, combined with shift in oestrus cycle stage, could be evidence of a hormonal disturbance remains unclarified and cannot be excluded. NO: Based on available data, trinexpac-ethyl is not regarded as an endocrine disruptor. DE: DE supports the opinion of the RMS that the effect of trinexpac-ethyl on the estrus cycle and weight of reproductive organs an endocrine disrupting potential cannot be excluded. Furthermore the increased incidence of thyroid follicular adenocarcinoma (combined chronic toxicity/carcinogenicity study in rat) and the increase pituitary relative weight (90- day rat study) might also not be considered as incidental findings. Overall these observations in dogs and rats studies with trinexpac-ethyl point to an inhibition of steroidogenesis or HPG axis suppression. There is a ToxCast report in the RAR and the original dashboard results were visited at https://comptox.epa.gov/dashboard/dsstoxdb/results?abbreviation=toxcast&exact=1&mass=0&search=95266-40-3&single_component=0. However, some tests regarding disruption of the other enzymes involved in the steroidogenesis pathway (besides aromatase) were not investigated. In fact the disruption phase of the steroidogenesis might be the cholesterol intake and conversion into pregnenolone by StAR and CYP11A1, both enzymes not investigated in the studies available. The original ToxCast dashboard from the website also shows that PXRE (preganane X receptor response element) is active. The pregnane X receptor is a ligand-activated transcription factor that heterodimerizes with the 9-cis retinoic acid receptor (RXR, NR2B) and binds response elements in the promoters of regulated genes to induce gene expression. Therefore, further endocrine pathways could be considered relevant (e.g., steroidogenesis, retinoid system, insulin receptor) and additional investigations including also (but not only)	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	hormone levels would be helpful. Meeting RMS stated that some of the ED-sensitive parameters were not evaluated in two-generation toxicity studies limiting assessment of ED properties. Some experts suggested to request further data, and mentioned potential suppression of steroidogenesis pathway as potential ED MoA, which was not sufficiently investigated even when using ToxCast data, as only receptor-mediated pathway was assessed, but not the downstream part of the steroidogenesis process. On the basis of effects observed in 1-year dog study (uterus weight, oestrogen cycling) and lack of evaluation of endocrine-sensitive parameters it was discussed if further evaluation of disruption of steroidogenesis pathway <i>in vitro</i> should be provided; it was noted that a comparative <i>in vitro</i> metabolism study between dog and human would have been useful for further assessment of human relevance of dog findings and the potential role of metabolites. The majority of experts (slight, 9 vs 7) could not conclude on the ED-properties based on available information of the substance and suggested to provide <i>in vitro</i> assays (e.g. steroidogenesis assay OECD TG456) and a comparative <i>in vitro</i> metabolism study between dog and human. A data gap will be included in the EFSA conclusion to reflect the view of the majority of experts. Experts' consultation fulfilled.	
Experts' consultation 2.5 The toxicological profile of potential dietary metabolites tricarballic acid, GA300405, CGA313458 and CPCA to be discussed by the experts.	Background Trinexapac-ethyl	Experts' consultation fulfilled. CGA275537 Data gap identified for genotoxic potential of the metabolite (chromosomal aberration endpoint) and repeated exposure if risk assessment is triggered by residues experts.

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
Pending on the updated literature search and data requirements on metabolites further metabolites might be included for discussion. See reporting table 2(53)	CGA275537 (Tricarballic acid) is a postulated metabolite in the crops (wheat, rape, grass, rice) and is considered to be dietary metabolite, or potential dietary metabolite. - Acute oral toxicity: The acute oral LD50 of CGA 275537 was found to be >2000 mg/kg bw for male rats, between 300 and 2000 mg/kg bw for female rats and between 300 and 2000 mg/kg bw for the sexes combined. - Ames test: negative. In <i>vitro</i> MN test: missing. No data on repeated exposure. EFSA: According to the literature tricarballic acid is an inhibitor of the enzyme aconitase and interferes with the Krebs cycle and appears to be a well-known compound. Did the literature search include this compound? LV preliminary comment: In vitro genotoxicity data are missing, to conclude on genotoxic potential. GA300405: CGA300405 is a postulated metabolite in the crops (wheat), and is considered to be dietary metabolite, or potential dietary metabolite. - Ames test: negative - Gene mutation (MLA): negative.	GA300405 Not genotoxic. Further data on repeated exposure would be needed if risk assessment is triggered by residues experts. CGA313458 Not genotoxic. Further data on repeated exposure would be needed if risk assessment is required by the residue experts. CGA224439 Not genotoxic. Considered of higher toxicity than the parent compound based on short term toxicity study (available to JMPR), which was not submitted to RMS for independent assessment. The data gap is proposed by experts to address the repeated exposure toxicity.

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	- In vitro MN: negative.  No data on repeated exposure. LV preliminary comment: It can be concluded that GA300405 do not have genotoxic potential. CGA313458: CGA313458 is a postulated metabolite in the crops (rape, rice, high temperature hydrolysis), and is considered to be dietary metabolite, or potential dietary metabolite. - The acute oral LD50 of CGA 313458 was found to be >2000 mg/kg bw for rats of both sexes. - Ames test: negative. - Gene mutation (V79/HPRT): negative. - In vitro CA: negative. No data on repeated exposure. LV preliminary comment: It can be concluded that CGA313458 do not have genotoxic potential. 	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	CGA224439 (Cyclopropane carboxylic acid): is a postulated metabolite in the crops (high temperature hydrolysis), and is considered to be dietary metabolite, or potential dietary metabolite • Ames test: negative. • Gene mutation (V79/HPRT): negative. • In vitro CA: negative.  LV preliminary comment: Can be considered as non genotoxic, but conclusion that CGA224439 is less toxic than parent could not be conclude. No data on repeated exposure. Metabolite common to aminocyclopyrachlor (90-day rat study submitted to JMPR; NOAEL of 10 mg/kg bw per day versus NOAEL of 34 mg/kg bw per day with trinexapac-ethyl). Preliminary comments from MS submitted before the meeting: AT: <u>CGA275537 (Tricarballic acid):</u> 300 < LD₅₀ < 2000 mg/kg bw AMES test negative; no other information on genotoxicity provided Available/provided information does not allow a conclusion on the potential genotoxicity or general toxicity. At least QSAR and read across information could be retrieved by the applicant, as well as case elaborated to conclude on the toxicity of this, apparently ubiquitous, substance. <u>CGA300405 (3-ethoxycarbonylpentanedioic acid):</u> AMES, gene mutation and chromosome aberration studies negative. No information available to conclude on general toxicity, if this information is considered necessary.	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	<u>CGA313458 (2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid):</u> LD₅₀ > 2000 mg/kg bw AMES, gene mutation and chromosome aberration studies negative. No information available to conclude on general toxicity, if this information is considered necessary. A sound case could have been elaborated by the notifier to conclude on the toxicity of this, apparently ubiquitous, substance. <u>CGA224439 (Cyclopropane carboxylic acid or CPCA):</u> AMES, gene mutation and chromosome aberration studies negative. From the information in C&L inventory of ECHA it appears that CPCA causes severe skin burns and eye damage (Skin Corr. 1A, H314), is harmful if swallowed (Acute Tox., H302), may cause damage to organs through prolonged or repeated exposure (STOT RE 2, H373). 90 days gavage rat study with CPCA (no access by the applicant) seems to show that CPCA is more toxic than trinexapac. No sufficient information has been provided by the applicant to address the general toxicity of CPCA. NO: <u>CGA275537 (Tricarballic acid):</u> 300 < LD₅₀ < 2000 mg/kg bw AMES test negative; no other information on genotoxicity provided This metabolite seems to be different from the mother substance. More data should be provided. <u>CGA300405 (3-ethoxycarbonylpentanedioic acid):</u> AMES, gene mutation and chromosome aberration studies negative. Are more data available, or a statement of the toxicity? <u>CGA313458 (2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid):</u> LD₅₀ > 2000 mg/kg bw AMES, gene mutation and chromosome aberration studies negative. Are more data available, or a statement of the toxicity? <u>CGA224439 (Cyclopropane carboxylic acid or CPCA):</u>	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	AMES, gene mutation and chromosome aberration studies negative. It is notified to ECHA with the classification causes severe skin burns and eye damage (Skin Corr. 1B, H314), is harmful if swallowed (Acute Tox. 4, H302), may cause damage to organs through prolonged or repeated exposure (STOT RE 2, H373). It thus seems have a different toxicological profile than the mother substance. This should be elaborated by the notifier. DE: Considering the studies with the potential dietary metabolites identified by the RMS (also presented at the LoEP), an approach for each one would be: • CGA179500 – from the ADME studies the amount of the administered dose found in urine and/ or bile still has to be clarified • CGA275537 – the classification as acute toxicity 4, H302 Harmful if swallowed for this metabolite is not observed for the parent compound; therefore, this metabolite might be considered of toxicological relevance. • CGA329773 – there are no sufficient studies and/or information to conclude about the toxicological relevance of this metabolite (i.e. missing repeated dose studies and/or organs toxicity) • CGA300405 – there are no sufficient studies and/or information to conclude about the toxicological relevance of this metabolite (i.e. missing repeated dose studies and/or organs toxicity) • CGA113745 – there are no sufficient studies and/or information to conclude about the toxicological relevance of this metabolite (i.e. missing repeated dose studies and/or organs toxicity) • CGA158377 – the current C&L for this metabolite include Acute eye irritation – irreversible effects H318 which is not covered but the current proposal for the parent compound; therefore, this metabolite might be considered of toxicological relevance. • CGA313458 - there are no sufficient studies and/or information to conclude about the toxicological relevance of this metabolite (i.e. missing repeated dose studies and/or organs toxicity) CGA224439 - there are no sufficient studies and/or information to conclude about the toxicological relevance of this metabolite (i.e. missing repeated dose studies and/or organs toxicity) Meeting RMS proposed that CGA275537, should be classified as harmful when swollen. With the QSAR all genotoxicity endpoints were investigated (i.e. chromosomal damage in vitro, in vivo, mutagenicity in vitro and	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	in vivo etc). It was noted that to rule out the genotoxic potential of the metabolite more than one QSAR prediction tool together with read-across should be applied as predictions by a single model is not sufficient. Experts concluded that further data will be needed to conclude on the genotoxic potential of the metabolite (chromosomal aberration endpoint) and repeated exposure if risk assessment is triggered by residues experts. GA300405 (see below) seems to be an ester of tricarballic acid and read-across for genotoxicity between the two might be applied (further analysis of the read-across should be performed-data gap). The experts noted that acute oral toxicity study with this metabolite indicated that it has higher acute oral toxicity than the parent compound. The substance as well was found to be registered under REACH and further data might be readily available. GA300405 RMS concluded that the metabolite is not genotoxic. The experts agreed. Further data on repeated exposure would be needed if risk assessment is triggered by residues experts. CGA313458 RMS considered the compound to be non-genotoxic. The experts agreed. No data on repeated exposure were available. Experts concluded that further data on repeated exposure would be needed if risk assessment is required by the residue experts. CGA224439 RMS concluded that the compound has no genotoxic potential. The experts agreed. An additional literature search showed that the compound has pyruvate metabolism disruption properties. RMS concluded that the compound can be considered of higher toxicity than the parent compound based on short term toxicity study, which was not submitted to RMS for independent assessment. The data gap is proposed by experts to address the repeated exposure toxicity. Experts' consultation is fulfilled.	
Experts' consultation 2.6 Reference values for	Background The RMS proposed to keep reference values as agreed during the previous peer review process:	Experts' consultation fulfilled. The experts agreed to keep ADI of 0.32 mg/kg

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting															
trinexapac-ethyl (ADI, ARfD, AOEL and AAOEL) to be confirmed/discussed by the experts. See also comments 2(56), 2(58), 2(59) and 2(60). See reporting table 2(57)	Summary (Regulation (EU) N°1107/2009, Annex II, point 3.1 and 3.6) <table border="1" data-bbox="1032 344 1733 667"> <thead> <tr> <th>Value (mg/kg bw (per day))</th><th>Study</th><th>Uncertainty factor</th></tr> </thead> <tbody> <tr> <td>0.32</td><td>dog , 1-year</td><td>100</td></tr> <tr> <td>NA</td><td></td><td></td></tr> <tr> <td>0.34</td><td>rat, 90-day</td><td>100</td></tr> <tr> <td>NA</td><td></td><td></td></tr> </tbody> </table> Acceptable Daily Intake (ADI) Acute Reference Dose (ARfD) Acceptable Operator Exposure Level (AOEL) Acute Acceptable Operator Exposure Level (AAOEL) Preliminary comments from MS submitted before the meeting: LV comment: LV supports the conclusion of RMS to maintain previously agreed reference values AT: Currently, ADI (0.32 mg/kg bw/d, 1 year dog) and AOEL (0.34 mg/kg bw/d, 90 days rat) have been derived. Pending the results of the discussion on the NOAEL in the 1 year dog study, both reference values might change, since 1 year dog study has been frequently used in the past for setting both, ADI and AOEL. NO: Agree with RMS to keep the current reference doses. DE: ADI: 0.014 mg/kg bw per day – based on the 1-year dog study NOAEL of 1.4 mg/kg bw per day and AF of 100 ARfD: not allocated – supporting RMS AOEL: 0.34 mg/kg bw per day – supporting RMS AAOEL: not allocated - supporting RMS Meeting RMS suggests to keep ADI 0.32 mg/kg bw per day based on 1-year dog study, AOEL 0.34 mg/kg bw per day based on 90-day rat study. The experts agreed.	Value (mg/kg bw (per day))	Study	Uncertainty factor	0.32	dog , 1-year	100	NA			0.34	rat, 90-day	100	NA			bw per day based on 1-year dog study and the AOEL 0.34 mg/kg bw per day based on 90-day rat study. The majority of experts agreed that there is no need for ARfD and AAOEL setting.
Value (mg/kg bw (per day))	Study	Uncertainty factor															
0.32	dog , 1-year	100															
NA																	
0.34	rat, 90-day	100															
NA																	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	Experts discussed if ARfD should be set using as starting point the NOAEL of 200 mg/kg bw per day in the rat developmental toxicity study, however the finding was observed at limit dose 1000 mg/kg bw per day. The effect might not have resulted from a single exposure, and the finding was of doubtful classification as malformation or variation. The majority of experts expressed the opinion that setting of ARfD is not necessary. The same conclusion is applicable for AAOEL. Experts' consultation fulfilled.	

REPORT OF PESTICIDES PEER REVIEW MEETING 171

TRINEXAPAC-ETHYL

Rapporteur Member State: LT

Specific comments on the active substance in the section

3. Residues

are already listed in the relevant reporting table. Comments submitted for this meeting are listed below.

1. Comments submitted for this meeting:

Date	Supplier	File Name
12 December 2017	LV	Preliminary comments incorporated in the Discussion table below

2. Documents submitted for meeting:

Date	Supplier	File Name
01 September 2009	RMS/EFSA	Reporting tables on conf and non-conf parts
04 December 2017	RMS	Trinexapac-ethyl evaluation table_section 3_2017-12-04.doc
04 December 2017	RMS	Trinexapac-ethyl_RAR_01_Volume_1_2017-12-04.pdf
04 December 2017	RMS	Trinexapac-ethyl_RAR_09_Volume_3CA_B-7_2017-12-04.pdf
04 December 2017	RMS	Trinexapac-ethyl_RAR_18_Volume_3CP_B-7_2017-03-31.pdf
04 December 2017	RMS	Trinexapac-ethyl_RAR_27_LOEP_2017-12-04.pdf

3. Documents tabled at the meeting:

None

Appendix 1: Discussion table: TRINEXAPAC-ETHYL

Appendix 1: Discussion Table, Trinexapac-ethyl

3. Residues

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
Experts' consultation 2. It is proposed to discuss the residue definition for enforcement and risk assessment in plants, processed products and products of animal origin in an expert meeting also considering the appropriateness of the metabolism studies the magnitude of residues and the toxicological proprieties of the identified relevant metabolites. See 2(42), 2(43),2(45), 2(49), 2(50), 2(51), 2(52) and 2(53). See also Experts' Consultation 1 See reporting table 3(41)	Feedback from tox meeting: • CGA224439 can be considered of higher toxicity than the parent compound based on short term toxicity study. Data gap proposed to address the repeated exposure toxicity. If risk assessment is triggered by residues experts, for • CGA275537, further data will be needed to conclude on the genotoxic potential of the metabolite (chromosomal aberration endpoint) and repeated exposure • CGA300405 further data on repeated exposure would be needed. GA300405 is non-mutagenic and non-clastogenic and non-aneugenic. • CGA313458: further data on repeated exposure would be needed. Non-genotoxic. <u>Primary crop metabolism:</u> The new OSR metabolism study (2015) did not analyse all relevant commodity fractions. Only the seeds were analysed while residues in forage and stover were not investigated. The study can therefore not be used to extrapolate to the entire P/O category. A supplementary old study is available, addressing pods and stalks residues, but identification was limited. In the new study, in the seeds trinexapac (acid) (CGA 179500) was the major compound identified (19% TRR free, 2.8% conj., to compare with supplementary study: 29% TRR free + 1.1% TRR) conj.) while the other big fraction was radioactivity linked to oleic acid (22.7% TRR). CGA 275537 was a minor metabolite in the seeds (1% TRR). As a cycloproyl label study was not conducted, it is not known whether other significant residue compounds could arise in OSR seeds. At best, a provisional RD, and only for seeds of oilseed crops could be derived with the available data which might be proposed as trinexapac. For cereal/grass crops, metabolism studies are available in wheat, rice and grass. In grains/seeds, trinexapac (acid), free and conjugated, was the major residue. A metabolite identified in the new wheat study (2015) as hydroxylated trinexapac (SYN	Primary crops: In view of the pending data request for a new metabolism study in cereals with the cycloproyl label and further clarification on metabolites, the <u>RD</u> for <u>RA</u> for the cereal/grass crop category should be provisional and should include • for cereal grains trinexapac (acid), free and conjugated. • for cereal fodder items /grass trinexapac (acid), free and conjugated plus CGA300405 For <u>monitoring</u> of residues in the cereal/grass crop category: trinexapac and its salts, expressed as trinexapac. Processed commodities: Unable to conclude on the relevant residues in processed commodities and hence on the appropriate residue definition of risk assessment (see data gap on hydrolysis studies). Data gap:

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	548584) was major (11.8% free /only 0.3% conjugated) and absolute levels of the free compound were also high (0.17 mg/kg) in the grains. The toxicity of OH-trinexapac is considered as covered by trinexapac reference values. Applicant communicated that OH-trinexapac is not stable outside of the matrix and therefore a method for quantification of residues cannot be validated. The applicant proposed the use of a CF derived from the metabolism study to account for the OH-trinexapac metabolite. It seems that the identity of this compound was not fully confirmed (by exclusion of any other possible structure). In view of this uncertainty and the requirement of a new metabolism study with the cyclopropyl label, further elucidation/confirmation of the identity and amounts of this compound is awaited, before a final decision can be taken regarding its relevance as a residue in cereal grains. In the older (1990ies) wheat study with earlier application (approx. BBCH 12-16), CGA329773 was major in grains (10.9% TRR; 0.05 mg/kg) while it was a minor metabolite in straw and in all rice commodities. CGA329773 was not identified in grains in the new wheat study with BBCH 37 application, and was minor in the other wheat commodities. It is noted that in the old wheat study, samples were stored over a much longer period before completion of analysis (up to 43 months) and it was not investigated whether or not this might have affected the residue composition. CGA329773 has no genotoxicity concern and is less toxic than the parent based on toxicity studies, and hence does not have to be considered in the RD for RA. The residue definitions were discussed considering the most abundant residues in cereal grain / fodder commodities and the available toxicological assessment. For <u>monitoring</u> of residues in the cereal/grass crop category, trinexapac (acid) alone is a sufficient marker, however the definition should be formally set as trinexapac and its salts, expressed as trinexapac (current definition for MRL setting taking into account the analytical method) In view of the pending data request for a new metabolism study in cereals with the cyclopropyl label and further clarification on metabolites, the <u>RD for RA</u> should be provisional and should include • for cereal grains trinexapac (acid), free and conjugated. • for cereal fodder items /grass trinexapac (acid), free and conjugated plus CGA300405	Considering the relevance of metabolite CGA300405 in cereal crop feed items, the potential for residues in animal commodities and finally the consumer risk assessment should be further addressed. Data gap: Further information should be submitted regarding the relevance of unique metabolites A, B and C identified in the grass study at significant levels, with a view to comprehensively address the metabolism for the entire category of cereal/grass crops. Data gap: Further clarification should be submitted by the applicant to explain the contradictory findings (stability vs. instability) in the standardised hydrolysis experiments.

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	Consideration should be given to CGA300405, a major residue in wheat fodder commodities in the new (2015) wheat metabolism study (present in forage and straw at equal or higher amounts than trinexapac), and moreover found at high absolute levels. The relevance of this metabolite CGA300405 with regard to livestock exposure (dietary burden) and the potential for carry-over of residues in animal commodities, and finally the consumer risk assessment should be further addressed. CGA275537 (tricarballic acid) and its conjugates was common to wheat, rice, OSR and grass and occurring in varied proportions and levels (free 19% TRR, up to 0.31 mg/kg in rice straw; conjugated up to 12% TRR and 0.66 mg/kg, grass). There relevance with regard to livestock dietary exposure might have to be further considered in view of the absolute levels and the open toxicity assessment. [EFSA post meeting addition: According to public literature, tricarballic acid is found in maize, barley, red beet, sugar beet and sugar maple along with citric acid and aconitic acid, both also identified minor compounds in wheat metabolism studies. As they are naturally occurring compounds in plants, and moreover tricarballic acid seems to be produced by rumen microorganisms, their inclusion in the RD for feed items appears irrelevant.] In grass, unique metabolites were observed when compared to the other cereal crop studies. Free and conjugated metabolites A, B and C (terephthalic acid, which is the starting material for the plastic PET) were identified. The relevance of these compounds with a view to comprehensively address metabolism for the entire category of cereal/grass crops on the basis of the available studies in wheat/rice and grass should be addressed by the applicant. For animals, in view of the residue situation in feed items and the findings in the available livestock studies the picture was distinct. In the metabolism studies with benzene ring labelled trinexapac-ethyl, trinexapac-ethyl was only detected in egg white while trinexapac (CGA 179500) was the major residue across all poultry and goat commodities. CGA 113745 was a major metabolite detected in liver. Awaiting further information on the nature of residues in livestock with regard to the cycloproyl moiety and the fate of the relevant metabolite CGA300405 in livestock, the RD should be provisionally set as follows:	

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
	<u>RD for RA:</u> • Poultry : trinexapac (acid) • Ruminant: trinexapac (acid) + metabolite CGA 113745 , expressed as trinexapac <u>Monitoring:</u> trinexapac (acid) and its salts, expressed as trinexapac To address the effect of food processing conditions on residues, four standard hydrolysis studies were submitted showing partially contradictory outcomes. Two studies were suggesting the stability of trinexapac-ethyl and trinexapac, resp. under hydrolysis conditions while the other two studies showed significant degradation under baking and sterilisation conditions. The experts were unable to conclude on the relevant residues in processed commodities. Further clarification by the applicant to explain the ambiguous findings in this standardised experiment is necessary. Preliminary comments submitted before experts' meeting: LV: RD for enforcement as "Sum of trinexapac acid and its salts, expressed as trinexapac acid" would be appropriate for cereals, pulses and oilseeds, animals and processed commodities. RD for risk assessment: Cereals, oilseeds: Sum of trinexapac acid and its salts, expressed as trinexapac acid Animals: Sum of trinexapac acid and its salts, expressed as trinexapac acid Processed commodities: depends on toxicological properties of metabolites CPCA (CGA 224439), CGA113745, CGA313458.	
Experts' consultation 1. To discuss if the submitted metabolism studies with radiolabelled test substance in the cyclohexane ring only	All plant and animal metabolism studies were conducted exclusively with the benzene ring label and not with the cyclopropyl moiety label. It was discussed whether nonetheless the available information may be sufficient to conclude on metabolism in plants and animals. A cleavage of parent compound was observed in the available metabolism studies. The fate of the split-off cyclopropyl moiety is unknown since not investigated. A hydrolysis study simulating processing confirms the cleavage of the parent molecule and shows formation of compound CGA224439. The experts attempted to estimate the relevance of metabolites bearing only the cyclopropyl	Data gap: A plant metabolism study with the cyclopropyl label in the cereal/grass crop category should be provided. Data gap: The nature of residues in livestock

Subject	Discussion Pesticides Peer Review Meeting	Conclusions Pesticides Peer Review Meeting
are appropriate to firmly address the metabolic pathway of the active substance and conclude on the residue definition for the representative use and for animal products, considering that according to OECD 501, 502 and OECD 503 separate studies labelling each ring or side chain of the molecule will normally be required, unless no cleavage is anticipated. It is note that apparently CPCA (CGA224439), when analysed, was found in grain prior to be processed and it is not clear if derived from hydrolysis degradation pathway only and its toxicological relevance. See 2(42), 2(53) and Experts' Consultation 2 See reporting table 3(72)	moiety with regard to livestock and animal exposure but agreed that this would result in high uncertainty. Amounts of CGA224439 were determined in grain in the processing studies above the LOQ (2-3 N studies, but levels will likely exceed LOQ also when considering 1 N rate). CGA224439 is expected of higher toxicity than the parent (see outcome of tox meeting). The experts agreed that a data gap should be identified for primary crop metabolism data in cereals with cycloproyl labelling to appropriately address the data requirements for at least the representative uses. In view of the importance of feed items from the intended uses and the expected residue levels, the nature of residues in livestock with regard to the cycloproyl moiety should also be addressed. Moreover, the potential for uptake of residues bearing the cycloproyl moiety in rotational crops and their identity should be investigated. Preliminary comments submitted before experts' meeting: LV: According to OECD 507 "The same labelling positions as in the available metabolism studies are preferable and should be used." This time radiolabel position was different. Could you, please, explain how these divergences influence the significance of this study compared to other high temperature hydrolysis studies? Especially, because metabolite CGA224439 is identified only in this study, maybe CGA224439 could be major metabolite also in plant metabolism if the same radiolabel position would be used. Toxicological properties of metabolite CGA224439 should also be assessed.	with regard to the cycloproyl moiety should be addressed. Data gap: The potential for uptake of residues bearing the cycloproyl moiety in rotational crops and their identity should be investigated.

TABLE OF CONTENTS

	Document
00	Cover page
01	Comments on the assessment report
02	Reporting table
03	Pesticides peer review meeting reports
04	Evaluation table
05	Comments on the additional information assessment
06	Comments on the draft EFSA conclusion

section 0 – General

0. General

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
No comments				

rapporteur LT

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Open point 1.1 RMS to update Vol.3 CA B.2.1.10 with the information in col.3 of the RT See reporting table 1(50)	The Vol.3 CA B.2.1.10 has been amended accordingly.			Addressed: The Vol.3 CA B.2.1.10 has been amended.
Open point 1.2 RMS to update Vol.3CA B.2 with the comments on acceptability of studies, where relevant, in an updated RAR. See reporting table 1(55)	The Vol.3 CA B2 has been amended accordingly.			Addressed: The Vol.3 CA B2 has been amended
Open point 1.3 RMS to harmonise the residue definition in air in a revised RAR. See reporting table 1(68)	The residue definition has been revised and harmonised as relevant in the revised RAR Vol.1 2.13.2, Vol.3 B.5.2.5: the residue definition in air is trinexapac-ethyl.			Addressed: The residue definition in air is trinexapac-ethyl.

rapporteur LT

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Open point 1.4 RMS to include the information on the guidance document according to the analytical methods are fully validated in a revised RAR. See reporting table 1(70)	The information on acceptability of methods validation as pointed out in the reporting table 1 (70) has been clarified in the revised Vol.3 CA B5.1.2			Addressed: The information on acceptability of methods validation as pointed out in the reporting table 1 (70) has been clarified in the revised Vol.3 CA B5.1.2
Open point 1.5 RMS to include the information on the acceptability of the methods in a revised RAR. See reporting table 1(71) See also comments 1(75), 1(80), 1(83)	With reference to comments in RT the Vol.3 CA B5 was accordingly amended by information on acceptability of the following methods and their study reports: 1(71) GRM020.01A 1(75) KCA 4.1.2/13-14 - 1(80) KCA 7.1.2/01 ref.F&B 1(83) KCA 4.2.19 GRM020.12A			Addressed: Vol.3 CA B5 was amended by information on acceptability of the following methods and their study reports: 1(71) GRM020.01A, 1(75) KCA 4.1.2/13-14 - 1(80) KCA 7.1.2/01 ref.F&B, 1(83) KCA 4.2.19 GRM020.12A
Data requirement 1.1 Additional validation data for the method GRM020.01A for	Additional validation data has not been provided. The applicant responded that GRM020.01A is a pre-registration method, and			Addressed: The validation report indicates that in this study final solutions were also analysed using the confirmatory ion transition, i.e.

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
confirmation of the analyte. See reporting table 1(73)	therefore a single transition is considered appropriate. The data requirement according to the SANCO/3029/00 rev.4 for confirmation of the analyte CGA179500 (free and conjugated) has not been met. Not all the criteria of the guidance document have been fulfilled.			the transition, m/z 223 to m/z 179. The method can be considered fit for purpose.
Data requirement 1.2 Applicant to submit methods GRM20.13A and GRM20.14A to be evaluated in a revised RAR. See reporting table 1(74)	The study reports of methods GRM20.13A and GRM20.14A and the GLP validation for metabolite CGA113745 determination in bran, wheat grain, flour and bread have been submitted by the applicant. The final results have been added and assessed in the revised Vol.5 CA B5.1.2.1			Addressed: The final results of the studies have been added and assessed in the revised Vol.5 CA B.5.1.2.1
Open point 1.6 RMS to correct the error in Table 4 concerning the right codes. See reporting table 1(76)	The report of GRM20.15A method (<i>Watson G., 2016 file no. CA876-1002</i>) p.31, Table 4 had incorrect code CGA224489 which was noted in the DRAR and further admitted by applicant. CGA224489 was also in Figures 3, 6, 23 on			Addressed: The error in Table 4 concerning the right codes was corrected.

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	p.35, p.38 and p.55 of study report). This was Addressed: misleading since derivatisation step applied and name ' <i>HQ derivatised CGA224489</i> ' used. The applicant informed on correct code no. CGA224439 and further revision/reissue of method into version B of GRM020.15. The RAR has been amended, reissued version awaited.			
Open point 1.7 RMS to include the information from col.3 of the RT concerning the solvent bridging in a revised RAR. See reporting table 1(77)	The Vol.3 CA B.5.1.2.2 has been amended accordingly by including the solvent bridging - information on solvent mixtures used for residues extraction in goat metabolism study (acetonitrile/water) comparable in polarity to solvents used for extraction of residues from commodities of animal origin (methanol/water).			Addressed: The Vol.3 CA B.5.1.2.2 has been amended by including the solvent bridging.
Open point 1.8 RMS to include the information from the	The Vol.3 CA B5 has been accordingly amended by including the applicant comment on the method			Addressed: The Vol.3 CA B5 has been amended including the comments on the method

rapporteur LT

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
col.3 of the RT in a revised Vol.3 CA B.8., method Richardson M., Cashmore A. (2016) See reporting table 1(79)	acceptability to fit for the purpose of a kinetic evaluation (fate and behaviour part of assessment).			acceptability.
Data requirement 1.3 Applicant to provide information on the extraction efficiency for the methods of pre-registration for plant and animal matrices in consideration to available metabolism studies performed. See reporting table 1(84)	The information on the extraction efficiency with reference to metabolism studies in regards to plant matrices has been provided with relevance to the methods GRM020.01A and GRM020.09A. For animal matrices the reference to goat metabolism study was provided with the solvent mixtures (water/methanol and acetonitrile/water) compared. The Vol.3 CA B5 has been accordingly amended.			Addressed: The information on the extraction efficiency with reference to metabolism studies was included in the revised Vol.3 B.5
Data requirement 1.4 Applicant to provide information on the extraction efficiency for the monitoring methods for plant matrices in	The applicant response with reference to the Metabolism of [¹⁴ C]- Trinexapac-ethyl in Oilseed rape study report has been included in the revised Vol. 3 CA B5.			Addressed: The applicant response with reference to the metabolism of [¹⁴ C]- trinexapac-ethyl in oilseed rape study report has been included in the revised Vol. 3 CA B5.

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
consideration to available metabolism studies performed. See reporting table 1(85)				
Open point 1.9 RMS to correct in the revised Vol.3 CA B.5 the text as indicated in the col.3 of the RT See also comment 1(90) See reporting table 1(88)	The text with reference to the Column 3 of the RT 1 (90) has been added in the revised Vol.3 CA B5			Addressed: The text with reference to the column 3 of the RT 1(90) has been added in the revised Vol.3 CA B5.
Open point 1.10 RMS to correct the typo in the title of table in Vol.3 CA B.5.2.2. See reporting table 1(89)	The typo in the title of table in Vol 3 CA part B.5.2.2 with relevance to reporting table 1 (89) has been corrected (<i>'products of plant origin'</i> to <i>'products of animal origin'</i>)			Addressed: The typo has been corrected.
Open point 1.11 RMS to include the information from the col.3 of the RT in a	The Vol.3 CA B5.2.3 has been amended accordingly by information on the hydrolysis in the method GRM020.04A and therefore			Addressed: The Vol.3 CA B5.2.3 has been amended by information on the hydrolysis in the method GRM020.04A.

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
revised Vol.3CA B.5 concerning the method for residues in soil. See reporting table 1(92)	any residues of CGA179500 determined being a sum of free CGA179500, salts of CGA179500 and hydrolysed trinexapac-ethyl.			
Open point 1.12 RMS to update the RAR Vol.3 CA, B.5.2.4 Methods for the determination of the active substance and/or metabolites in water based on the updated version of the report. See reporting table 1(93)	The Vol.3 CA B5.2.4 has been amended accordingly based on updated version of the report – Amendment 1 of the ILV study report.			Addressed: The Vol.3 CA B5.2.4 has been amended based on updated version of the report.
Open point 1.13 RMS to include the information from the col.3 of the RT in a revised Vol.3CA B.5 concerning the method for the determination of residues in water See reporting table	The Vol.3 CA B5.2.4 has been amended accordingly. The method GRM020.02A is capable to separately determine trinexapac-ethyl and CGA179500(salts included).			Addressed: The Vol.3 CA B5.2.4 has been amended. The method GRM020.02A is capable to separately determine trinexapac-ethyl and CGA179500 (salts included).

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
1(94)				
Data requirement 1.5 Applicant to submit the method for body fluid/tissues: CGA179500_11025 and OECD summary CGA179500_11026 See reporting table 1(98)	The study report of QuEChERS method for body fluids/tissues has been submitted by the applicant. The results have been included and assessed in the revised Vol.3 B5.2.6			Addressed: The submitted method has been assessed in the revised Vol.3 B.5.2.6
Data requirement1.6 Applicant to further address the concerns raised by the RMS regarding the analytical methods for diet analysis of trinexapac-ethyl and for diet/plasma analysis of metabolite CGA329773 used in 10 studies (Oral 90-day study in rats and dogs, 1 year dog study, Carcinogenicity study in rats and mice, Two-Generation Reproduction	The summary information on analytical methods available in the mentioned 10 toxicological study reports (under KCA 5.3.2, KCA 5.3.3, KCA 5.5.1, KCA 5.5.2, KCA 5.7.1, KCA 5.8.2) with relevance to Vol.6 CA assessment has been provided by the applicant with relevance to KCA 4.1.2, assessed and included in the revised Vol.3 CA B5.1.2.6.			Addressed: The summary information on analytical methods available in the mentioned 10 toxicological study reports was included in the revised Vol.3 CA B.5 and the methods were found fit for purpose.

section 1 – Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
toxicity study in rats, Subchronic neurotoxicity studies in rats, 28-day dietary immunotoxicity study in mice, 28-day study in rats on metabolite CGA 329773, in vivo micronucleus test in rats on metabolite CGA 329773) since a conclusion on whether they fit-for-purpose and support the toxicological studies could not be reached. See reporting table 1(100)				

2. Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Data requirement 2.1 Applicant to provide a figure illustrating the metabolic pathway of trinexapac in the rat. See reporting table 2(4)	LT: Additional data are reported in the revised RAR.			Fulfilled. A table instead of a figure was provided. EFSA considered this point fulfilled.
Data requirement 2.2 Applicant to provide a comparative <i>in vitro</i> metabolism study for trinexapac, including an assessment of the metabolism in key animal test species (including dog) and possible identification of specific human metabolites. See reporting table 2(5) See also comments 2(2), 2(3).	LT: Applicant (Trinexapac Task force) provided a comparative <i>in vitro</i> rat and human metabolism study only (<i>Paul D., 2017</i>). Additional data is reported in the revised RAR. No information was provided on dogs. The inclusion of the dog in a comparative <i>in vitro</i> metabolism study would have been valuable due to observed differences of toxicological profile of trinexapac-ethyl between dogs and rats.			Fulfilled considering that the study was submitted. However, the dog was not included in this study and it was suggested by the experts as a data gap to address human relevance of potential endocrine-mediated effects in dogs.

section 2 – Mammalian toxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Data requirement 2.3 Applicant to provide the pilot 7-week oral feeding study in dogs (Spoede S et al, 1989) and robust summary report. See reporting table 2(13) See also expert consultation in 2(14).	LT: The study and summary report has been provided and included in the revised Volume 3 and Volume 1.			Fulfilled.
Expert consultation 2.1 Experts to discuss the toxicological endpoints in the dog studies, including changes in brain and reproductive organs. See reporting table 2(14) See also data requirement in 2(13). See also comments 2(15), 2(16) and 2(17).	LT: Will be discussed by the MSs experts.	<u>Pesticides Peer Review Meeting 170 (11 – 14 December 2017):</u> Experts' consultation fulfilled. Majority of experts agreed that appropriate NOAEL for the 1-year dog study should be set NOAEL at 31.6 mg/kg bw per day (1000 ppm) based on changes in uterus weight, changes in oestrous cycle, changes in brain, on clinical signs (faeces mucoid/bloody, M & F), ↓ terminal body weight (M), haematological changes		Majority of experts agreed that appropriate NOAEL for the 1-year dog study should be set NOAEL at 31.6 mg/kg.

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
		(↓RBC, ↓HCT, ↓HGB) (F).		
Data requirement 2.4 Applicant to provide detailed summary reports for <i>in vitro</i> genotoxicity studies: - Deparade E. (1988), study report No. 871414 - Deparade E. (2001a), study report No. 20001169 - Dollenmeier P. (1988), study report No. 871415 - Geleick D. (1993), study report No. 931004 - Hertner (1988), study report No. 871411 - Meyer (1988), study report No. 871413 RMS to provide update and also correction in an amended RAR, this action is needed according to SANCO/10180/2013-rev.1. See reporting table 2(18)	LT: detailed summary reports for six <i>in vitro</i> genotoxicity studies have been provided and have been included by the RMS in the revised Volume 3, B.6.4. New evaluation of six old studies has been performed by the RMS.			Fulfilled
Expert consultation 2.2	LT: Will be discussed by	<u>Pesticides Peer Review</u>		The weight of evidence

rapporteur LT

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Experts to discuss the amended results of the genotoxicity studies with trinexapac-ethyl. See data requirements in 2(18) and 2(69). See also open point in 2(22). See reporting table 2(18)	the MSs experts.	<u>Meeting 170 (11 – 14 December 2017):</u> Experts' consultation fulfilled. The weight of evidence suggests that trinexapac-ethyl is unlikely to be genotoxic <i>in vivo</i>.		suggests that trinexapac-ethyl is unlikely to be genotoxic <i>in vivo</i>.
Open point 2.1 RMS to provide an updated non-confidential RAR with the genotoxicity studies provided by Cheminova A/S. See reporting table 2(22) See also expert consultation in 2(18).	LT: A complete assessment of the results of five genotoxicity studies on the active substance submitted by Cheminova A/S has been included in the revised RAR Volume 3, B.6.4. from the confidential Vol 4 Cheminova. Additionally, the results from these five genotoxicity studies have been summarised in the revised RAR Volume 1, 2.6.4 and the list of references (Volume 2, A.6). List of Endpoints (Section 2) has been updated.			Addressed.

section 2 – Mammalian toxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Data requirement 2.5 Applicant to provide more detailed historical control data for the rat developmental toxicity study. See reporting table 2(27)	LT: More detailed historical control data for the rat developmental toxicity study has been submitted by the applicant: the applicant has submitted an historical control data from separate 12 developmental toxicity studies from 297 pregnant females. However, these data have not been combined in a single package and SD has not been reported.			Fulfilled
Expert consultation 2.3 Experts to discuss the developmental toxicity studies with trinexapac-ethyl. See reporting table 2(27) See also comment 2(28).	LT: Will be discussed by the MSs experts.	<u>Pesticides Peer Review Meeting 170 (11 – 14 December 2017):</u> Experts' consultation fulfilled. The agreed rat developmental NOAEL is 200 mg/kg bw per day. No consensus was achieved by experts regarding the proposal for classification of the substance based on the observed findings of asymmetrically shaped		The agreed rat developmental NOAEL is 200 mg/kg bw per day. No consensus was achieved by experts regarding the proposal for classification of the substance based on the observed findings of asymmetrically shaped sternebra, with 8 experts out of 16 supporting classification. Thus in EFSA conclusion no proposition for classification will be suggested as proposed by RMS.

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
		sternebra, with 8 experts out of 16 supporting classification. Thus in EFSA conclusion no proposition for classification will be suggested as proposed by RMS.		
Data requirement 2.6 Applicant to submit further detailed information on ToxCast results regarding endocrine-disruption potential of trinexapac-ethyl. See reporting table 2(31)	LT: Further detailed information on ToxCast regarding endocrine-disruption potential of trinexapac-ethyl has been submitted and included in the revised Volume 3 and Volume 1.			Fulfilled
Expert consultation 2.4 Potential for endocrine disruption of trinexapac-ethyl to be discussed by the experts. See reporting table 2(31) See data requirements in 2(31) and 2(33). See also comments 2(32), 2(34), 2(35), 2(36), 2(37), 2(38) and 2(39).	LT: Will be discussed by the MSs experts.	<u>Pesticides Peer Review Meeting 170 (11 – 14 December 2017):</u> Experts' consultation fulfilled. The majority of experts (slight, 9 vs 7) could not conclude on the ED-properties based on available information of the substance and suggested to provide <i>in</i>		The majority of experts (slight, 9 vs 7) could not conclude on the ED-properties based on available information of the substance and suggested to provide <i>in vitro</i> assays (e.g. steroidogenesis assay OECD TG456) and comparative metabolism study between dog and human.

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
		<i>vitro</i> assays (e.g. steroidogenesis assay OECD TG456) and comparative metabolism study between dog and human. A data gap will be included in the EFSA conclusion to reflect the view of the majority of experts.		
Data requirement 2.7 Applicant to provide a more detailed summary of the study by Böhmler G. et al., 2006. See reporting table 2(33) See also expert consultation in 2(31).	LT: A more extended summary of the study (Böhmler G. et al., 2006) and the study itself has been provided and included in the revised Volume 3.			Fulfilled
Open point 2.2 RMS to add the detailed assessment of the toxicological profile of citric acid in a revised RAR. See reporting table 2(40)	LT: The detailed assessment of the toxicological profile of citric acid has been included in the revised RAR Volume 3, B.6.8.1.11 and Volume 1, 2.6.9.1.			Addressed.

rapporteur LT

section 2 – Mammalian toxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
See expert consultation at 2(53).				
Data requirement 2.8 Applicant to provide a literature search (covering the last ten years) for the toxicological properties of the tricarballylic acid metabolite, 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid (CGA329773) and CPCA (CGA224439). Based on currently available information further data would be needed to conclude on genotoxicity (<i>in vitro</i> chromosome aberration test) and general toxicity (repeated toxicity study) for metabolite tricarballylic acid. See reporting table 2(42) See also comment 2(70).	LT: A literature search review for the following metabolites CGA275537, CGA329773, Hydroxylated CGA179500, CGA300405, CGA351210, SYN540405 and SYN540406 has been provided and has been included in the revised RAR Volume 3. This search was done in 31st August 2017 and covered the last twelve years. It should be noted that the applicant has not submitted a further/additional literature search review for the metabolite CPCA (Cyclopropane carboxylic acid, CGA224439). Regarding metabolite tricarballylic acid (CGA275537), the applicant has not submitted			Data gap for literature search on metabolite CPCA (Cyclopropane carboxylic acid, CGA224439).

rapporteur LT

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
See also comments 2(43), 2(50), 2(51), 2(52) and 2(53). See expert consultation at 2(53).	additional data to conclude on genotoxicity (<i>in vitro</i> chromosome aberration test) and general toxicity (repeated toxicity study).			
Data requirement 2.9 Applicant to provide validation of the analytical method used to quantitate plasma CGA329773 levels (to be assessed under B.5) or additional evidence of bone marrow exposure in the micronucleus test with CGA329773. See reporting table 2(45) See also comments 2(44) and 2(46). See expert consultation at 2(53).	LT: The applicant repeatedly has submitted a standalone toxicokinetic report (Woods K., 2004) with description of analytical method without validation results. <i>"The methodology used in the analysis of the toxicokinetics samples had not been validated"</i> according to the Statement of GLP Compliance and Authentication and which was signed by the Study Director Clay P. All this information has been included in the revised RAR Volume 3. Additionally, his analytical method was considered by the RMS in Volume 3, chapter B.5.1.2. and B.5.1.2.6.			Fulfilled considering that the methodology used in the analysis of the toxicokinetics samples had not been validated.

rapporteur LT

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
	Regarding additional evidence of bone marrow exposure in the micronucleus test with CGA329773, the applicant provided the statement. All this information has been included in the revised RAR Volume 3. In addition, a consideration of the RMS LT regarding exposure of the bone marrow has been included in the revised RAR Volume 3.			
Data requirement 2.10 In vitro genotoxicity studies already performed for the metabolite CGA179500 (trinexapac acid) to be provided to the RMS for their inclusion in the revised RAR. See reporting table 2(47) See expert consultation at 2(53).	LT: three <i>in vitro</i> genotoxicity studies (Ames assay, Gene mutation assay and Micronucleus Test in vitro) for the metabolite CGA179500 (trinexapac acid) have been provided. They have been evaluated by the RMS and have been included in the revised RAR Volume 3, Volume 1, Volume 2 and LoEP.			Fulfilled.

rapporteur LT

section 2 – Mammalian toxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Data requirement 2.11 Based on currently available information further data would be needed to conclude on general toxicity (repeated toxicity study) for metabolite 3-ethoxycarbonylpentanedioic acid. See reporting table 2(50) See expert consultation at 2(53).	LT: the applicant has not submitted further data to conclude on general toxicity (repeated toxicity study) for metabolite 3-ethoxycarbonylpentanedioic acid (CGA300405).			Fulfilled. The metabolite CGA300405 is unlikely to be genotoxic. Further data on repeated exposure might be not needed pending on further data to confirm the rapid hydrolysis to tricarballic acid (see section 3).
Open point 2.3 RMS to include the supplementary consideration in the text of the revised RAR and to supplement a conclusion regarding equal short-term toxicity of CGA113745 and CGA158377 than the parent substance. See reporting table 2(51)	LT: the supplementary consideration and conclusion regarding equal short-term toxicity of CGA113745 and CGA158377 than the parent substance have been included by the RMS in the text of the revised RAR Volume 1.			Addressed.

rapporteur LT

section 2 – Mammalian toxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Data requirement 2.12 Based on currently available information further data would be needed to conclude on general toxicity (repeated toxicity study) for metabolite <i>CGA313458</i> (2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid). See reporting table 2(52) See expert consultation at 2(53).	LT: the applicant has not submitted further data to conclude on general toxicity (repeated toxicity study) for metabolite <i>CGA313458</i> (2-(4-cyclopropyl-2,4-dioxo-butyl)butanedioic acid).			Fulfilled. <i>CGA313458</i> is unlikely to be genotoxic. Further data on repeated exposure might be needed pending on clarification on relevance of metabolite in processing commodities (see Section 3)
Data requirement 2.13 A 90-day rat study on cyclopropane carboxylic acid (CPCA) was submitted to JMPR for the assessment of aminocyclopyrachlor (JMPR, 2014). The study should be submitted to the RMS for an independent assessment of the study. It is noted that the EFSA	LT: A 90-day rat study on cyclopropane carboxylic acid (CPCA) has not been submitted to the RMS for an independent assessment of the study because data for cyclopropane carboxylic acid (CPCA) are not owned by the applicant. The applicant has submitted only consideration regarding suitability of ADI for			Data gap 90-day rat study on <i>CGA224439</i> available to JMPR to address the repeated exposure toxicity.

rapporteur LT

section 2 – Mammalian toxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
guidance on residue definition has not been taken note at the Standing Committee and therefore cannot be applied. Consequently the use of the TTC as proposed in this guidance is not yet agreed for the peer review. See reporting table 2(53) See also data requirements 2(42), 2(45), 2(47), 2(50) and 2(52)	cyclopropane carboxylic acid (CPCA) based on the NOAEL reported in this study.			
Expert consultation 2.5 The toxicological profile of potential dietary metabolites tricarballic acid, GA300405, CGA313458 and CPCA to be discussed by the experts. Pending on the updated literature search and data requirements on metabolites further metabolites might be included for discussion.	LT: Will be discussed by the MSs experts.	<u>Pesticides Peer Review Meeting 170 (11 – 14 December 2017):</u> Experts' consultation fulfilled. CGA275537 Data gap identified for genotoxic potential of the metabolite (chromosomal aberration endpoint) and repeated exposure if risk assessment is triggered by residues experts.		Available information on the toxicological profile of metabolites indicated that CGA313458 is unlikely to be genotoxic. Further data on repeated exposure might be needed pending on clarification on relevance of metabolite in processing commodities (see Section 3). CGA224439 is not genotoxic. It is considered of higher toxicity than the parent compound based on 90-day rat toxicity study available to JMPR (JMPR, 2014) which was not submitted to the RMS for an

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
See reporting table 2(53)		GA300405 Not genotoxic. Further data on repeated exposure would be needed if risk assessment is triggered by residues experts. CGA313458 Not genotoxic. Further data on repeated exposure would be needed if risk assessment is required by the residue experts. CGA224439 Not genotoxic. Considered of higher toxicity than the parent compound based on short term toxicity study (available to JMPR), which was not submitted to RMS for independent assessment. The data gap is proposed by experts to address the repeated exposure toxicity.		independent assessment. A data gap is proposed to address the repeated exposure toxicity and updated literature search to include this metabolite. Hydroxylated CGA179500 (SYN54584) is considered covered by trinexapac (CGA179500) as well as by trinexapac-ethyl (i.e. at least as toxic as the parent). For tricarballic acid (CGA275537) there is no sufficient data for a final conclusion on genotoxicity and no data for repeated exposure (comparison to parent or specific reference values) are available. However, considering the natural occurrence of tricarballic acid, further data are not needed (see Section 3). The metabolite CGA300405 is unlikely to be genotoxic. During the peer review meeting it was mentioned that the metabolite showed a higher acute oral toxicity than the parent. Further data on repeated exposure might be

section 2 – Mammalian toxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
				not needed pending on further data to confirm the rapid hydrolysis to tricarballic acid (see section 3). CGA329773 is unlikely to be genotoxic and repeated toxicity data indicated less toxic than parent. CGA158377 and CGA113745 are unlikely to be genotoxic. Repeated toxicity data indicate comparable toxicity than parent.
Expert consultation 2.6 Reference values for trinexapac-ethyl (ADI, ARfD, AOEL and AAOEL) to be confirmed/discussed by the experts. See reporting table 2(57) See also comments 2(56), 2(58), 2(59) and 2(60).	LT: Will be discussed by the MSs experts.	<u>Pesticides Peer Review Meeting 170 (11 – 14 December 2017):</u> Experts' consultation fulfilled. The experts agreed to keep ADI of 0.32 mg/kg bw per day based on 1-year dog study and the AOEL 0.34 mg/kg bw per day based on 90-day rat study. The majority of experts agreed that there is no need for ARfD and AAOEL setting.		The experts agreed to keep ADI of 0.32 mg/kg bw per day based on 1-year dog study and the AOEL 0.34 mg/kg bw per day based on 90-day rat study. The majority of experts agreed that there is no need for ARfD and AAOEL setting
Open point 2.4	LT: both options (bystander and resident			Addressed.

section 2 – Mammalian toxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to present both options (bystander and resident exposure estimates for both distances) in a revised RAR. See reporting table 2(65)	exposure estimates for both distances) have been presented in the revised RAR Volume 3, Volume 1, and LoEP.			
Data requirement 2.14 Robust study summaries to be provided to the RMS for the genotoxicity studies reported by Helm AG. See reporting table 2(69)	LT: Robust summaries of two Ames tests on the active substance have been provided by the applicant (Helm) and have been included in the revised RAR Volume 3, Volume 1, Volume 2 and LoEP.			Fulfilled.
Open point 2.5 RMS to reconsider the equivalence between technical materials once the technical specification(s) is(are) agreed and supported by a complete toxicity datapackage. See reporting table 2(72)	LT: RMS will reconsider the equivalence between technical materials once the technical specification(s) is(are) agreed and supported by a complete toxicity data package. Currently (RAR ver.2), RMS estimates the equivalence of different sources to the reference specification proposed by the RMS.			The equivalence between technical materials should be reconsidered once the technical specification is agreed and supported by a complete toxicity data package.

3. Residues

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Open point 3.1 Storage recoveries in Table B.7.1.1-1 for Study 1 (K-CA 6.1/01) should report the uncorrected values. In these conditions, residues of trinexapac acid (CGA 179500) in wheat straw can be considered as stable for up to 12 months. RMS to amend the RAR and the LoEP accordingly. See reporting table 3(3)	Vol.3 B.7.1.1, Vol.1 2.7.1 and LoEP was amended accordingly in a revised DRAR (Dec. 2017).			Addressed. The uncorrected recoveries were added to a revised RAR Freezer storage stability of trinexapac in wheat straw is demonstrated up to 12 months.
Open point 3.2 RMS to provide detailed summary of the validation of analytical method and any deviation from guidance OECD 506 to enable conclusion on the compliance with current standards of the storage	Detailed summary of the validation of analytical method and deviations from OECD 506 of the storage stability Study 1 (KIIA 6.3.2.1 /01) is included in a revised RAR. Storage stability study is considered acceptable (see Vol 3 B.7.1.1)			Addressed. A detailed assessment of the storage stability study 1 provided

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
stability Study 1(KIIA 6.3.2.1 /01) in a revised RAR. See reporting table 3(4)				
Open point 3.3 RMS to provide a detailed evaluation and any deviation from guidance OECD 506 of the storage stability study in matrices of animal (bovine) origin to enable concluding that stability of trinexapac acid covering the length of storage of the samples from the feeding study is adequately addressed. See reporting table 3(10)	Detailed evaluation and deviations from OECD 506 of the storage stability study in matrices of animal (bovine) origin were included in the revised dRAR. Study is considered acceptable and covering the length of storage in feeding study (see Vol 3 B.7.1.2)			Addressed. A detailed assessment of the storage stability in matrices of animal origin provided
Data requirement 3.1 Applicant to provide stability for trinexapac acid in cereal grains and straw covering the maximum length of storage of the samples from the residue trials.	No new studies provided. Exact length of storage of every sample was provided for studies "Andrews G. (2015) Trinexapac-Ethyl - Residue Study on Winter Barley in northern France and Germany in 2013.			See Data gap in Data requirement 3.5 Additional storage stability needed. It is expected that the new storage stability study applies same conditions of preparation and analysis of the samples as for the

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
See reporting table 3(13)	Syngenta File No. A8587F_10138 (KCA 6.3.1/01) and Andrews G. (2015a) Trinexapac-Ethyl - Residue Study on Winter Barley in Italy and Spain in 2013. Syngenta File No. A8587F_10132 (KCA 6.3.1/03).			samples from residue trials. As residues are expected to decline between 12 to 24 months in straw, it is advisable to include additional sampling points.
Open point 3.4 RMS to assess the data and reconsider the validity of residue data accordingly. Trials not adequately supported by storage stability shall be excluded from the assessment. See also 3(4)	RMS assessed submitted data and reconsidered the validity of residue trials in light of storage stability. The length of storage and the conclusion if this time is covered by storage stability data are included in the revised dRAR for every supervised field trial Vol 3 B.7.3.			Addressed Validity of residue data reconsidered in light of supported stability.
Data requirement 3.2 Applicant to provide storage stability studies for the metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) covering the	Storage stability studies for the metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) were provided by the applicant.			See Data gap in Data requirement 3.5 Storage stability data were provided and assessed. Results from processing studies are not valid as not covered by demonstrated storage stability for metabolites CGA113745

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
length of storage of the samples from processing studies. See reporting table 3(15)				and CGA313458. Evaluation in Open point 3.5
Open point 3.5 RMS to assess the storage stability data and to conclude on the validity of the residue levels of CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) determined in the processing studies as per storage stability. See reporting table 3(15)	RMS assessed the storage stability data for metabolites CGA313458, CGA113745 and CGA224439 in the revised dRAR (see Vol 3 B.7.1.1). Metabolite CGA113745 appeared to be unstable and therefore all data in the processing studies are considered not valid. For metabolite CGA313458, residue data in barley bran, wheat bran, flour and bread samples are not covered by storage stability data, and consequently not valid (see Vol 3 B.7.5.3). Additional data on the magnitude of metabolites CGA313458 and CGA113745 should be provided, as well as storage stability data for			Addressed Storage stability data assessed.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	metabolite CGA113745 in smaller steps during the first month of storage. CGA113745 samples should be analysed as soon as possible, CGA313458 samples – during the demonstrated stable storage period.			
Open point 3.6 RMS to provide a detailed evaluation and any deviation from guidance OECD 501 of the submitted metabolism studies in cereals/grass (wheat, rye, rice, grass) and pulses/oilseeds (OSR) and to conclude on acceptability and their appropriateness to derive the residue definition for at least the representative uses. The RAR and the LoEP shall be revised accordingly. See Expert consultation 1	Old metabolism studies of wheat, rice grass and oilseed rapes were re-evaluated by RMS LT. Deviations from OECD 501 and acceptability of studies are provided in Vol 3 B.7.2.1. RAR and LoEP are revised accordingly. The proposed residue definitions will be discussed at Expert consultation.			Addressed. A detailed assessment of the metabolism studies in cereals and OSR has been provided

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
See reporting table 3(18)				
Open point 3.7 RMS committed to report the correct extractability values for straw and grain of the metabolism study in spring wheat (Study 7) in a revised RAR. See reporting table 3(26) See also 3(18) and Experts' consultation 1	The corrects value of extractability in straw (64.8 %) was inserted in table B.7.2.1-11 in a revised RAR Vol 3 B.7.2.1			Addressed.
Open point 3.8 RMS committed to revise the RAR accordingly. See reporting table 3(28)	The sentence on N rate in grass metabolism study compared to Gap authorised in EU was deleted in Vol. 3, B.7.2.1 and Vol. 1, Level 2.7.2, as use on grass in not authorised in EU.			Addressed.
Data requirement 3.3 Applicant to submit the GLP study (CGA163935_10838) related to hydroxylated trinexapac acid (SYN548584). See reporting table 3(29)	GLP study (CGA163935_10838) related to hydroxylated trinexapac acid (SYN548584) was submitted by the applicant and reported in Vol. 3 B.7.2.1 as study 8.			See Data gap in Experts' consultation 1 Applicant reported that SYN548584 (12%; 0.18 mg eq/kg in grain, 5%; 0.1 mg/kg in hay) was unstable outside the plant matrix. The

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
				compound could not be synthesized and analysed in field trials. The structure was assigned based on exclusion criteria among three potential positions of the hydroxyl group. Due to the structural similarity to trinexapac, its toxicity is likely to be at least equivalent to parent. Evaluation in Open point 3.9
Open point 3.9 RMS to evaluate the information in a revised RAR. See reporting table 3(29)	GLP study (CGA163935_10838) related to hydroxylated trinexapac acid (SYN548584) was evaluated and consider acceptable by the RMS LT in a revised RAR. Vol. 3 B.7.2.1 study 8.			Addressed The study was assessed.
Open point 3.10 RMS to provide a detailed evaluation and any deviation from guidance OECD 503 on the submitted metabolism studies in poultry and ruminants and to conclude on acceptability	Additional details to metabolism studies on poultry and ruminants were added in a revised RAR. Old metabolism studies on poultry (study 2, Müller 1993) and ruminants (study 2, Müller 1993a) are considered			Addressed. A detailed assessment of the old studies on the nature of residues in poultry and ruminants provided

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
and their appropriateness to derive residue definition in products of animal origin. The RAR and the LoEP shall be revised according to the acceptability conclusions. See also Experts' consultation 1 See reporting table 3(30)	supplementary. As the results are comparable to new metabolism studies provided (according to OECD 503) no essential changes will be made in Vol. 1 and LoEP.			
Data requirement 3.4 Applicant to submit information against the data requirement of Regulation (EU) No 283/2013. The argument that no agreed test method or guidance is available is not considered a valid justification. Detailed circumstances in which animal fish metabolism and feeding studies are triggered are described in SANCO/11187/2013. See reporting table 3(34)	No metabolism study on fish was provided. Additional argumentation based on the lack of: dietary burden calculation method, method for studying the nature of residues in fish; an agreed and practicable method for quantitatively studying the transfer of residues of concern into fish tissues was provided by the applicant and reported in revised DRAR (Dec. 2017) Vol1. 2.7.2.			Data gap Relevance of residues in the fish diet and information against the residues data requirements on fish The representative uses refer to products that are used as feed items in aquaculture, residues of trinexapac in these crops are >0.01 mg/kg, RD-RA in cereal feed items is provisional (pending new metabolism study) and, by the time, includes CGA300405.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Open point 3.11 RMS to assess information provided in a revised RAR. See reporting table 3(34)	RMS considers the argumentation provided as not valid justification and believes that at least a dietary burden calculation as recommended in SANCO/11187/2013 should be submitted. See revised DRAR (Dec. 2017), Vol.1, 2.7.2.			Addressed Argumentation of the applicant assessed as not satisfactory
Open point 3.12 RMS to assess the argumentation provided by the applicant in a revised RAR. See reporting table 3(35)	The argumentation provided was assessed in revised RAR Vol. 3 B.7.2.2			Addressed for -Tricarballic acid is naturally present in grass and it is endogenously formed in ruminant rumen from aconitic acid (CGA312753). Compare with other potential sources, intake from wheat straw is lower. - Metabolite CGA351210 was found only in the OSR supplementary metabolism study. No residue definition was derived for the group of pulses/oilseeds.
Open point 3.13	Proposed residue			Addressed.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS is requested to reconsider the residue definition for enforcement and for risk assessment in raw commodities and processed products and to provide detailed explanation on how the different CFs used in the assessment were derived in a revised RAR and LoEP See reporting table 3(38) See also 3(39), 3(40), 3(46), 3(51), 3(53), 3(59), 3(71), 3(76), 3(80) and Experts' Consultation 2	definitions were reconsidered in Vol. 1 level 2.7.3. Additional explanations on derived CF were included in revised RAR Vol. 3 B.7.3			Explanations provided. However, Section 2.7.3 and Table 2.7.3-1 in vol 1 still to be updated according to the outcome of Experts' Consultation 2. The derived PF/CF are not valid. The residue definition for processed products is open and processing data not supported by storage stability.
Experts' consultation 2. It is proposed to discuss the residue definition for enforcement and risk assessment in plants, processed products and products of animal origin in an expert meeting also considering the appropriateness of the	Will be discussed at experts consultation.	<u>Pesticides Peer Review 171 (13-15 December 2017):</u> Primary crops: In view of the pending data request for a new metabolism study in cereals with the cycloproyl label and further clarification on metabolites, the <u>RD for RA</u> for the		Primary Crops: RD for risk assessment (provisional): <u>Cereal grains:</u> Trinexapac (acid), free and conjugated <u>Cereal fodder items/grass:</u> sum of trinexapac (acid), free and conjugated, and CGA300405 (expressed as

section 3 – Residues

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
metabolism studies the magnitude of residues and the toxicological proprieties of the identified relevant metabolites. See reporting table 3(41) See 2(42), 2(43),2(45), 2(49), 2(50), 2(51), 2(52) and 2(53). See also Experts' Consultation 1		cereal/grass crop category should be provisional and should include - for cereal grains trinexapac (acid), free and conjugated. - for cereal fodder items /grass trinexapac (acid), free and conjugated plus CGA300405 For <u>monitoring</u> of residues in the cereal/grass crop category: trinexapac and its salts, expressed as trinexapac. Processed commodities: Unable to conclude on the relevant residues in processed commodities and hence on the appropriate <u>residue definition of risk</u> Data gap: Considering the relevance of metabolite CGA300405 in cereal crop feed items, the potential for residues in animal commodities and		trinexapac or separated, pending toxicological relevance) RD for monitoring Cereals/grass: Trinexapac (acid) and its salts, expressed as trinexapac Processed commodities: open Animal products: RD for risk assessment <u>Poultry</u> : trinexapac (acid) <u>Ruminants</u>: trinexapac (acid) plus metabolite CGA113745, expressed as trinexapac. RD for monitoring : Trinexapac (acid) and its salts, expressed as trinexapac Data gap The relevance in feed items and the potential carry over of residues in animal commodities of the major feed metabolite CGA300405 Data gap

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
		finally the consumer risk assessment should be further addressed. Data gap: Further information should be submitted regarding the relevance of unique metabolites A, B and C identified in the grass study at significant levels, with a view to comprehensively address the metabolism for the entire category of cereal/grass crops. Data gap: Further clarification should be submitted by the applicant to explain the contradictory findings (stability vs. instability) in the standardised hydrolysis experiments.		Further information regarding the relevance of unique metabolites A, B and C, identified in the grass, with a view to comprehensively address the metabolism for the entire category of cereal/grass crops Data gap Further clarification to explain the contradictory findings (stability vs. instability) in the standardised hydrolysis experiments to address nature of residues in processing commodities
Open point 3.14 RMS to reconsider proposing residue definitions restricted to cereals and oilseeds in the revised RAR. See reporting table 3(42)	As metabolism studies were provided with crops from two categories, it is not possible to propose residue definition for all plants. RMS agrees, that residue definitions should be restricted to cereals			Addressed The new metabolism study on oilseed rape (OSR) analysed only seeds. Experts could not derive a residue definition for the pulses/oilseeds group.

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	and pulses and oilseeds alone. RAR have been amended accordingly.			
Open point 3.15 RMS to amend the RAR revising information on the guidance followed to conduct the supervised residue field trials on barley and wheat. According to the applicant, all trials were conducted according to OECD 509. See reporting table 3(56)	All trials indeed were conducted according to OECD 509, although not all results are covered by storage stability data. Additional explanations were included in the revised RAR Vol. 3 B.7.3			Addressed
Data requirement 3.5 Applicant to provide details of the location where each single residue trial was conducted and the distance from the located near sites. See reporting table 3(58)	Details of the near located trial sites was provided by the applicant.			Data gap Additional residue data in barley and in wheat straw from independent field trials compliant with the GAP and in processed commodities, supported by demonstrated storage stability and/or storage stability for each individual component of the

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
				residue definition for risk assessment in cereal/grass and processed products covering the maximum length of storage of the trial samples.
Open point 3.16 RMS to add information on the trial location and to conclude on the total number of valid and independent residue trials available per each crop and geographical region in a revised RAR. See reporting table 3(58)	Nearest test sites were 29 km apart in UK and 9 km apart in FR. RMS considers all trials to be independent. RAR was revised accordingly.			EFSA is of the opinion that a number of residue field trials is not independent, since conducted in proximity (i.e. 9 to 15 km apart) with same experimental conditions under similar climatic conditions. RMS is kindly requested to comment if disagrees or to update MRL proposal and linked information in the RAR. It is noted that an accurate selection could not be conducted based on post code area only. Applicant may therefore consider providing additional information to demonstrate that, despite the adjoining location, these field trials are independent. In details, <u>Barley NEU</u> -Replicate trials (UK) SO17

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
				6QA(1) and YO62 TD(2) (distance about 15 km) <u>Barley SEU</u> -Replicate trials (IT) 27010 (3) and 26866 (about 15 km) -trial TK0178795 not cover by stability (stored 24.5 months) <u>Wheat NEU</u> -replicate trials (FR) 60490(7) and 60113(8) (about 9 km) The highest value was selected for the calculations since the crop variety was different.
Open point 3.17 RMS to proportionally scale residue values of the entire SEU datasets to nominal application rates and, if statistically appropriate to marge datasets, to scale NEU datasets prior to the merge. Results should be checked carefully as being a potential outlier and exclusion from dataset	Both NEU and SEU datasets were scaled and merged (as being similar according to Mann-Whitney U test). Although some values were suspected to be outliers in MRL calculator, they were not excluded from the assessment. Consequently MRL proposals for wheat and barley grain and straw, input values for the exposure assessment and			Addressed. Residue data checked for potential outlier, merge and scaling to 1N. However, the RAR still need to be updated in light of the outcome of Expert consultation 1 and, eventually, independency of trials (see Open point 3.16) by recalculating input values for risk assessment and dietary burden(see Open point 3.19) and MRL proposal accordingly.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
justified (i.e. accidental contamination). MRL proposals for wheat grain and straw, input values for the exposure assessment and the livestock dietary burden calculation and the proposed CF shall be recalculated accordingly in the revised RAR. See also 3(13), 3(38), (58) and Experts' consultation 2 See reporting table 3(62)	the livestock dietary burden calculation and the proposed CF were recalculated accordingly in the revised RAR.			EFSA is taking care to update the LoEP.
Open point 3.18 RMS to include additional information on the feeding study in ruminants to enable an evaluation of equivalence to OECD 505 and to conclude on acceptability and the resulting residues in products of animal origin taking into account the LOQ of the analytical method used.	Additional details have been included in Vol. 3 B.7.4.2. Taking into account highly exaggerated feeding dose levels (9N to 100N) and low residue levels found, LOQ of 0.02 mg/kg is considered acceptable. Study is considered suitable for evaluation.			Addressed. Details provided.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
See also Experts' consultation 2 See reporting table 3(66)				
Open point 3.19 RMS to add the residue definition in Table 2.7.5-1/2 and in the LoEP. See reporting table 3(68)	Proposed residue definitions were added in Vol. 1 Table 2.7.5-1/2 and in the LoEP.			Addressed However Table 2.7.5-1 and -2) of Vol 1. of Vol 1 still need to be updated according to the outcome of Experts consultation 1 (i.e. update RD-RA for fodder items/grass, revise input values for wheat grain and straw (see column E of Open point 3.17), use default PFs . Additionally, the N rate of the metabolism and feeding studies. EFSA is taking care to update the LoEP.
Open point 3.20 RMS to provide a detailed evaluation and any deviation from guidance OECD 508 for the original processing studies and to conclude on acceptability	Results from original processing studies study 2, 3 and 7 (Maffezzoni, 1999a; Maffezzoni, 1999b and Maffezzoni, 1999f) were not used in the calculation of processing factors as residues in			Addressed.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
and their valid to derive reliable PFs/CFs according to the residue definitions. The RAR and the LoEP shall be revised accordingly. See reporting table 3(70)	grain (RAC) were below LOQ, therefore these studies were not re-evaluated by the RMS LT. Processing factors derived from studies 1, 4, 5, 6 and 8 are considered not reliable due to unclear impact of 6-12 months storage at ambient temperature of grain prior processing and were not used in the assessment. Study 13 was considered acceptable without observed deviations from OECD 508. The RAR and the LoEP is revised accordingly			
Experts' consultation 1: To discuss if the submitted metabolism studies with radiolabelled test substance in the cyclohexane ring only are appropriate to firmly address the metabolic pathway of the active substance and conclude	Will be discussed at experts meeting.	<u>Pesticides Peer Review 171 (13-15 December 2017):</u> Data gap: A plant metabolism study with the cycloproyl label in the cereal/grass crop category should be provided.		Data gap The nature of residues in primary crops for at least the representative use, in rotational crops and in livestock with regard to the cycloproyl moiety and further attempt to elucidate/confirm the structure and amounts of the metabolite SYN548584

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
on the residue definition for the representative use and for animal products, considering that according to OECD 501, 502 and OECD 503 separate studies labelling each ring or side chain of the molecule will normally be required, unless no cleavage is anticipated. It is note that apparently CPCA (CGA224439), when analysed, was found in grain prior to be processed and it is not clear if derived from hydrolysis degradation pathway only and its toxicological relevance. See 2(42), 2(53) and Experts' Consultation 2 See reporting table 3(72)		Data gap: The nature of residues in livestock with regard to the cycloproyl moiety should be addressed. Data gap: The potential for uptake of residues bearing the cycloproyl moiety in rotational crops and their identity should be investigated.		
Open point 3.21 RMS and recalculate PF and CF considering that only two studies (each with 2 sampling replicate	PF and CF were recalculated taking into assessment average value for two replicates of two processing studies. RAR was amended accordingly.			Addressed However these figures are not valid as not fully supported by storage stability and the residue definition in processed products is not set.

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
values) were conducted. The RAR and LoEP shall be revised accordingly. See reporting table 3(74)				
Open point 3.22 RMS to provide evidence of compliance of the rotational crop metabolism studies submitted to OECD 502 and to conclude on acceptability and that metabolism of trinexapac-ethyl in rotational crops is appropriately addressed. The RAR and the LoEP shall be revised accordingly. See Experts' consultation 1 See reporting table 3(77)	The original rotational crop metabolism study (Krauss, 1992) was re-evaluated by RMS and considered acceptable but not fully addressing metabolism of trinexapac-ethyl in rotational crops. N rate was lower and first plant back interval too long than recommended in OECD 502 (0.75 N and 99 days respectively). TRR was ≤ 0.001 mg/kg in all commodities, but circumstances of crop failure or closely rotated crops (7-30 DAT) were not assessed. For this reason a new rotational crop metabolism study (Quistad, Kovatchev, 2010) was conducted (1.65 N rate and appropriate plant back			Addressed Studies were re-evaluated.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	intervals) fully addressing metabolism of trinexapac-ethyl in rotational crops. Results in both studies are comparable, as TRR >0.01 mg/kg were observed only at 30 days plant back interval. Conclusions were added in Vol. 3 B.7.6.1, no changes in Vol. 1 and LoEP.			
Data requirement 3.6 Applicant to provide magnitude of residues of the metabolite CGA113745 and CGA313458 in barley and wheat processed commodities. See reporting table 3(81)	Studies of magnitude of residues of the metabolite CGA113745 and CGA313458 in barley and wheat processed commodities were provided January 2017. (see Vol 3 B.7.5.3)			See Data gap in Data requirement 3.5 The data provided. Results on magnitude of residues in processed product not valid. Samples not supported by storage stability. Evaluation in Open point 3.23
Open point 3.23 RMS to evaluate these studies in a revised RAR. See reporting table 3(81)	Studies were submitted January 2017 and were already evaluated in the first version of dRAR. Although metabolite CGA113745 appeared to be unstable and all data considered not reliable.			Addressed Processing studies evaluated.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	For CGA 313458 results in bran, flour and bread were not covered by storage stability.(see Vol 3 B.7.5.3)			
Data requirement 3.7 Applicant to provide the residue study in honey. See reporting table 3(83)	Applicant informed that a honey residue study is in progress and will be available during first quarter 2018.			Data gap Residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom with regards to trinexapac and its degradation products
Open point 3.24 RMS to evaluate the study on honey in a revised RAR. See reporting table 3(83)	RMS will evaluate residue study in honey as soon as the study is available.			See Data requirement 3.7
Data requirement 3.8 Applicant to carry out more extensive literature search involving additional metabolites as proposed and combining different terms with the metabolites. Results for all	More extensive literature search involving additional metabolites as proposed and combining different terms with the metabolites was provided by the applicant and inserted in Vol. 3 B.7 Appendix I.			Addressed.

Rapporteur: LT

section 3 – Residues

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
potentially relevant or unclear for relevance of the open literature and inclusion/exclusion criteria to be documented. See reporting table 3(98)				
Open point 3.25 RMS to assess appropriateness of the methodology and the results of the open literature research conducted by the applicant in a revised RAR. See reporting table 3(98)	RMS considers the literature search to be appropriate and conducted as recommended in EFSA Journal 2011;9(2):2092. See Vol. 3 B.7.8			Addressed.

section 4 – Environmental fate and behaviour

4. Environmental fate and behaviour

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Open point 4.1 RMS to provide an amended RAR clarifying that metabolite WaterM3Hydrolysis has been identified as SYN549299 and giving further details. The name of this metabolite should be used consistently in the whole RAR and also in the LoEP. See reporting table 4(2) See also comments 4(39), 4(40) and 4(41).	Addressed.			Addressed.
Data requirement 4.1 Applicant to provide for parent compound and metabolites degradation studies using acidic soils. See reporting table 4(3)	No additional degradation studies for parent compound and metabolites using acidic soils were provided by the applicant. Following statement was received from the applicant regarding this issue: <i>"The Applicant confirms that the soils used in all the aerobic</i>			Addressed. Additional aerobic soil degradation studies using acidic soils might not be expected to provide any further information on the rate of degradation of parent compound and its metabolites, which is also confirmed by the results of the hydrolytic

section 4 – Environmental fate and behaviour

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
	<i>soil degradation studies do not have pH values measured under 6.0; however, all the soils used in the aerobic degradation studies comply with the OECD guidance which recommends that the pH values are selected between 5.5 and 8.0. When analysing the whole data set supplied in the dossier for the degradation rates, there is no indication that the rates obtained are dependent of the pH and therefore the soils presented in the latest submission are appropriate for use in the risk assessment."</i>			degradation.
Open point 4.2 RMS to provide an amended RAR including additional information on the different extraction methods used in the aerobic degradation studies by Hellstern (2008), Adam	Addressed.			Addressed.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
(2014) and Walther (2008). See reporting table 4(7)				
Open point 4.3 RMS to provide an amended RAR and LoEP deleting the degradation endpoints derived from the second incubation of Maryland soil in the study by Spare (1992a), because it cannot be concluded that the biomass did not decline and the storage time for the second aerobic incubation was too long and at high temperature (2 months at 25°C). Therefore the geometric mean DT50 value for trinexapac-ethyl will be 0.13 days. See reporting table 4(10) See also comment 4(4).	Addressed.			Addressed.
Open point 4.4	Addressed.			Addressed.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to provide an amended LoEP correcting the pH values for Loam (Gartenacker) and Sandy Clay Loam (18 Acres) soils from the study by Adam (2014) in order to be consistent the values reported in Vol. 3, B.8 (CA) (Table 8.1.1.1-21, p 26). The correct values should be 7.2 and 6.47 respectively. See reporting table 4(15)				
Data requirement 4.2 Applicant to provide the degradation rate study and the FOCUS kinetic assessment for metabolite CGA275537. Furthermore, applicant to update the exposure assessment for metabolite CGA275537. See reporting table 4(18)	Addressed.			Addressed.
Open point 4.5	Addressed.			Addressed.

Rapporteur LT

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to evaluate the degradation rate study, the FOCUS kinetic assessment and the updated exposure assessment for metabolite CGA275537 and to provide an amended RAR and LoEP including all new information. See reporting table 4(18)				
Open point 4.6 RMS to provide an amended RAR and LoEP adding persistence endpoint derived using SFO model for metabolite trinexapac (CGA 179500) in the Gartenacker (Adam 2014) soil. See reporting table 4(24) See also comment 4(29).	Addressed.			Addressed.
Open point 4.7	Addressed.			Addressed.

Rapporteur LT

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to provide an amended RAR deleting the t-test or confidence intervals for alpha or beta values of FOMC fit in studies KCA 7.1.2.1.1/01, KCA 7.1.2.1.1/02, KCA 7.1.2.1.2/02, KCA 7.2.2.3/02. See reporting table 4(27)				
Open point 4.8 RMS to provide an amended LoEP specifying that the two indicative rates of degradation on soil photolysis reported for trinexapac-ethyl were obtained in a dry irradiated experiment (DT ₅₀ of 5.7 days) and in a moist irradiated experiment (DT ₅₀ of 0.7days). See reporting table	Addressed.			Addressed.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
4(28)				
Open point 4.9 RMS to provide an amended LoEP adding the alpha, beta, k1, k2 and g values as needed where the rate of degradation endpoints result from a biphasic fit. See reporting table 4(31)	Addressed.			Addressed.
Data requirement 4.3 Applicant to provide adsorption studies with soil pH >7 for trinexapac-ethyl and trinexapac. See reporting table 4(32)	No additional adsorption studies with soil pH >7 for trinexapac-ethyl and CGA179500 were provided by the applicant. Following statement was received from the applicant regarding this issue: <i>"The Applicant agrees that sorption for trinexapac-ethyl and CGA179500 might be dependent on pH, and that the adsorption is expected to increase in decreasing soil pH. However, in the case of trinexapac-ethyl and</i>			Addressed. It was concluded that the adsorption of trinexapac-ethyl and its metabolites was pH dependent (lowest adsorption at high pH). In view of the pKa of trinexapac-ethyl and trinexapac, adsorption experiments should have been performed with soils of pH >7. Therefore, the lowest K _{foc} values related to soil with pH >7 were accepted as worst case and used for exposure assessment.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	<i>CGA179500, an adsorption measurement was made at the pH value of 7.5. Since the pKa value for trinexapac-ethyl is 4.57 and the pKa values for CGA179500 are 3.93 and 5.32, parent and metabolite would be almost completely dissociated at pH = 7.5 and therefore the KFOC values reported in this soil are not going to differ significantly with increasing pH (to a recommended maximum of 8).</i> <i>Consequently, the minimum KFOC values obtained for parent and CGA179500 at pH = 7.5 can be considered worst case and used as such in the risk assessment. This position is more conservative than using a geometric mean obtained from acidic or alkaline soils in two separate assessments.</i> <i>This approach, which was</i>			

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	<i>presented in the original Annex 1 submission, was agreed by EFSA and the 2005 RMS. It appears in the EU LoEP for trinexapac-ethyl.</i>			
Open point 4.10 RMS to provide an amended RAR moving the study by Spare (1990) on the adsorption/desorption of trinexapac acid under paragraph 8.1.3.1.2. See reporting table 4(33)	Addressed.			Addressed.
Data requirement 4.4 Applicant to provide the adsorption study for metabolite CGA275537. Furthermore, applicant to update the exposure assessment for metabolite CGA275537. See reporting table 4(34)	Addressed.			Addressed. It was concluded that the adsorption of metabolite CGA275537 was pH dependent (lowest adsorption at high pH). Therefore, the lowest K _{foc} value related to soil with pH >7 was accepted as worst case and used for exposure assessment.
Open point 4.11	Addressed.			Addressed.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to evaluate the adsorption study and the updated exposure assessment for metabolite GA275537 and to provide an amended RAR and LoEP including all new information. See reporting table 4(34)				
Open point 4.12 RMS to provide an amended RAR correction the typo error of name IUPAC name of pure [¹⁴ C]-Trinexapac in the hydrolysis degradation study by Adam (2008). See reporting table 4(37)	Addressed.			Addressed.
Data requirement 4.5 Applicant to provide information on the effect of water treatment	No additional information on the effect of water treatment processes on the nature of residues when surface water or			Data gap: Information to address the effect of water treatment processes on the nature of residues of both the active

section 4 – Environmental fate and behaviour

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
processes on the nature of residues when surface water or groundwater are abstracted for drinking water. See reporting table 4(44)	groundwater are abstracted for drinking water were provided by the applicant. Following statement was received from the applicant regarding this issue: <i>"The Applicant would like to highlight that there isn't at this time a guidance document on how to provide acceptable information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water."</i>			substance and its identified metabolites potentially present in surface and groundwater, when surface water or groundwater are abstracted for drinking water, were not provided in order to assess the consumer risk from the consumption of drinking water.
Open point 4.13 RMS to provide an amended RAR including information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water. 4(44)	No additional information provided by the applicant on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water.			See data gap in data requirement 4.5.

section 4 – Environmental fate and behaviour

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Data requirement 4.6 Applicant to provide new PECsoil calculations using: - for trinexapac-ethyl the highest not-normalised DT₅₀ value derived from the Capay soil (0.72 days) - for metabolite CGA179500 the DT₅₀ value obtained in the Maryland soil normalized only for the temperature and not for the moisture content - for metabolite CGA275537 the new degradation endpoints (see data requirement and open point in comments 4(18)). See reporting table 4(50)	For trinexapac-ethyl the highest not-normalised DT50 value derived from the Capay soil (0.72 days) for PEC soil calculations was not used by the applicant, the argumentation is provided below: <i>"As the endpoint used in the evaluation does not impact the risk assessment and is higher than the value proposed by the EFSA, exposure calculations in soil have not been carried out again."</i> PEC soil for trinexapac-ethyl with DT ₅₀ of 0.72 days was re-calculated by the RMS, obtained values are provided in the RAR and LoEP. Data requirements for CGA179500 and CGA275537 are addressed.			Addressed.
Open point 4.14	Addressed.			Addressed.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to evaluate the updated PECsoil calculations and to provide an amended RAR and LoEP including all new information. See reporting table 4(50)				
Open point 4.15 RMS to correct Table 8.2 in Vol 3 (CP) using the correct solubility endpoints for parent and metabolite CGA179500; this action is needed according to SANCO/10180/2013-rev.1 See reporting table 4(59)	Addressed.			Addressed.
Open point 4.16 RMS to provide an amended RAR addressing the discrepancy between the application date in	Clarification, provided by the applicant: <i>"The Applicant should have made a note of this discrepancy between the two reports in the Top Up submission. The more</i>			Addressed.

section 4 – Environmental fate and behaviour

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Jokioinem scenario used in Bramley (2016) and the one used in Gabsi (2015a). See reporting table 4(61)	<i>appropriate application date for winter cereals in the Jokioinen scenario was only investigated, then reported, when carrying out the specific photolysis modelling, which explains why the two reports (one on microbial degradation and one on photolytic degradation) do not have the same approach.</i> <i>This discrepancy was addressed in modelling report CGA163935_10840, which was included in the most up to date Document M-CP Section 9 supplied with the latest version of the Caddy in April 2017."</i> The new study(Nickisch, D. 2017 was evaluated in the amended RAR, data results provided in LoEP. Addressed.			
Open point 4.17 RMS to provide an amended RAR correcting in Table 8.1.4-11 (Vol. 3,	Correct endpoint is noted in the Table 8.1.4-11. However, PECgw values from study Bramley, Y., 2016 were not used for the			Addressed.

section 4 – Environmental fate and behaviour

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
B.8 (CP) the application rate of metabolite CGA179500 in spring cereals, being the correct value 82 g/ha. See reporting table 4(64)	risk assessment.			
Data requirement 4.7 Applicant to provide new PECgw calculations using: - the interception for cereals at BBCH 25 set to 20% - for trinexapac-ethyl the geometric mean DT₅₀ value of 0.13 days (see open point in comment 4(10)) - for metabolite CGA275537 the new degradation and adsorption endpoints (see data requirement and open point in comments 4(18) and 4(34)) - application to the soil surface	- crop interception of 20 % was used in the modelling; - for trinexapac-ethyl the geometric mean DT₅₀ value of 0.15 days was used (the applicants argumentation: <i>"as the endpoint used in the evaluation does not impact the risk assessment and is higher than the value proposed by the EFSA, exposure calculations in groundwater water was considered to be acceptable"</i>). - for metabolite CGA275537 new degradation endpoints were used in the modelling, - for adsorption minimum			Addressed. Note: in the updated RAR a plant uptake factor of 0 was used for PECgw calculations for parent compound and its metabolites. However, in the LoEP it is reported a plant uptake factor of 20%, which seems to be an editorial error. This error will be corrected in the LoEP.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
See reporting table 4(67)	K _{FOC} of 4.35 mL/g and 1/n = 0.76 should be used for modelling. The mobility input parameters used in the exposure calculations (K _{FOC} = 1 and 1/n = 1) are worst case in compare to the experimental values obtained in the mobility experiment. The changes will not impact the outcome of the leaching assessment.			
Open point 4.18 RMS to evaluate the updated PECgroundwater calculations and to provide an amended RAR and LoEP including all new information. See reporting table 4(67) See also open point 4(61).	Addressed.			Addressed.
Data requirement 4.8 Applicant to provide new PECsw and sed	• for trinexapac-ethyl the geometric mean DT ₅₀ value of 0.15 days was used (the applicants argumentation: "			Addressed.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
calculations considering: - for trinexapac-ethyl the geometric mean DT₅₀ value of 0.13 days (see open point in comment 4(10)) - for metabolite CGA275537 the new degradation and adsorption endpoints (see data requirement and open point in comments 4(18) and 4(34)) - for metabolite CGA275537 Step 1&2 should be done considering "no drift". See reporting table 4(73)	<i>0.13 days is proposed by the EFSA (EFSA (2017), Ref. JT/DK/mc (2017) – out-18296921). As the endpoint used in the evaluation does not impact the risk assessment and is higher than the value proposed by the EFSA, exposure calculations in surface water have not been carried out again".</i> for metabolite CGA275537 the new degradation and adsorption endpoints were used, "no drift" option was chosen for Step 1-2 calculations.			
Open point 4.19 RMS to evaluate the updated new PEC _{sw} and sed calculations and to provide an amended RAR and LoEP including all new information. See reporting table 4(73) See also comment 4(23).	Addressed.			Addressed.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Open point 4.20 RMS to provide an amended RAR adding the sediment compartment in the table reporting the residues requiring further assessment in Vol. 1. See reporting table 4(78) See also comment 4(23).	Addressed.			Addressed.
Open point 4.21 RMS to provide an amended LoEP adding metabolite CGA275537 in surface water and sediment in the list of residues requiring further assessment. See reporting table 4(79) See also comment 4(23).	Addressed.			Addressed.
Data requirement 4.9 Applicant to provide an updated literature search	Addressed.			Data gap: Metabolite M2 was not included in the updated literature search.

section 4 – Environmental fate and behaviour

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting/EFSA request for RMS' action	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
including metabolites CGA275537, , M2 and. WaterM3Photolysis. See reporting table 4(84)				
Open point 4.22 RMS to provide an amended RAR including the updated literature search considering also metabolites CGA275537, CGA300405, M2 and. WaterM3Photolysis. See reporting table 4(84)	Addressed.			See data requirement 4.9 Addressed.
Open point 4.23 RMS to provide an amended RAR and LoEP using for metabolite CGA179500 the code or the name 'trinexapac'. Note: 'trinexapac-ethyl' refers to the active substance. See reporting table 4(85)	Addressed.			Addressed.

section 5 - Ecotoxicology

5. Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Expert consultation 5.1 Experts to discuss the endpoint to be used in the long term risk assessment for birds. In particular, the relevance of the reduction in eggs production at 600 ppm observed in Hakin 1991a should be discussed. See reporting table 5(1)	December 2017: The NOEC for reproduction was set at 600 ppm level. The results of the study will be discussed at the TC. Please refer to the Vol.3, B9 AS, B.9.1.1.3	<u>Pesticides Peer Review Meeting TC 160 (08 December 2017):</u> <u>Open point</u> RMS to amend the Risk assessment for birds by using the NOAEL of 200 ppm both in the RAR and LoEP.	January 2018: The risk assessment for birds was amended where necessary. Please refer to the Vol.3, 9 AS, B.9.1.1.3, Vol.3, B9 PPP, B.9.1.1 and LoEP.	Addressed The risk assessment was revised in line with the meeting agreements.
Data requirement 5.1 Applicant to provide the study report and a study summary for the available amphibian test. See reporting table 5(2)	December 2017: The study report and the study summary were provided by the applicant and the summary has been added to the RAR, please refer to the Vol.3, B9 AS, B.9.1.4			Addressed A summary of the acute amphibian study was included in the RAR.
Open point 5.1 RMS to include the information on the calculated LogPow for metabolites in a revised	December 2017: The calculated log Pow values of trinexapac-ethyl metabolites have been added to the RAR, please refer to the Vol.3, B9 PPP,			See data requirement 5.2

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RAR. This should include a study summary detailing how the LogPow values were derived for metabolites. See reporting table 5(3)	B.9.2.1, table B.9.2.1-6			
Data requirement 5.2 Applicant to provide the study report and a detailed study summary of the study at the basis of the LogPow derivation for trinexapac-ethyl metabolites. In addition, from the provided overview in the reporting table it is not clear whether LogPow values are available for the surface water metabolites M2 (3-carboxylic acid ethyl ester-7-hydroxypropyl-5-oxo,7-hydroxyheptanoic acid) and WaterM3Photolysis and these are needed.	December 2017: The calculated log Pow values of trinexapac-ethyl metabolites have been provided by the applicant, please refer to the Vol.3, B9 PPP,B.9.2.1, table B.9.2.1-6			Addressed A low risk via secondary poisoning for trinexapac-ethyl and its pertinent metabolites is concluded.

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
See reporting table 5(3)				
Data requirement 5.3 Applicant to provide a list of relevant plant metabolites. Applicant to provide further information to address the risk to birds and mammals for the relevant plants metabolites. See reporting table 5(4) See also 5(5).	December 2017: The list of plant metabolites has been provided by the applicant, please refer to the Vol.3, B9 PPP, B.9.2.1, table B.9.2.1-6 and revised risk assessment was included, please refer to the Vol.3, B9 PPP, B.9.2.2			Data gap Additional information to address the risk to birds and mammals for the plants metabolites was not provided. It is noted that the plant metabolite CGA179500 is found in hen/goat metabolism and could be considered covered by the available risk assessment. Metabolite CGA 275537 is naturally found in animals' metabolism; therefore, a low risk to birds and mammals could be concluded for this metabolite.. From the available mammalian toxicity data CGA329773 is not expected to be more toxic than trinexapac-ethyl, therefore, a low risk for this metabolite to mammals can be concluded. Data gap Further information is needed to address the risk to birds and mammals for the plants metabolites SYN548584, CGA351210, SYN540406,

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
				NOA433257, SYN540405, and CGA224439, CGA300405.
Open point 5.2 RMS to include all valid endpoints for birds and mammals in the list of endpoints. See reporting table 5(6)	December 2017: The LoEP has been updated with all valid endpoints.			Addressed. For easier reference, in the case of mammals the ecotoxicologically relevant endpoint only was kept in the list of endpoints for the long term toxicity. Data for metabolite CGA158377 were removed since this metabolite is not identified as a residue for further assessment for birds. In addition, the endpoint for metabolite CGA329773 was corrected to indicate that it refer to a short-term toxicity rather than a long-term toxicity endpoint.
Open point 5.3 RMS to include all valid endpoints for the metabolites for mammals in the list of endpoints. See reporting table 5(7)	December 2017: The LoEP has been updated with all valid endpoints for the metabolites for mammals.			Addressed
Data requirement 5.4	December 2017: The Applicant provided			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Applicant to provide the EC10 and EC20, or a justification for not providing those, for the study Putt 1991 (reproductive toxicity study for <i>Daphnia magna</i>). See reporting table 5(10)	calculations to show the EC10 and EC20 values for the study Putt 1991, please refer to the Vol.3, B9 AS, B.9.2.5.1			
Data requirement 5.5 Applicant to provide the results of the analytical verifications of the tested concentrations for the aquatic toxicity studies. It should be specified were relevant, whether trinexapac ethyl or trinexapac acid were measured. See reporting table 5(10)	December 2017: Additional data on analytical verifications were provided by the applicant and were added to the RAR, please refer to the Vol.3, B9 AS and to the Vol.3, B9 PPP. In these data the studies either analysed for trinexapac-ethyl (CGA163935) or trinexapac acid (CGA179500), but not both.			Addressed
Open point 5.4 RMS to include the EC10 and EC20 for Sousa	December 2017: The LoEP has been updated.			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
1991 in the list of endpoints. See reporting table 5(12)				
Open point 5.5 RMS to include an assessment of the validity criteria for the study from Fackler 1990. See reporting table 5(13)	December 2017: The assessment of validity criteria were included by RMS, please refer to the Vol.3, B9 AS, B.9.2.2.3			Addressed
Open point 5.6 RMS to include an assessment of the validity criteria for the study from Fackler 1991. See reporting table 5(14)	December 2017: The assessment of validity criteria were included by RMS, please refer to the Vol.3, B9 AS, B.9.2.2.3			Addressed
Data requirement 5.6 In line with the data requirement (Reg. EU No 283/2013), the bioconcentration factors shall be expressed as a function of both total wet	December 2017: The applicant provided following statement: "The bioconcentration factors were only measured for edible, non-edible and whole body tissue in these old studies (Fackler 1990			Addressed

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
weight and of the lipid content of the fish. Applicant to provide further information to address this point. See also 5(13). See reporting table 5(14)	and Fackler 1991) done according to the protocol at that time. However both studies are with <i>Lepomis macrochirus</i> which typically has a lipid content of around 5%, and the BCFs were calculated with an assumed lipid content of 5%. Even if lipid values of 1 or 10% were used there would still be very little change in the resultant BCFs. From these data where the measured BCFs ranged from 1.3 to 11 there are no indications of concerns from bioaccumulation. The observed values are all well below any regulatory trigger values."			
Open point 5.7 RMS to include in a revised RAR, the additional information concerning the level of solvent used in the study from Smith et al. (1990).	December 2017: The additional information concerning the level of solvent was included by RMS, please refer to the Vol.3, B9 AS, B.9.2.4.1			Addressed

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
See reporting table 5(16)				
Data requirement 5.7 Applicant to provide further details on the oxygen levels during the acute toxicity test with aquatic invertebrates- Mysids, Sousa (1991). It is noted that according to OPPTS 850.1035 (Mysid Acute Toxicity test guideline) the oxygen level in the test should be maintained within 60 and 105% saturation. In Sousa (1991) a drop in oxygen was observed in all treatment except control and this may have an influence on the results of the study. See reporting table 5(17)	December 2017: The additional information concerning the oxygen levels during the acute toxicity test with aquatic invertebrates- Mysids, Sousa (1991) was provided by the applicant, please refer to the Vol.3, B9 AS, B.9.2.4.1, CA 8.2.4.1/04 Sousa J.V. (1991)			Addressed The additional information requested was provided. It is noted that the drop in the oxygen level was observed only after 72 hours in all treatments and after 48 hours at the highest treatment level. It cannot be completely ruled out which would be the influence of this drop on the results of the study. One option would be to consider the endpoint at 72 hours, however, in a conservative approach the lowest endpoint (obtained at 96h) was considered. It is acknowledged that there are uncertainties in the endpoint derived from this study. Therefore, a footnote was added to the list of endpoint indicating that 'A drop in oxygen was observed in all treatment except control at the end of the study (72-96 h), oxygen level range 44-

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
				58%'. Addressed
Data requirement 5.8 Applicant to provide further information to address the risk to sediment organisms for CGA179500 (trinexapac acid). See reporting table 5(18)	December 2017: The applicant provided following statement: "No toxicity test with the sediment dwelling midge <i>Chironomus</i> spp. was deemed necessary for trinexapac acid (CGA179500). CGA179500 is lower toxicity to aquatic organisms than the parent, but slightly more persistent in the aquatic system than the parent (DT ₅₀ in the total system is 14 to 18 days). However CGA179500 is not likely to persist in sediments due to its low K _{FOC} (140 mL/g). This is confirmed in the water sediment studies where the quantity of CGA179500 in the sediment phase never reaches more than 6.9% AR."			
Open point 5.8 RMS to include additional details on the	December 2017: The additional information concerning the biological finding			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
assessment of the studies from Hoberg (1991a) and Hoberg (1991c). See reporting table 5(20)	biomass/yield/growth rate in the control and in the treatments) was included by RMS, please refer to the Vol.3, B9 AS, B.9.2.6.1			
Data requirement 5.9 Applicant to provide additional details from the study Hoberg (1991b), this should include an assessment of the validity criteria. See reporting table 5(20)	December 2017: The additional information concerning the yield and specific growth rate was provided by the applicant, please refer to the Vol.3, B9 AS, B.9.2.6.1			Addressed It is noted that for this study the compliance with the validity criteria (OECD 201, latest version) cannot be fully demonstrated, therefore, the study was invalidated.
Data requirement 5.10 Applicant to provide additional details of the biological finding (biomass/yield/growth rate in the control and in the treatments) for the study effects on algal growth- Maetzler 2001. This should include the recalculated EC10 and EC20 values. See reporting table 5(21)	December 2017: The additional information concerning the yield, specific growth rate data and the recalculated ECx values was provided by the applicant, please refer to the Vol.3, B9 AS, B.9.2.6.1			Addressed

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Open point 5.9	December 2017: According to the EFSA all old algae studies were re-evaluated according to new relevant validity criteria reported in updated or new guidelines, the RAR was revised accordingly, the risk assessment and LoEP were updated where necessary, please refer to the Vol.3, B9 AS, B.9.2.6, Vol.3, B9 PPP, B.9.4			Addressed
The validity criteria of the OECD 201 apply to <i>Anabaena flos-aquae/Navicula pelliculosa</i> . Please revise the RAR accordingly; the studies with these species not meeting the validity criteria should be invalidated and the risk assessment should be updated as necessary. See reporting table 5(23)				
Data requirement 5.11 Applicant to provide further details on the results i.e. biological finding (biomass/yield/growth rate in the control and in the treatments) for the study effects on algal growth- Grade 1995c. See reporting table 5(24)	The additional information concerning the yield, specific growth rate data and the recalculated ECx values was provided by the applicant, please refer to the Vol.3, B9 AS, B.9.2.6.2			Addressed
Open point 5.10	December 2017: Algae study from Grade			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to invalidate the study from Grade (2001b; KCA 8.2.6.2/04) since the validity criteria according to the most recent version of the OECD 201 are not met. See reporting table 5(25)	was invalidated by RMS as this study does not meet the validity criteria, it is considered not valid and is not used in the risk assessment. please refer to the Vol.3, B9 AS, B.9.2.6.2			
Open point 5.11 RMS to include further details on the EC10 and EC20 derivation for Seeland-Fremer & Emnet 2015a. See reporting table 5(26)	December 2017: The additional information concerning the EC10 and EC20 was included by RMS, please refer to the Vol.3, B9 AS, B.9.2.6.2			Addressed It is noted that the obtained EyC20 was removed from the list of endpoints since it was not considered sufficiently reliable on the basis of the confidence interval.
Open point 5.12 RMS to provide in a revised RAR a reasoning for the chronic endpoint to be used in risk assessment (NOEC or EC ₁₀). See reporting table 5(29)	December 2017: The additional information concerning the chronic endpoint to be used in the risk assessment (NOEC or EC ₁₀) was included in the RAR by RMS where necessary, please refer to the Vol.3, B9 AS			Addressed
Open point 5.13	December 2017:			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
RMS to include additional details of the biological finding and an assessment of the validity criteria for the study on the effects of trinexapac-ethyl on aquatic macrophytes-Grade (2001) in a revised RAR. RMS to correct in the LoEP the endpoint from the same study; the endpoint is based on mean measured and not on the nominal concentration (as reported in the LoEP). See reporting table 5(31)	The additional information concerning the biological finding was included by RMS, please refer to the Vol.3, B9 AS, B.9.2.7.1 The LoEP has been updated.			
Open point 5.14 RMS to include in the study summary of the study effects on aquatic Macrophytes- Kirkwood (2015) the EC10 and EC20 values with confidence intervals	December 2017: The additional information concerning the EC10 and EC20 was included by RMS, please refer to the Vol.3, B9 AS, B.9.2.7.1			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
(95%) and their assessment. See reporting table 5(32)				
Open point 5.15 RMS to include additional details of the biological finding possibly in a tabular format for the study - effects on aquatic macrophytes- Grade (2001)- trinexapac acid. See reporting table 5(33)	December 2017: The additional information concerning the biological finding was included by RMS, please refer to the Vol.3, B9 AS, B.9.2.7.2			Addressed
Data requirement 5.12 Applicant to provide the endpoints expressed in term of mean measured concentrations for the study effects on aquatic Macrophytes- Brown and Maynard 2003; the tested concentrations were not maintained within 20% of the nominal. See reporting table 5(34)	December 2017: The requested new endpoints have been calculated using the mean measured concentrations and have been provided by the applicant, please refer to the Vol.3, B9 PPP, B.9.3.1			Addressed

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Open point 5.16 RMS to revise the endpoints from the study K-CP 10.2.1/04 Brown, R. J. & Maynard, S. J., (2003) and to correct as necessary in the list of endpoints and in the revised RAR. See reporting table 5(35)	December 2017: The revised endpoints were included in the RAR and LoEP was updated as necessary, please refer to the Vol.3, B9 PPP, B.9.3.1			Addressed
Open point 5.17 RMS to correct the risk assessment for algae by using the endpoint expressed in term of growth rate. See reporting table 5(36)	December 2017: Endpoints for algae were reported as growth rate And the risk assessment was updated where necessary, please refer to the Vol.3, B9 PPP and the Vol.3, B9 AS			Addressed. It is noted that in the case of aquatic plants the endpoint in term of biomass was used in the risk assessment. The risk assessment for aquatic plants was corrected by EFSA by using the endpoint in term of growth rate also in the case of aquatic plants for trinexapac-ethyl and its pertinent metabolites.
Data requirement 5.13 From the available acute toxicity data for	December 2017: The applicant provided following statement: "These additional data from			Addressed The argumentation provided is considered sufficient. Further data on <i>Mysidopsis bahia</i> are not considered necessary for

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
trinexapac-ethyl <i>Mysidopsis bahia</i> seems to be the most sensitive species of aquatic invertebrates. However, a chronic toxicity test is not available for this species. The applicant is given the possibility to provide further information to address this point. See reporting table 5(37) See also 5(17)	an acute study on <i>Mysidopsis bahia</i> are not a standard requirement in the EU but are required for the US EPA, and were therefore included in the dossier. There is no chronic study available. Trinexapac-ethyl inhibits gibberellin biosynthesis in plants, and this results in stem growth inhibition via inhibition of internodal elongation. Given this mode of action it is likely that the chronic risk assessment will be driven by aquatic plants, and this has been confirmed with the lowest RAC of 20 µg /L being obtained from the study with the rooted aquatic plant <i>Myriophyllum spicatum</i>. The use of the <i>Myriophyllum</i> endpoint ensures an acceptable chronic risk to aquatic organisms."			trinexapac-ethyl noting that that a wide margin of safety is obtained at FOCUS step 2 level for all aquatic organisms. Noting also the uncertainties in the <i>Mysidopsis bahia</i> endpoint. See also data requirement 5.7
Open point 5.18 RMS to include all valid	December 2017: The LoEP has been updated.			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
aquatic toxicity endpoints in the LoEP. See reporting table 5(38)				
Data requirement 5.14 Applicant to provide a detailed study summary for effects on bees-Hoxter 1990. See reporting table 5(42)	December 2017: The additional information concerning biological findings and evaluation of the endpoints derived by Hoxter (1990) was provided by the applicant, please refer to the Vol.3, B9 AS, B.9.3.1.1			Addressed Some details on this study were included in the RAR. The validity criteria were clearly not met (mortality in the solvent control 20%) and a reference control was not performed in the test.
Open point 5.19 RMS to include a summary table of the biological observations for the study on bees-Bocksch (2004). See reporting table 5(43)	December 2017: The summary tables of the biological observations were included by RMS, please refer to the Vol.3, B9 PPP, B.9.5.1			Addressed
Open point 5.20 RMS to make sure that the endpoint from the study effects on bees-Ruhland 2014 is consistently and correctly	December 2017: December 2017: The endpoints from the study effects on bees-Ruhland 2014 were corrected and consistently			Addressed

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
reported in the revised RAR and in the list of endpoints. In addition, RMS to include additional details on the mortality, sublethal effects and behavioural abnormalities assessment in the revised RAR. See reporting table 5(44)	reported in the RAR and in the LoEP. Additional details on the sublethal effects and behavioural abnormalities were included by RMS, please refer to the Vol.3, B9 PPP, B.9.5.1.2			
Data requirement 5.15 Applicant to provide additional information on potential sub-lethal effects of trinexapac-ethyl on honeybees (e.g. effects on HPG). See reporting table 5(44)	December 2017: The applicant provided such information: "The toxicity of A8587F to honey bees was determined in a 10-day continuous feeding test in the laboratory (Ruhland, 2014). In this study the 10-day LC50 was determined to be 2.355 g a.s./kg food and the 10-day LD50 based on consumption per bee was determined to be 46.6 µg a.s./bee/day. Effects on HPG have not been assessed as there are			Data gap Further information on potential sub-lethal effects of trinexapac-ethyl on honeybees (e.g. effects on HPG)

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	currently no standard guidelines for such a study."			
Data requirement 5.16 Applicant to provide the available chronic toxicity study on honeybee larvae. See reporting table 5(46) See also 5(45)	December 2017: The requested new study has been provided by the applicant, please refer to the Vol.3, B9 AS, B.9.3.1.2			Addressed The requested study was provided and considered in the risk assessment.
Open point 5.21 RMS to assess the additional information on chronic toxicity to larvae, this includes the document 'Comment on trinexapac honeybee', embedded in column 2 of the reporting table. See reporting table 5(46)	December 2017: The new chronic toxicity to larvae study (Kleebaum, 2016) and additional information on comparison of the new study and the previously submitted study (Kleebaum, 2014) were evaluated by RMS, please refer to the Vol.3, B9 AS, B.9.3.1.2			Addressed
Data requirement 5.17 Applicant to provide an updated risk assessment	December 2017: The requested an updated risk assessment for honeybees according to the			A risk assessment via exposure to contaminated water was not provided (data gap). A screening assessment for

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
for honeybees according to the EFSA Bee Guidance Document. This should include: i) a risk assessment via exposure to contaminated water ii) information/assessment of the potential for accumulative effects iii) in accordance with Regulation (EU) 283/2013, a consideration of the risk to bees from metabolites. It is suggested that the methodology in the EFSA (2013) Bee guidance is followed to identify which plant metabolites should be assessed. See reporting table 5(51) See also 5(46), 5(52) and 5(53)	EFSA Bee Guidance Document was provided by the applicant, please refer to the Vol.3, B9 PPP, B.9.6.1 Also the applicant provided following statement: "Guttation is not frequent in crops such as wheat and barley so there should be no need for a risk assessment via contaminated water, however a contaminated water risk assessment has also been added to the dossier. Similarly a risk assessment for plant metabolites has been added to the dossier. Trinexapac-ethyl and its metabolites all have Log P values of less than 3 so this suggests that they would not bioaccumulate in animals. Trinexapac-ethyl is essentially of low toxicity to bees and there is no suggestion of accumulative effects in the chronic bee			exposure via guttation water was provided, however, the obtained ETR could not be reproduced; if the water solubility reported in the list of endpoint is considered (21.1 g/L) a high risk via exposure to guttation water could not be excluded (data gap). It is noted that the RAR included a screening risk assessment for metabolites; however, this assessment was not considered sufficient and could not be fully reproduced by EFSA (data gap)

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	studies.”			
Open point 5.22 RMS to include all valid bee toxicity endpoints in the LoEP. See reporting table 5(54)	December 2017: The LoEP has been updated.			Addressed
Open point 5.23 RMS to include the risk assessment for bees in line with EFSA (2013) in the LoEP. See reporting table 5(55) See also 5(51)	December 2017: The LoEP has been updated.			See data requirement 5.17
Open point 5.24 RMS to report in the list of endpoints the substrate used in the tests on other arthropod species, extended laboratory tests, aged residue tests. See reporting table 5(56)	December 2017: The LoEP has been updated.			Addressed

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Data requirement 5.18 No chronic studies performed with the active substance are available for earthworms and other non-target soil macro- and mesofauna. Applicant to provide further information/a case in support of the bridging of the chronic toxicity data on earthworms and other non-target soil macro- and mesofauna from the formulation to the active substance. See reporting table 5(59)	December 2017: The applicant provided following statement: "The chronic studies submitted are done with the representative formulation (A8587F 250 g/L formulation of trinexapac-ethyl) and we consider that, as has been done previously, this meets the requirement for active substance data for a solo formulation. Logically the formulated product containing its various formulation additives is going to be more toxic than the technical active substance. In addition, the dossier also includes a new chronic earthworm study for trinexapac acid (CGA179500)."			Addressed The available data on earthworms and other non-target soil macro- and mesofauna are considered sufficient to address the risk of trinexapac-ethyl. It is noted that an additional study on trinexapac acid was provided which is considered valid. There is a relatively high variability between replicates which make it difficult to interpret the results of this study. Considering that at 24.3 mg/kg 12% effects on reproduction were observed the endpoint was set at 8.1 mg/kg. The proposed endpoint in the RAR was 24.3 mg/kg.
Data requirement 5.19 Applicant to provide the new earthworm data for CGA300405, Luhurs (2015).	December 2017: A new chronic toxicity study on earthworms with the metabolite CGA300405 has been provided by the applicant, please refer to the Vol.3, B9 AS, B.9.4.1			Addressed The study was provided and it is considered valid.

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
See reporting table 5(61)				
Data requirement 5.20 Applicant to provide the new Collembola data for CGA300405, Luhurs (2015). See reporting table 5(62)	December 2017: A new toxicity study on Collembola with the metabolite CGA300405 has been provided by the applicant, please refer to the Vol.3, B9 AS, B.9.4.2			Addressed The study was provided and it is considered valid.
Data requirement 5.21 Applicant to provide the new toxicity study on Hypoaspis for CGA300405, Luhurs (2015). See reporting table 5(63)	December 2017: A new toxicity study on Hypoaspis with the metabolite CGA300405 has been provided by the applicant, please refer to the Vol.3, B9 AS, B.9.4.2			Addressed The study was provided and it is considered valid.
Data requirement 5.22 A case/further information may be needed to address the risk to soil microorganisms for trinexapac acid. See reporting table 5(66)	December 2017: The applicant provided following statement: "In the aerobic soil degradation studies trinexapac acid was the major transformation product, with formation rates up to 98% after 1 day. This rapid			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
	transformation from the parent to trinexapac acid is expected to be similarly fast in this soil micro-organism study. On this basis a separate SMO study for trinexapac acid is not considered necessary, since it can be assumed that the soil organisms will have been exposed to trinexapac acid in the test with the parent. Alternatively a NOEL can be conservatively estimated based on toxicity of parental compound trinexapac-ethyl under the assumption that metabolites are up to 10 times more toxic than parental compound. Using this assumption all the TERs exceed the relevant trigger values indicating no unacceptable risk to soil organisms."			
Data requirement 5.23 Applicant to provide the new study on the effects	December 2017: A new toxicity study on the effects on carbon and nitrogen transformation			Addressed

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
on carbon and nitrogen transformation with the metabolite CGA300405. See reporting table 5(67)	with the metabolite CGA300405 has been provided by the applicant, please refer to the Vol.3, B9 AS, B.9.5			
Expert consultation 5.2 Experts to discuss the ecotoxicological relevance of the effects on radicle elongation observed in the study Chetram 1991. See reporting table 5(70)	December 2017: Further information on the radicle elongation observed in the seed germination test and its' ecological relevance for non-target plant communities was presented in the revised RAR (Please refer to the Vol.3, B9 AS, B.9.7) in support to the discussion.	<u>Pesticides Peer Review Meeting TC 160 (08 December 2017):</u> No action for the RMS.	Noted.	Noted
Data requirement 5.24 Applicant to provide a detailed study summary for the study on the effects on non-target terrestrial plants from Chetram (1991). See reporting table 5(70)	December 2017: The applicant provided study summary for the study on the effects on non-target terrestrial plants from Chetram (1991). Please refer to the Vol.3, B9 AS, B.9.7			Addressed

section 5 - Ecotoxicology

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Open point 5.25 RMS to indicate in the list of endpoints that Walder (2003) were neither performed under GLP nor according nor were guideline studies. See reporting table 5(71)	December 2017: The LoEP has been updated.			Addressed
Open point 5.26 RMS to provide further consideration in Vol.4 on whether the batches used in the ecotoxicological testing are compliant with the technical specifications. See reporting table 5(77)	January 2017: RMS provided further consideration on whether the batches used in the ecotoxicological testing are compliant with the technical specifications, please refer to the Vol.4			Data gap and critical area of concern The compliance of the batches used in the ecotoxicological tests with the technical specifications cannot be fully demonstrated.
Data requirement 5.25 Applicant to provide an updated literature search in line with the EFSA guidance (2011) on open literature search covering the trinexapac-methyl	December 2017: A new literature search with an updated list of metabolites has been completed and submitted by the applicant, please refer to the Vol.3, B9 AS, B.9.11.1			Data gap: An updated literature search was provided. However, most of the relevance criteria are not agreed since they refer more to the quality of the studies rather than to the relevance. In addition, not all the pertinent plant metabolites

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
metabolites relevant for the environmental risk assessment. See reporting table 5(78)				were covered by the search (data gap). The unique criteria which seems to be related to relevance assessment is the number 12 (Appropriate and relevant geoclimatic conditions (setting), appropriate application method and rates (exposure) and observation data (biological relevance) to derive endpoints). The RMS evaluation of the literature search is missing.
Open point 5.27 RMS to include additional details on how the literature search was performed e.g. identifiers used in the search for the active substance and the metabolites. In addition the criteria for assessing the reliability and relevance of the studies should be included. See reporting table 5(78)	December 2017: An additional details on how the literature search was included in the RAR by RMS, please refer to the Vol.3, B9 AS, B.9.11.1			See data requirement 5.25

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Open point 5.28 RMS to update the classification and labelling section in the list of endpoints considering that the C&L of trinexapac-ethyl was not yet harmonised. The precautionary statements are not needed and should be removed, the acute and chronic classification and the related M-Factor should be reported, as necessary. See reporting table 5(79)	December 2017: The classification was updated in the LoEP			Addressed
Data requirement 5.26 The applicant is given the possibility to submit further data to address the endocrine disruption in non-target organisms. The ecotoxicity data available for trinexapac-ethyl are not be	December 2017: The applicant provided following statement: "We have submitted all the available data and a complete set of the required ecotoxicity studies including reproductive studies on birds, fish and aquatic invertebrates, and			The available ecotoxicological data are not sufficient to conclude on the endocrine disruption potential of trinexapac-ethyl. Pending on the outcome of the data gap in Section 2, further ecotoxicological tests might be necessary to address the potential endocrine disrupting

section 5 - Ecotoxicology

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
sufficient to conclude on endocrine disruption in non-target organisms. See also 2(31) and 2(36). See reporting table 5(80)	conducted a comprehensive literature search. No suggestions of endocrine disruption were seen in any of these studies."			properties of trinexapac-ethyl.
Open point 5.29 RMS to include all valid endpoints in the LoEP. It seems that only the part of the endpoints was included whilst all valid endpoints should be included. See reporting table 5(82)	December 2017: The LoEP has been updated.			Addressed

Volume 4**1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis**

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Open point 1.1 RMS to update the revised Vol.4 C.1.2.2 by information on the chiral centres. See reporting table confidential 1(2)	The Vol.4 C.1.2.2 has been accordingly amended by adding the information on the chiral centres of the impurities 2, 5, 6, 9, 10, 11 and 12.			Addressed: The Vol.4 C.1.2.2 has been amended by adding the information on the chiral centres of the impurities.
Open point 1.2 RMS to amend the Vol.4s with the proper CAS numbers See reporting table confidential 1(4)	The Vol.4 C.1.2 has been accordingly amended by adding the information on the CAS numbers of trinexapac ethyl and trinexapac with relevance to their keto/enol forms.			Addressed: The Vol.4 C.1.2 has been amended by adding the information on the CAS numbers of trinexapac ethyl and trinexapac
Open point 1.3 EFSA to note in the conclusion that no agreement on a common specification was reached See reporting table confidential 1(8)	Addressed by EFSA. Noted as necessary information in EFSA conclusion thereon.			Addressed: EFSA noted in the conclusion that no agreement on a common specification was reached.

2. Effects on human and animal health

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
Data requirement (Syngenta) 2.1 Additional and comprehensive structural activity relationship analysis (referred to as 'additional analysis') based on additional relevant model (e.g. OECD Toolbox) and open literature search on impurities to see whether they raise any concerns for carcinogenicity, reproductive toxicity, immunotoxicity, phototoxicity and neurotoxicity endpoints. See reporting table confidential 2(1)	LT: Additional structural activity relationship analysis based on additional relevant model (VEGA, Core version 1.2.3) and open literature search for six impurities (CGA158377, CGA267934, CGA264326, CGA190042, CGA252938, NOA427417) has been provided and this data was included in the revised Volume 4. However, since it was acknowledged that the structural activity prediction using VEGA and DEREK NEXUS was of limited validity, further data required for six impurities. The literature search did not reveal any publications of relevance to this assessment.			EFSA considered the last assessment of the toxicological relevance of impurities on the basis of available information in Annex C. Previous assessment done by the RMS should be deleted. For the assessment of the toxicological relevance of impurities EFSA considered the following main lines of evidence in comparison the active substance (whether the impurities might alter the toxicological profile of the active substance) 1. Specific studies and harmonised classification on impurities. 2. Read-across. 3. QSAR analysis for genotoxicity and skin sensitisation. 4. Level tested in the toxicity studies. <u>CGA158377</u>: read across from

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
				CGA113745 was considered acceptable for CGA158377 (see reporting table). CGA113745 is unlikely to be genotoxic. Repeated toxicity data indicate comparable toxicity than active substance. The presence of CGA158377 as impurity in the technical specification might be the responsible for the skin sensitisation potential of trinexepac-ethyl; CGA158377 has harmonised classification as skin sensitizer. On this basis the impurity is considered relevant. EFSA considers that no further data are needed. The maximum content should be the level tested in the fortified skin sensitisation study (i.e. 6 g/kg) <u>Toluene</u>: based on its hazard (harmonised classification as reproductive toxicant) the impurity is considered relevant. According to classification and labelling of mixtures a maximum content of 30 g/kg would be acceptable for reproductive toxicants category 2. <u>Impurities showing a potential</u>

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
				<u>for skin sensitisation on the basis of QSAR.</u> Given the current proposal for classification and labelling for skin sensitisation of the active substance their potential hazard (skin sensitisation) is considered covered by the active substance (impurities are not expected to alter the toxicological profile of the active substance regarding skin sensitisation). <u>Impurity 5:</u> this impurity is considered potentially relevant on the basis of QSAR analysis for genotoxicity (chromosome aberration). It is recommended to further address the potential for genotoxicity or to considered it as relevant and then to set its maximum content at the level of 3 g/Kg (i.e. the level tested in the in vitro CA test). <u>Impurity 9:</u> this impurity is considered potentially relevant on the basis of QSAR analysis for genotoxicity (chromosome aberration). It is recommended to further address the potential for genotoxicity or to considered

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
				it as relevant and then to set its maximum content at the level of 3.7 g/Kg (i.e. the level tested in the in vitro CA test). <u>Batches used in toxicity studies compared to the technical specification:</u> It is currently not possible to conclude on whether the current specification is supported from the toxicological point of view. In particular, the genotoxic potential of two impurities showing alerts for genotoxicity should be further clarified in order to exclude their relevance or their level should be lowered to acceptable limits. The applicant should also clarify/confirm the purity of toxicity studies.
Open point 2.1 RMS to reconsider the skin	LT: The RMS reconsidered the skin sensitisation potential of trinexapac-ethyl technical material based on			See overall assessment above under data requirement 2.1.

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
sensitisation potential of trinexapac-ethyl technical material based on the content of a relevant impurity (i.e. CGA158377) and potentially relevant impurities (i.e. CGA267934, CGA190042, CGA252938 and NOA42741). Should trinexapac-ethyl be considered skin sensitiser (as proposed by Syngenta) the maximum content of (potentially) relevant impurities might set at the level proposed in the technical specification. See reporting table confidential 2(2)	the content of a relevant impurity (i.e. CGA158377) and potentially relevant impurities (i.e. CGA267934, CGA190042, CGA252938 and NOA42741) in the revised Volume 3 and 4. The LLNA study (<i>Durando J., 2017</i>) is summarised and evaluated in the RAR Volume 3, chapter B.6.2.6. Skin sensitization (Study 3). The positive response was observed in the Local lymph node assay and it was concluded that trinexapac-ethyl (fortified) fulfilled the criteria for classification Skin Sens. 1B, H317 under the conditions of this study. Trinexapac-ethyl is considered by the RMS skin sensitiser. The maximum content of relevant and potentially relevant impurities might be set at the level proposed by RMS in the technical specification. It should be noted that this level of the impurity CGA158377 is lower			

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
	of the level at which it is in the technical specification proposed by the applicant (Syngenta).			
Data requirement (Syngenta) 2.2 Applicant (Syngenta) to present a robust scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of relevant impurity CGA158377. Local lymph node assay with spiked batch material to address skin sensitisation potential. Additional and comprehensive structural activity relationship analysis based on additional relevant model (e.g. OECD Toolbox) and open literature search on these four specific impurities (CGA267934, CGA190042, CGA252938 and NOA427417) to see	LT: Local lymph node assay (<i>Durando J., 2017</i>) with spiked batch material was submitted and reported in the revised Volume 3, Volume 1 and LoEP. Trinexapac-ethyl is considered by the RMS skin sensitiser as it fulfilled the criteria for classification Skin Sens. 1B, H317 under the conditions of this study. The maximum content of relevant and potentially relevant impurities might be set at the level proposed by RMS in the technical specification. Additional structural activity relationship analysis based on additional relevant model (VEGA, Core version 1.2.3) and open literature search for specific impurities (CGA267934, CGA190042, CGA252938, NOA427417) has been provided and this			See overall assessment above under data requirement 2.1.

Column A Conclusions from the Reporting Table	Column B Rapporteur Member State comments (reference to addenda where necessary)	Column C Recommendations of the Pesticides Peer Review Meeting	Column D Rapporteur Member State homework (reference to addenda where necessary)	Column E EFSA conclusion
whether they raise any concerns for the skin sensitisation. Robust summary reports of the local lymph node study (Betts C J, 2006) with a batch of non-spiked trinexapac-ethyl Syngenta technical material (Batch No SMO5D180). Batch No SMO5D180 used in this study should be compared with the proposed technical specification. See reporting table confidential 2(2)	data was included in the revised Volume 4. Three impurities (CGA267934, CGA252938 and NOA427417) might be regarded as the potentially relevant impurities based on a weight of evidence approach. Robust summary reports of the local lymph node study (<i>Betts C J, 2006</i>) with a batch of non-spiked trinexapac-ethyl Syngenta technical material (Batch No SMO5D180) has been provided and it was included in the revised Volume 3. However, the study is limited and the study acceptability as well as reliability is considered to be questionable. Therefore, there was no need to compare Batch No SMO5D180 used in this study with the proposed technical specification in the revised Volume 4.			
Data requirement (Syngenta) 2.3	LT: Bacterial reverse mutation (Ames) and HPRT			See overall assessment above

<u>Column A</u> Conclusions from the Reporting Table	<u>Column B</u> Rapporteur Member State comments (reference to addenda where necessary)	<u>Column C</u> Recommendations of the Pesticides Peer Review Meeting	<u>Column D</u> Rapporteur Member State homework (reference to addenda where necessary)	<u>Column E</u> EFSA conclusion
Bacterial reverse mutation (Ames) and HPRT mammalian gene mutation assays with spiked batch material to support the technical specification. See reporting table confidential 2(3)	mammalian gene mutation assays (<i>Woods I., 2017</i> and <i>Gilby B., 2017</i>) with spiked batch material have been provided and they were presented in the revised Volume 3. Whether these assays support the technical specification is considered in the revised Volume 4.			under data requirement 2.1.
Data requirement 2.4 Applicant (Syngenta) to present a robust scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of impurity toluene. See reporting table confidential 2(4)	LT: No additional data were submitted			See overall assessment above under data requirement 2.1.

TABLE OF CONTENTS

	Document
00	Cover page
01	Comments on the assessment report
02	Reporting table
03	Pesticides peer review meeting reports
04	Evaluation table
05	Comments on the additional information assessment
06	Comments on the draft EFSA conclusion

Report of Pesticides Peer Review written procedure on additional information

TRINEXAPAC-ETHYL

Rapporteur Member State: LT

Comments on the assessment report are listed in the relevant reporting table. Comments submitted during the written procedure on the points for clarification are listed in Appendix 1.

Documents submitted for written procedure:

Date	Supplier	File Name
4.12.2017	RMS	Trinexapac-ethyl evaluation table_2017-12-04.zip (all sections)
4.12.2017	RMS	Trinexapac-ethyl_evaluation table confidential_2017-12-04.zip
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_ADAMA_2017-09-01.doc
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_Cheminova 2_Youth_2017-09-01.docx
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_Cheminova_1_Huifeng_2017-09-01.docx
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_HELM_AG_2017-09-01.doc
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_SYNGENTA_2017-09-01.doc
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Non confidential_2017-09-01.doc
4.12.2017	RMS	Trinexapac-ethyl_RAR_pdf_2017-12-04.zip
4.12.2017	RMS	Trinexapac-ethyl_RAR_27_LOEP_2017-12-04.doc

Appendix 1: Discussion table written procedure: Trinexapac-ethyl

Appendix 1: Discussion Table Written Procedure, Trinexapac-ethyl

1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
1	Data requirement 1.1 Additional validation data for the method GRM020.01A for confirmation of the analyte. See reporting table 1(73)	DE: Not addressed. However, we do not consider the validation of a second ion transition for a pre-registration method necessary. AT: not considered	Addressed: The validation report indicates that in this study final solutions were also analysed using the confirmatory ion transition, i.e. the transition, m/z 223 to m/z 179. The method can be considered fit for purpose.
2	Data requirement 1.2 Applicant to submit methods GRM20.13A and GRM020.14A to be evaluated in a revised RAR. See reporting table 1(74)	DE: Data requirement fulfilled. AT: not considered	Addressed: The final results of the studies have been added and assessed in the revised Vol.5 CA B.5.1.2.1
3	Data requirement 1.3 Applicant to provide information on the extraction efficiency for the methods of pre-	DE: The data requirement is fulfilled. However, information such as the percentage of compounds included in the residue definition for risk assessment (here: trinexapac-acid) in extracts should be reported for all solvent systems used. AT: not considered	Addressed: The information on the extraction efficiency with reference to metabolism studies was included in the revised Vol.3 B.5

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	registration for plant and animal matrices in consideration to available metabolism studies performed. See reporting table 1(84)		
4	Data requirement 1.4 Applicant to provide information on the extraction efficiency for the monitoring methods for plant matrices in consideration to available metabolism studies performed. See reporting table 1(85)	DE: Data requirement fulfilled. AT: not considered	Addressed: The applicant response with reference to the metabolism of [¹⁴C]-trinexapac-ethyl in oilseed rape study report has been included in the revised Vol. 3 CA B5.
5	Data requirement 1.5 Applicant to submit the method for body fluid/tissues: CGA179500_11025 and OECD summary CGA179500_11026 See reporting table 1(98)	DE: Data requirement fulfilled. AT: not considered	Addressed: The submitted method has been assessed in the revised Vol.3 B.5.2.6

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
6	Data requirement1.6 Applicant to further address the concerns raised by the RMS regarding the analytical methods for diet analysis of trinexapac-ethyl and for diet/plasma analysis of metabolite CGA329773 used in 10 studies (Oral 90-day study in rats and dogs, 1 year dog study, Carcinogenicity study in rats and mice, Two-Generation Reproduction toxicity study in rats, Subchronic neurotoxicity studies in rats, 28-day dietary immunotoxicity study in mice, 28-day study in rats on metabolite CGA 329773, in vivo micronucleus test in rats on metabolite CGA 329773) since a conclusion on whether they fit-for-purpose and support the toxicological studies could not be	DE: Data requirement fulfilled. Despite of possible deficiencies in reporting of the data, all methods seemed to have used analytical techniques that can be considered state-of-the art at the time when the study was conducted. Therefore we would assume that methods were fit-for-purpose. We are also of the opinion that new vertebrate studies should be avoided at all costs. AT: not considered	Addressed: The summary information on analytical methods available in the mentioned 10 toxicological study reports was included in the revised Vol.3 CA B.5 and the methods were found fit for purpose.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	reached. See reporting table 1(100)		

2. Mammalian toxicology

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
1	Data requirement 2.1 Applicant to provide a figure illustrating the metabolic pathway of trinexapac in the rat. See reporting table 2(4)	DE: Data requirement not addressed. Comment 2(4) in reporting table refers to Vol.3 B.6.1. A figure illustrating the metabolic pathway of trinexapac in the rat was not found in the revised chapter of the RAR. AT: no comments	A table instead of a figure was provided. EFSA considered this point fulfilled.
2	Data requirement 2.2 Applicant to provide a comparative <i>in vitro</i> metabolism study for trinexapac, including an assessment of the metabolism in key animal test species (including dog) and possible	DE: Addressed The applicant has submitted a comparative <i>in vitro</i> rat and human metabolism study which was reported in the revised RAR. However, the dog was not included in this study. AT: no comments	Fulfilled considering that the study was submitted. However, the dog was not included in this study and it was suggested by the experts as a data gap to address human relevance of potential endocrine-mediated effects in dogs.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	identification of specific human metabolites. See reporting table 2(5) See also comments 2(2), 2(3).		
3	Data requirement 2.3 Applicant to provide the pilot 7-week oral feeding study in dogs (Spoede S et al, 1989) and robust summary report. See reporting table 2(13) See also expert consultation in 2(14).	DE: Addressed The pilot 7-week oral feeding study in dogs (Spoede S et al, 1989) was reported in the revised RAR. AT: no comments	Fulfilled.
4	Data requirement 2.4 Applicant to provide detailed summary reports for <i>in vitro</i> genotoxicity studies: - Deparade E. (1988), study report No. 871414 - Deparade E. (2001a),	DE: Addressed The required studies were reported in the revised RAR. AT: no comments	Fulfilled

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	study report No. 20001169 - Dollenmeier P. (1988), study report No. 871415 - Geleick D. (1993), study report No. 931004 - Hertner (1988), study report No. 871411 - Meyer (1988), study report No. 871413 RMS to provide update and also correction in an amended RAR, this action is needed according to SANCO/10180/2013-rev.1. See reporting table 2(18)		
5	Data requirement 2.5 Applicant to provide more detailed historical control data for the rat developmental toxicity study. See reporting table 2(27)	DE: Addressed Additional data and comments of the RMS were reported in the revised RAR. AT: no comments	Fulfilled

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
6	Data requirement 2.6 Applicant to submit further detailed information on ToxCast results regarding endocrine-disruption potential of trinexapac-ethyl. See reporting table 2(31)	DE: Addressed Additional data and comments of the RMS were reported in the revised RAR. AT: no comments	Fulfilled
7	Data requirement 2.7 Applicant to provide a more detailed summary of the study by Böhmler G. et al., 2006. See reporting table 2(33) See also expert consultation in 2(31).	DE: Addressed The study by Böhmler G. et al., 2006 is reported in the revised RAR. AT: no comments	Fulfilled
8	Data requirement 2.8 Applicant to provide a literature search (covering the last ten years) for the toxicological properties of	DE: Addressed The applicant has submitted a further literature search review for the following metabolites: CGA275537, CGA329773, Hydroxylated CGA179500, CGA300405, CGA351210, SYN540405 and SYN540406. This search was done in 31st August 2017 and covered the last twelve years. The results are reported in the revised RAR.	Data gap for updated literature search on CPCA (CGA224439).

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	the tricarballic acid metabolite, 4-(cyclopropanecarbonyl)-3,5-dihydroxy-benzoic acid (CGA329773) and CPCA (CGA224439). Based on currently available information further data would be needed to conclude on genotoxicity (<i>in vitro</i> chromosome aberration test) and general toxicity (repeated toxicity study) for metabolite tricarballic acid. See reporting table 2(42) See also comment 2(70). See also comments 2(43), 2(50), 2(51), 2(52) and 2(53). See expert consultation at 2(53).	AT: no comments	
9	Data requirement 2.9	DE: No comment.	The conclusion whether the method fits-for-purpose and supports the

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Applicant to provide validation of the analytical method used to quantitate plasma CGA329773 levels (to be assessed under B.5) or additional evidence of bone marrow exposure in the micronucleus test with CGA329773. See reporting table 2(45) See also comments 2(44) and 2(46). See expert consultation at 2(53).	AT: no comments	toxicological study could not be reached
10	Data requirement 2.10 In vitro genotoxicity studies already performed for the metabolite CGA179500 (trinexapac acid) to be provided to the RMS for their inclusion in the revised RAR. See reporting table 2(47)	DE: Addressed In vitro genotoxicity studies performed for the metabolite CGA179500 were submitted by the applicant and were reported in the revised RAR. AT: no comments	Fulfilled.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	See expert consultation at 2(53).		
11	Data requirement 2.11 Based on currently available information further data would be needed to conclude on general toxicity (repeated toxicity study) for metabolite 3-ethoxycarbonylpentanedioic acid. See reporting table 2(50) See expert consultation at 2(53).	DE: Not addressed In response to the Reporting table comment 2(50) at renewal, the applicant has not submitted additional data. AT: no comments	Please refer to experts' consultation on metabolites.
12	Data requirement 2.12 Based on currently available information further data would be needed to conclude on general toxicity (repeated toxicity study) for metabolite <i>CGA313458</i> (2-(4-cyclopropyl-2,4-dioxo-	DE: Not addressed In response to the Reporting table comment 2(52) at renewal, the applicant has not submitted additional data. AT: no comments	Please refer to experts' consultation on metabolites.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	butyl)butanedioic acid). See reporting table 2(52) See expert consultation at 2(53).		
13	Data requirement 2.13 A 90-day rat study on cyclopropane carboxylic acid (CPCA) was submitted to JMPR for the assessment of aminocyclopyrachlor (JMPR, 2014). The study should be submitted to the RMS for an independent assessment of the study. It is noted that the EFSA guidance on residue definition has not been taken note at the Standing Committee and therefore cannot be applied. Consequently the use of the TTC as proposed in this guidance is not yet agreed for the peer	DE: Not completely addressed An explanation was submitted by the notifier and was reported in the revised RAR. However, a 90-day study on CPCA was not submitted. AT: no comments	Data gap 90-day study on CPCA

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	review. See reporting table 2(53) See also data requirements 2(42), 2(45), 2(47), 2(50) and 2(52)		
14	Data requirement 2.14 Robust study summaries to be provided to the RMS for the genotoxicity studies reported by Helm AG. See reporting table 2(69)	DE: Addressed Study summaries of the studies by Helm AG were reported in the revised RAR. AT: no comments	Fulfilled.

3. Residues

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
1	Data requirement 3.1 Applicant to provide stability for trinexapac acid in cereal grains and	DE: Data requirement should be satisfied by follow-up investigations on existing storage stability studies.	Agreed Data gap for storage stability data

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	straw covering the maximum length of storage of the samples from the residue trials. See reporting table 3(13)	AT: not considered	
2	Data requirement 3.2 Applicant to provide storage stability studies for the metabolites CGA313458, CGA113745 and cyclopropane carboxylic acid (CGA224439) covering the length of storage of the samples from processing studies. See reporting table 3(15)	DE: Data requirement should be supported by follow-up investigations on existing storage stability studies. AT: not considered	Agreed Data gap for storage stability data and/or new processing studies, pending finalisation of the residue definition for processed products.
3	Data requirement 3.3 Applicant to submit the GLP study (CGA163935_10838) related to hydroxylated trinexapac acid (SYN548584). See reporting table 3(29)	DE: Data requirement considered fulfilled. Please refer also to the discussions held during the expert meeting on the residue definition (Experts' consultation 2). AT: not considered	Comment noted. Data gap for further attempts to confirm the structure and amounts of SYN548584, in view of the requirement of a new metabolism study with the cyclopropyl label
4	Data requirement 3.4 Applicant to submit information against the	DE: No comment. AT: not considered	Data gap Relevance of residues in the fish diet and information against the residues

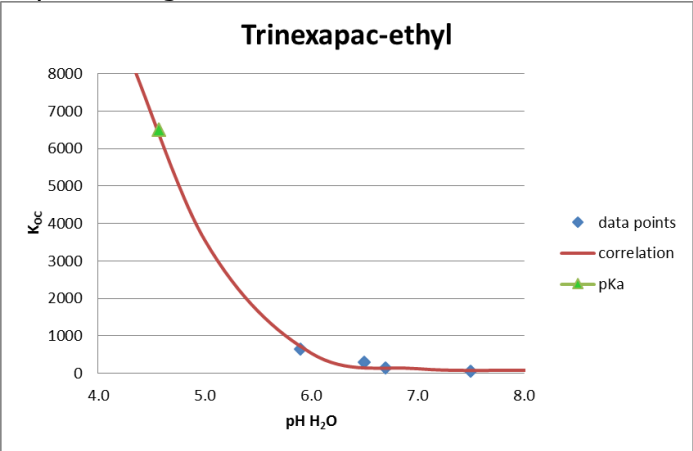
No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	data requirement of Regulation (EU) No 283/2013. The argument that no agreed test method or guidance is available is not considered a valid justification. Detailed circumstances in which animal fish metabolism and feeding studies are triggered are described in SANCO/11187/2013. See reporting table 3(34)		data requirements on fish The representative uses refer to products that are used as feed items in aquaculture, residues of trinexapac in these crops are >0.01 mg/kg, RD-RA in cereal feed items is provisional (pending new metabolism study) and, by the time, includes CGA300405.
5	Data requirement 3.5 Applicant to provide details of the location where each single residue trial was conducted and the distance from the located near sites. See reporting table 3(58)	DE: No more details found in the amended report, but postal codes give clear indications on the zone. This data request is not based on any explicit requirement in the Regulation and the referred to guidance documents. We therefore do not support this requirement. AT: not considered	Comment noted. A number of residue trials resulted as not independent since conducted with same experimental conditions under similar climatic conductions (i.e. 9 to 15 km apart). Data gap for additional independent residue trials or information to demonstrate that, despite adjoining location, these trials can be considered as independent, pending the finalisation of the residue definition in cereals.
6	Data requirement 3.6	DE: Data on the magnitude of CGA113745 in processed commodities	Agreed

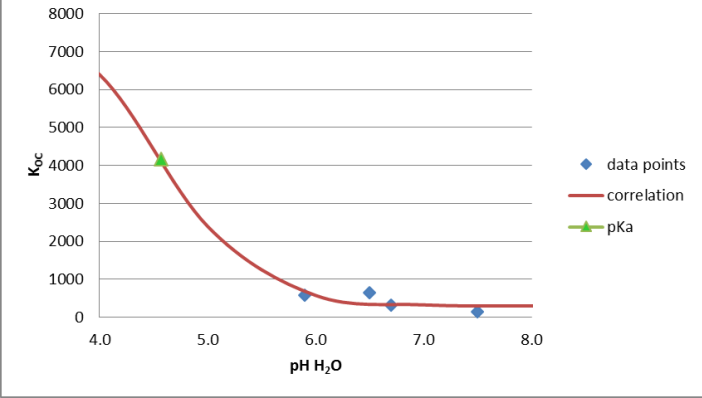
No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Applicant to provide magnitude of residues of the metabolite CGA113745 and CGA313458 in barley and wheat processed commodities. See reporting table 3(81)	are still required due to chromatography and stability reasons (agreement to RMS position). AT: not considered	see Data gap in Data requirement 3.2
7	Data requirement 3.7 Applicant to provide the residue study in honey. See reporting table 3(83)	DE: Study announced. Open requirement. AT: not considered	Agreed Data gap to address residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom with regards to trinexapac and its degradation products.
8	Data requirement 3.8 Applicant to carry out more extensive literature search involving additional metabolites as proposed and combining different terms with the metabolites. Results for all potentially relevant or unclear for relevance of the open literature and inclusion/exclusion criteria	DE: Additional assessment noted and considered acceptable. AT: not considered	Agreed. Addressed.

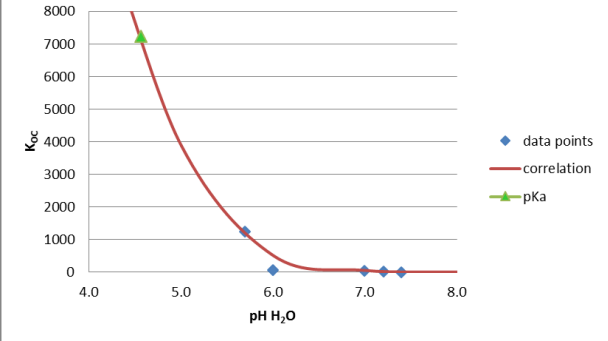
No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	to be documented. See reporting table 3(98)		

4. Environmental fate and behaviour

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
1	Data requirement 4.1 Applicant to provide for parent compound and metabolites degradation studies using acidic soils. See reporting table 4(3)	DE: We agree that the degradation of trinexapac-methyl with a pKa of 4.57 might be pH dependent with longer DT ₅₀ values in more acidic soils. Besides, when converting the pH of the soils for which DT ₅₀ values are available to equivalent pH values in water, all exhibit a pH >7. Thus, with the currently available pH range, no conclusion on a pH dependency of degradation is possible AT: not considered	Addressed. Additional aerobic soil degradation studies using acidic soils might not be expected to provide any further information on the rate of degradation of parent compound and its metabolites, which is also confirmed by the results of the hydrolytic degradation.
2	Data requirement 4.2 Applicant to provide the degradation rate study and the FOCUS kinetic assessment for metabolite CGA275537. Furthermore, applicant to update the exposure assessment for metabolite CGA275537.	DE: No comment. AT: not considered	Addressed.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	See reporting table 4(18)		
3	Data requirement 4.3 Applicant to provide adsorption studies with soil pH >7 for trinexapac-ethyl and trinexapac. See reporting table 4(32)	DE: We plotted the available K_{foc} values of Trinexapac-ethyl and Trinexapac together with the pK_a on a sigmoid curve using the following equation implemented in Input Decision to derive theoretical K_{foc} values and the pK_a for Trinexapac-ethyl: $K_{OC} = \frac{K_{OCn} + K_{OCa} \times 10^{(pH - pK_a)}}{1 + 10^{(pH - pK_a)}}$ The resulting curves support a pH dependency of the adsorption of Trinexapac-ethyl and Trinexapac. However, we agree that also from the sigmoidal curves it seems conservative enough to use the K_{foc} values in alkaline soils (even the mean of the available values is considered conservative enough by us) both for Trinexapac-ethyl and Trinexapac and no further adsorption values in more acidic soils are required for groundwater risk assessment. 	Addressed. It was concluded that the adsorption of trinexapac-ethyl and its metabolites was pH dependent (lowest adsorption at high pH). In view of the pK_a of trinexapac-ethyl and trinexapac, adsorption experiments should have been performed with soils of pH >7. Therefore, the lowest K_{foc} values related to soil with pH >7 were accepted as worst case and used for exposure assessment.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
		CGA179500  AT: not considered	
4	Data requirement 4.4 Applicant to provide the adsorption study for metabolite CGA275537. Furthermore, applicant to update the exposure assessment for metabolite CGA275537. See reporting table 4(34)	DE: We also plotted the available Kfoc values of CGA275537 together with the pKa of Trinexapac-ethyl on a sigmoid curve using the following equation implemented in Input Decision to derive theoretical Kfoc values and the pKa for Trinexapac-ethyl. The curve confirms the pH dependency found for the adsorption of the metabolite. We also agree with the updated adsorption parameters used by the RMS for exposure assessment	Addressed. It was concluded that the adsorption of metabolite CGA275537 was pH dependent (lowest adsorption at high pH). Therefore, the lowest Kfoc value related to soil with pH >7 was accepted as worst case and used for exposure assessment.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
		CGA 275537  AT: not considered	
5	Data requirement 4.5 Applicant to provide information on the effect of water treatment processes on the nature of residues when surface water or groundwater are abstracted for drinking water. See reporting table 4(44)	DE: No comment. AT: not considered	Data gap: Information to address the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface and groundwater, when surface water or groundwater are abstracted for drinking water, were not provided in order to assess the consumer risk from the consumption of drinking water.
6	Data requirement 4.6	DE: No comment.	Addressed.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Applicant to provide new PECsoil calculations using: • for trinexapac-ethyl the highest not-normalised DT₅₀ value derived from the Capay soil (0.72 days) • for metabolite CGA179500 the DT₅₀ value obtained in the Maryland soil normalized only for the temperature and not for the moisture content • for metabolite CGA275537 the new degradation endpoints (see data requirement and open point in comments 4(18)). See reporting table 4(50)	AT: not considered	
7	Data requirement 4.7 Applicant to provide new PECgw calculations using: • the interception for cereals at BBCH 25 set to 20% • for trinexapac-ethyl the	DE: There seems to be a mistake in the LoEP. The 20% interception were added as crop uptake factor for a.s. and metabolites, but was also stated in the application scenario of winter and spring cereals. We believe, that a crop uptake factor of 0 should be used for PECgw modelling of Trinexapac-ethyl and metabolites (and was used in the groundwater modelling described in Vol 3, B8 (CP)). AT: not considered	Addressed. As reported in the updated RAR a plant uptake factor of 0 was used for parent compound and its metabolites. The LoEP will be amended accordingly.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	geometric mean DT_{50} value of 0.13 days (see open point in comment 4(10)) - for metabolite CGA275537 the new degradation and adsorption endpoints (see data requirement and open point in comments 4(18) and 4(34)) - application to the soil surface See reporting table 4(67)		
8	Data requirement 4.8 Applicant to provide new PEC_{sw} and sed calculations considering: - for trinexapac-ethyl the geometric mean DT_{50} value of 0.13 days (see open point in comment 4(10)) - for metabolite CGA275537 the new degradation and adsorption endpoints	DE: No comment. AT: not considered	Addressed.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	(see data requirement and open point in comments 4(18) and 4(34)) • for metabolite CGA275537 Step 1&2 should be done considering "no drift". See reporting table 4(73)		
9	Data requirement 4.9 Applicant to provide an updated literature search including metabolites CGA275537, CGA300405, M2 and. WaterM3Photolysis. See reporting table 4(84)	DE: No comment. AT: not considered	Data gap: Metabolite M2 was not included in the updated literature search.

5. Ecotoxicology

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
1	Data requirement 5.1	DE: Agreement.	Addressed A summary of the acute amphibian

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Applicant to provide the study report and a study summary for the available amphibian test. See reporting table 5(2)	AT: Noted.	study was included in the RAR.
2	Data requirement 5.2 Applicant to provide the study report and a detailed study summary of the study at the basis of the LogPow derivation for trinexapac-ethyl metabolites. In addition, from the provided overview in the reporting table it is not clear whether LogPow values are available for the surface water metabolites M2 (3-carboxylic acid ethyl ester-7-hydroxypropyl-5-oxo,7-hydroxyheptanoic acid) and WaterM3Photolysis and these are needed. See reporting table 5(3)	DE: Agreement. AT: Noted.	Addressed A low risk via secondary poisoning for trinexapac-ethyl and its pertinent metabolites is concluded.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
3	Data requirement 5.3 Applicant to provide a list of relevant plant metabolites. Applicant to provide further information to address the risk to birds and mammals for the relevant plants metabolites. See reporting table 5(4) See also 5(5).	DE: No comment. AT: Noted.	Data gap: Additional information to address the risk to birds and mammals for the plants metabolites was not provided. It is noted that the plant metabolite CGA179500 is found in hen/goat metabolism and could be considered covered by the available risk assessment. Metabolite CGA 275537 is naturally found in animals' metabolism; therefore, a low risk to birds and mammals could be concluded for this metabolite.. From the available mammalian toxicity data CGA329773 is not expected to be more toxic than trinexapac-ethyl, therefore, a low risk for this metabolite to mammals can be concluded. Data gap Further information is needed to address the risk to birds and mammals for the plants metabolites SYN548584, CGA351210, SYN540406, NOA433257, SYN540405, and CGA224439, CGA300405.
4	Data requirement 5.4	DE: No comment.	Addressed

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Applicant to provide the EC10 and EC20, or a justification for not providing those, for the study Putt 1991 (reproductive toxicity study for <i>Daphnia magna</i>). See reporting table 5(10)	AT: Noted.	
5	Data requirement 5.5 Applicant to provide the results of the analytical verifications of the tested concentrations for the aquatic toxicity studies. It should be specified were relevant, whether trinexapac ethyl or trinexapac acid were measured. See reporting table 5(10)	DE: No comment. AT: Noted.	Addressed
6	Data requirement 5.6 In line with the data requirement (Reg. EU No 283/2013), the bioconcentration factors	DE: No comment. AT: Noted.	Addressed

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	shall be expressed as a function of both total wet weight and of the lipid content of the fish. Applicant to provide further information to address this point. See also 5(13). See reporting table 5(14)		
7	Data requirement 5.7 Applicant to provide further details on the oxygen levels during the acute toxicity test with aquatic invertebrates- Mysids, Sousa (1991). It is noted that according to OPPTS 850.1035 (Mysid Acute Toxicity test guideline) the oxygen level in the test should be maintained within 60 and 105% saturation. In Sousa (1991) a drop in oxygen was observed in all treatment excepts control	DE: No comment. AT: Noted. Could RMS please clarify the rationale to consider the oxygen saturation drop in the treatment groups having no effect on the mortality? It appears difficult to compare with the mortality in the control group where the oxygen saturation remained $\geq 58\%$.	Addressed The additional information requested was provided. It is noted that the drop in the oxygen level was observed only after 72 hours in all treatments and after 48 hours at the highest treatment level. It cannot be completely ruled out which would be the influence of this drop on the results of the study. One option would be to consider the endpoint at 72 hours, however, in a conservative approach the lowest endpoint (obtained at 96h) was considered. It is acknowledged that there are uncertainties in the endpoint derived from this study. Therefore, a footnote was added to the list of endpoint indicating that 'A

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	and this may have an influence on the results of the study. See reporting table 5(17)		drop in oxygen was observed in all treatment except control at the end of the study (72-96 h), oxygen level range 44-58%’.
8	Data requirement 5.8 Applicant to provide further information to address the risk to sediment organisms for CGA179500 (trinexapac acid). See reporting table 5(18)	DE: In line with Volume 3CP, B 8.2.2, Table 8.2.2-1, the maximum occurrence of CGA179500 is 6.9 %. Moreover, the toxicity towards <i>Daphnia magna</i> seems to be low as the acute LD ₅₀ = 111 mg a.s./L. The toxicity of the active substance Trinexapac-ethyl towards Daphnids is slightly higher with an LD ₅₀ > 142 mg/L. But also the chronic toxicity towards Daphnids of the a.s. is not very high with a NOEC = 2.4 mg a.s./L. The conduction of a test with sediment organisms according to the current guidance for aquatic organisms is triggered by an occurrence > 10 % in sediment in combination with high toxicity towards daphnids (NOEC < 0.1 mg/L). Both trigger values are not met in this case, even if a 10fold higher toxicity of the metabolite compared towards the a.s. is assumed. AT: Noted.	Addressed
9	Data requirement 5.9 Applicant to provide additional details from the study Hoberg (1991b), this should include an assessment of the validity criteria. See reporting table 5(20)	DE: No comment. / Agreement. AT: Noted. Agree with RMS.	Addressed It is noted that for this study the compliance with the validity criteria (OECD 201, latest version) cannot be fully demonstrated, therefore, the study was invalidated.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
10	Data requirement 5.10 Applicant to provide additional details of the biological finding (biomass/yield/growth rate in the control and in the treatments) for the study effects on algal growth- Maetzler 2001. This should include the recalculated EC10 and EC20 values. See reporting table 5(21)	DE: Agreement. AT: Noted.	Addressed
11	Data requirement 5.11 Applicant to provide further details on the results i.e. biological finding (biomass/yield/growth rate in the control and in the treatments) for the study effects on algal growth- Grade 1995c. See reporting table 5(24)	DE: Agreement. AT: Noted. The study was accepted by RMS.	Addressed

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
12	Data requirement 5.12 Applicant to provide the endpoints expressed in term of mean measured concentrations for the study effects on aquatic Macrophytes- Brown and Maynard 2003; the tested concentrations were not maintained within 20% of the nominal. See reporting table 5(34)	DE: Agreement. AT: Noted. Agree with RMS recalculation.	Addressed
13	Data requirement 5.13 From the available acute toxicity data for trinexapac-ethyl <i>Mysidopsis bahia</i> seems to be the most sensitive species of aquatic invertebrates. However, a chronic toxicity test is not available for this species. The applicant is given the possibility to provide further information to address this point.	DE: Support! As <i>Mysidopsis bahia</i> is much more sensitive towards Trinexapac-ethyl compared with <i>Daphnia magna</i>, the chronic test on invertebrates should be conducted with <i>Mysidopsis bahia</i>, independently from the standard data requirements for plant protection products. AT: The long-term NOEC for fish (0.41 mg trinexapac-ethyl/L) is in the range of the endpoint of <i>Myriophyllum</i> (EyC50 = 0.20 mg a.s./L), thus the argument presented by the applicant that the RAC of <i>Myriophyllum</i> is likely to be the lowest is questioned. Considering the high sensitivity of <i>Mysidopsis bahia</i> in the acute test it appears to be likely that this species is also susceptible to a chronic/long-term exposure.	Addressed The argumentation provided is considered sufficient. Further data on <i>Mysidopsis bahia</i> are not considered necessary for trinexapac-ethyl noting that that a wide margin of safety is obtained at FOCUS step 2 level for all aquatic organisms. Noting also the uncertainties in the <i>Mysidopsis bahia</i> endpoint. See also data requirement 5.7

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	See reporting table 5(37) See also 5(17)		
14	Data requirement 5.14 Applicant to provide a detailed study summary for effects on bees- Hoxter 1990. See reporting table 5(42)	DE: No comment. AT: Noted.	Addressed Some details on this study were included in the RAR. The validity criteria were clearly not met (mortality in the solvent control 20%) and a reference control was not performed in the test.
15	Data requirement 5.15 Applicant to provide additional information on potential sub-lethal effects of trinexapac-ethyl on honeybees (e.g. effects on HPG). See reporting table 5(44)	DE: No comment. AT: Noted.	Data gap Further information on potential sub-lethal effects of trinexapac-ethyl on honeybees (e.g. effects on HPG)
16	Data requirement 5.16 Applicant to provide the available chronic toxicity study on honeybee larvae. See reporting table 5(46)	DE: No comment. AT: Noted.	Addressed The requested study was provided and considered in the risk assessment.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	See also 5(45)		
17	Data requirement 5.17 Applicant to provide an updated risk assessment for honeybees according to the EFSA Bee Guidance Document. This should include: i) a risk assessment via exposure to contaminated water ii) information/assessment of the potential for accumulative effects iii) in accordance with Regulation (EU) 283/2013, a consideration of the risk to bees from metabolites. It is suggested that the methodology in the EFSA (2013) Bee guidance is followed to identify which plant metabolites should be assessed. See reporting table 5(51) See also 5(46), 5(52) and 5(53)	DE: No comment. AT: Noted.	A risk assessment via exposure to contaminated water was not provided (data gap). A screening assessment for exposure via guttation water was provided, however , the obtained ETR could not be reproduced; if the water solubility reported in the list of endpoint is considered (21.1 g/L) a high risk via exposure to guttation water could not be excluded (data gap). It is noted that the RAR included a screening risk assessment for metabolites; however, this assessment was not considered sufficient and could not be fully reproduced by EFSA (data gap)

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
18	Data requirement 5.18 No chronic studies performed with the active substance are available for earthworms and other non-target soil macro- and mesofauna. Applicant to provide further information/a case in support of the bridging of the chronic toxicity data on earthworms and other non-target soil macro- and mesofauna from the formulation to the active substance. See reporting table 5(59)	DE: Agreement with EFSA. Please give a short explanation or bridging statement regarding the comparability of endpoints for soil organisms conducted with the formulation in order to predict the toxicity of the active substance. AT: Noted.	Addressed The available data on earthworms and other non-target soil macro- and mesofauna are considered sufficient to address the risk of trinexapac-ethyl. It is noted that an additional study on trinexapac acid was provided which is considered valid. There is a relatively high variability between replicates which make it difficult to interpret the results of this study. Considering that at 24.3 mg/kg 12% effects on reproduction were observed the endpoint was set at 8.1 mg/kg. The proposed endpoint in the RAR was 24.3 mg/kg.
19	Data requirement 5.19 Applicant to provide the new earthworm data for CGA300405, Luhurs (2015). See reporting table 5(61)	DE: No comment. AT: Noted.	Addressed The study was provided and it is considered valid.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
20	Data requirement 5.20 Applicant to provide the new Collembola data for CGA300405, Luhurs (2015). See reporting table 5(62)	DE: No comment. AT: Noted.	Addressed The study was provided and it is considered valid.
21	Data requirement 5.21 Applicant to provide the new toxicity study on Hypoaspsis for CGA300405, Luhurs (2015). See reporting table 5(63)	DE: No comment. AT: Noted.	Addressed The study was provided and it is considered valid.
22	Data requirement 5.22 A case/further information may be needed to address the risk to soil microorganisms for trinexapac acid. See reporting table 5(66)	DE: Please include the discussion in Column 3 in the RAR. In our point of view, the explanation given in Column 3 is suitable in order to close the data gap. AT: Noted.	Addressed
23	Data requirement 5.23	DE: No comment.	Addressed

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Applicant to provide the new study on the effects on carbon and nitrogen transformation with the metabolite CGA300405. See reporting table 5(67)	AT: Noted.	
24	Data requirement 5.24 Applicant to provide a detailed study summary for the study on the effects on non-target terrestrial plants from Chetram (1991). See reporting table 5(70)	DE: This point was discussed in PPR TC 160. AT: Noted.	Addressed
25	Data requirement 5.25 Applicant to provide an updated literature search in line with the EFSA guidance (2011) on open literature search covering the trinexapac-methyl metabolites relevant for the environmental risk assessment. See reporting table 5(78)	DE: No comment. AT: Noted.	Data gap An updated literature search was provided, however, not all the pertinent plant metabolites were covered by the search i.e. NOA433257 and CGA224439 were not covered.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
26	Data requirement 5.26 The applicant is given the possibility to submit further data to address the endocrine disruption in non target organisms. The ecotoxicity data available for trinexapac-ethyl are not be sufficient to conclude on endocrine disruption in non-target organisms. See also 2(31) and 2(36). See reporting table 5(80)	DE: According to the PRAPer Discussion 170 (11 – 14.12.2017) of the human toxicology section, point 2.4, Trinexapac-ethyl might act as endocrine disruptor. As a first screen in order to identify possible endocrine effects of chemicals, the fish screening assay OECD TG 229 could be conducted. AT: Noted.	The available ecotoxicological data are not sufficient to conclude on the endocrine disruption potential of trinexapac-ethyl. Pending on the outcome of the data gap in Section 2, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of trinexapac-ethyl.

Report of Pesticides Peer Review written procedure on additional information

TRINEXAPAC-ETHYL

Rapporteur Member State: LT

Comments on the assessment report are listed in the relevant reporting table. Comments submitted during the written procedure on the points for clarification are listed in Appendix 1.

Documents submitted for written procedure:

Date	Supplier	File Name
4.12.2017	RMS	Trinexapac-ethyl evaluation table_2017-12-04.zip (all sections)
4.12.2017	RMS	Trinexapac-ethyl_evaluation table confidential_2017-12-04.zip
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_ADAMA_2017-09-01.doc
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_Cheminova 2_Youth_2017-09-01.docx
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_Cheminova_1_Huifeng_2017-09-01.docx
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_HELM_AG_2017-09-01.doc
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Confidential_SYNGENTA_2017-09-01.doc
01.09.2017	RMS/EFS A	Trinexapac-ethyl_Reporting table_Non confidential_2017-09-01.doc
4.12.2017	RMS	Trinexapac-ethyl_RAR_pdf_2017-12-04.zip
4.12.2017	RMS	Trinexapac-ethyl_RAR_27_LOEP_2017-12-04.doc

Appendix 1: Discussion table written procedure: Trinexapac-ethyl

Appendix 1: Discussion Table Written Procedure, Trinexapac-ethyl

Volume 4

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
1	Data requirement (Syngenta) 2.1 Additional and comprehensive structural activity relationship analysis (referred to as 'additional analysis') based on additional relevant model (e.g. OECD Toolbox) and open literature search on impurities to see whether they raise any concerns for carcinogenicity, reproductive toxicity, immunotoxicity, phototoxicity and neurotoxicity endpoints. See reporting table confidential 2(1)	DE: Data requirement fulfilled. Further discussion on use and interpretation of QSAR analysis needed – see below. Also, the interpretation of the QSAR analysis by the RMS appears in part contradictory. For example, on page 84 it is concluded that "CGA264326 triggered alert for developmental toxicity according to the results of (Q)SAR analysis using VEGA (moderate reliability, could be out of the applicability domain). The RMS considers that these alerts cannot be disregarded and it is considered in the New summary of the toxicological profile of the impurities ...". However, within this New summary on page 100, it is concluded by the RMS that the substance is "Not toxicologically relevant". Our understanding would be that toxicological relevance cannot be excluded, but based on the max. concentration of 2 g/kg, it is not of concern. Please clarify.	EFSA considered the last assessment of the toxicological relevance of impurities on the basis of available information in Annex C. Previous assessment done by the RMS should be deleted. For the assessment of the toxicological relevance of impurities EFSA considered the following main lines of evidence in comparison the active substance (whether the impurities might alter the toxicological profile of the active substance) 1. Specific studies and harmonised classification on impurities. 2. Read-across. 3. QSAR analysis for genotoxicity and skin sensitisation. 4. Level tested in the toxicity studies.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
			<u>CGA158377</u>: read across from CGA113745 was considered acceptable for CGA158377 (see reporting table). CGA113745 is unlikely to be genotoxic. Repeated toxicity data indicate comparable toxicity than active substance. The presence of CGA158377 as impurity in the technical specification might be the responsible for the skin sensitisation potential of trinexapac-ethyl; CGA158377 has harmonised classification as skin sensitizer. On this basis the impurity is considered relevant. EFSA considers that no further data are needed. The maximum content should be the level tested in the fortified skin sensitisation study (i.e. 6 g/kg) <u>Toluene</u>: based on its hazard (harmonised classification as reproductive toxicant) the impurity is considered relevant. According to classification and labelling of mixtures a maximum content of 30 g/kg would be acceptable for reproductive toxicants category 2.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
			<u>Impurities showing a potential for skin sensitisation on the basis of QSAR.</u> Given the current proposal for classification and labelling for skin sensitisation of the active substance their potential hazard (skin sensitisation) is considered covered by the active substance (impurities are not expected to alter the toxicological profile of the active substance regarding skin sensitisation). <u>Impurity 5:</u> this impurity is considered potentially relevant on the basis of QSAR analysis for genotoxicity (chromosome aberration). It is recommended to further address the potential for genotoxicity or to considered it as relevant and then to set its maximum content at the level of 3 g/Kg (i.e. the level tested in the in vitro CA test). <u>Impurity 9:</u> this impurity is considered potentially relevant on the basis of QSAR analysis for genotoxicity (chromosome aberration). It is recommended to

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
			further address the potential for genotoxicity or to considered it as relevant and then to set its maximum content at the level of 3.7 g/Kg (i.e. the level tested in the in vitro CA test). Batches used in toxicity studies compared to the technical specification: It is currently not possible to conclude on whether the current specification is supported from the toxicological point of view. In particular, the genotoxic potential of two impurities showing alerts for genotoxicity should be further clarified in order to exclude their relevance or their level should be lowered to acceptable limits. The applicant should also clarify/confirm the purity of toxicity studies.
2	Data requirement	DE: Data requirements fulfilled. Further discussion on use and	See Data requirement (Syngenta)

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	(Syngenta) 2.2 Applicant (Syngenta) to present a robust scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of relevant impurity CGA158377. Local lymph node assay with spiked batch material to address skin sensitisation potential. Additional and comprehensive structural activity relationship analysis based on additional relevant model (e.g. OECD Toolbox) and open literature search on these four specific impurities (CGA267934, CGA190042, CGA252938 and NOA427417) to see whether they raise any concerns for the skin sensitisation.	interpretation of QSAR analysis needed – see below. A justification was provided to support the levels of CGA158377. From table C.1.4.2.2.-4 it appears that the RMS requests further QSAR predictions to address remaining concerns regarding carcinogenicity and reproductive toxicity for this and other impurities. However, we doubt that the predictive performance of currently available QSAR tools can appropriately address those endpoints. For example, the impurity toluene did not trigger Derek Nexus alerts (page 78) but is classified H361d and STOT RE2! A LLNA with spiked material was submitted. QSAR prediction for the specified impurities were performed using Derek Nexus and VEGA. The presentation of the methodological details and the results is sufficient. However, in accordance with current guidance, an expert tool such as Derek should be combined with a statistical model. Unfortunately, the impurities were apparently outside the prediction domain for the additional tools used (VEGA). Therefore, peer review should be initiated to discuss the quality of the QSAR analysis. In particular the approach to disregard alerts triggered by VEGA based on the justification “outside of domain” should be questioned as these alerts are obviously triggered by the part of the molecule inside domain (and should thus be taken seriously). Structural elements outside domain cannot be predicted and absence of “alerts” should be interpreted with care. A literature search was provided, but relevant publications could not be identified.	2.1.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Robust summary reports of the local lymph node study (Betts C J, 2006) with a batch of non-spiked trinexapac-ethyl Syngenta technical material (Batch No SMO5D180). Batch No SMO5D180 used in this study should be compared with the proposed technical specification. See reporting table confidential 2(2)	According to Volume 4 chapter C.1.4.2.1, the study by Betts, 2006 was submitted and summarized in Volume 3 B.6. However, the reliability of this study was questioned and the results were not further considered.	
3	Data requirement (Syngenta) 2.3 Bacterial reverse mutation (Ames) and HPRT mammalian gene mutation assays with spiked batch material to support the technical specification. See reporting table confidential 2(3)	DE: Data requirement fulfilled.	Fulfilled.
4	Data requirement 2.4	DE: Not fulfilled. Currently, a maximum content of <1 g/kg would be acceptable.	See Data requirement (Syngenta) 2.1.

No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Applicant (Syngenta) to present a robust scientific case to support higher than the maximum acceptable content ($\geq 0.1\%$) of impurity toluene. See reporting table confidential 2(4)		

TABLE OF CONTENTS

	Document
00	Cover page
01	Comments on the assessment report
02	Reporting table
03	Pesticides peer review meeting reports
04	Evaluation table
05	Comments on the additional information assessment
06	Comments on the draft EFSA conclusion

Background			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
1.	Conclusion text, paragraph 3 page 7	LT: Typo error trinexap <u>c</u> instead of trinexap <u>a</u> c.	Typo corrected.
2.	Draft EFSA Conclusion Section 9 – Concerns Issues that could not be finalised	DE: The concern identified by EFSA that potential endocrine disrupting properties of trinexapac have not been fully elucidated is supported.	Noted. Thank you.
3.	Draft EFSA Conclusion Section 9 – Concerns Issues that could not be finalised	DE: The concern expressed by EFSA that the consumer risk assessment could not be finalised, due to data gaps regarding residues in primary and rotational crops, livestock and processed commodities, is supported.	Noted. Thank you.
4.	Draft EFSA Conclusion Section 9 – Concerns Critical areas of concern	DE: The critical concern identified by EFSA with regard to the technical specification of trinexapac is supported.	Noted. Thank you.

Identity, physical/chemical/technical properties and methods of analysis

Member States' comments on the draft EFSA Conclusion on Trinexapac (RMS: LT) (co-RMS: LV)
Pesticides Peer Review Written Procedure: February 2018

(23.02.2018) 3/22

No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
1.	Conclusions of the evaluation, Identity (page 8)	LT: A data gap was identified for the content of two possible relevant impurities of the batches relevant for Adama source. The RMS opinion, in consideration with the EU peer review, is that the first source (Huifeng) was meant there, however the confirmation would be appreciated.	Yes, this is confirmed, however this is not mentioned in the text for confidentiality reasons.
2.	EFSA Conclusion, The active substance and formulated product, page 8; and List of endpoints, Identity, Chemical name (IUPAC, CA)	LT: The amendments of the IUPAC names considering the isomerism are highly appreciated. It would nevertheless be important to clarify whether the further revised version of the RAR (with the IUPAC names accordingly amended) would be of relevance.	There is no need to revise the RAR, as the changes can be followed from the RT and evaluation table.
3.	List of endpoints, Identity of relevant impurities (CA)	LT: If this is relevant and with reference to the revised RAR Vol 4 and identity assessment, it could be noted that the decreased content of relevant impurity CGA158377 (3 g/kg, supported by the representative batches of large scale production) had been proposed for the Syngenta trinexapac-ethyl source and this was agreed upon in peer review process by MS as well as by the applicant (2017). In regards to the relevant impurities information the source of trinexapac-ethyl (Syngenta) could be indicated.	Agree. However in Section 2 a limit of 6 g/kg was set with the data gap: "Once the representativeness of the Syngenta Crop Protection AG's technical specification is supported by toxicity studies, further assessment of the equivalence between technical materials of different applicants should be done (data gap)."
4.	List of endpoints, Methods of analysis	LT: The information on methods for relevant impurities determination in formulation could be added:	Agree. The LoEP has been updated.

Identity, physical/chemical/technical properties and methods of analysis			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
	Plant protection product	<i>Toluene</i> : GC-FID; <i>CGA158377</i> : Open	
5.	List of endpoints, Residue definitions for monitoring purposes	LT: Provided the residue definition for body fluids and tissues is the "sum of trinexapac and its salts expressed as trinexapac", the text in regards to trinexapac-ethyl classification could seem to be unnecessary.	Agree. The text concerning trinexapac-ethyl has been deleted.
6.	Draft EFSA Conclusion, Section 1, third paragraph	LT: It should be noted with relevance to the section 2 that neither detailed summary of QSAR data report nor detailed summaries of toxicological studies on the active substance/impurities or references relied on were submitted in the Dossier Document J by ADAMA Agriculture BV (Source Max Rudong) for the purpose of active substance renewal in order to establish equivalence of the impurity profile (Tier II). Due to lack of data, toxicological equivalence of the proposed specification for Trinexapac-ethyl technical to the proposed reference specification for renewal could not be established following a Tier II assessment. Hence, RMS LT proposes a data gap to address evaluation of toxicological equivalence of the proposed technical specification for Trinexapac-ethyl technical, relevant for Adama Agriculture BV (Source Max Rudong).	Agree. However in Section 2 there was already a data gap identified for this purpose: "Once the representativeness of the Syngenta Crop Protection AG's technical specification is supported by toxicity studies, further assessment of the equivalence between technical materials of different applicants should be done (data gap)."

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
1.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, second paragraph	RMS LT: Different chemical names of impurity CGA158377 (CAS No 88805-65-6) are indicated in the RAR Volume 3CA /Volume 4 Syngenta and in Draft EFSA Conclusion/LoEP: Draft EFSA Conclusion Section 1, Section 7 Data gaps, LoEP Section 1: <i>ethyl (1RS)-ethyl 3-hydroxy-5-oxocyclohex-3-ene-1-carboxylate</i> Draft EFSA Conclusion Appendix B Used compound codes: <i>ethyl (1RS)-ethyl 3-hydroxy-5-oxocyclohex-3-ene-1-carboxylate</i> or <i>ethyl 3,5-dioxocyclohexane-1-carboxylate</i> Draft EFSA Conclusion Section 2 and Trinexapac-ethyl RAR Volume 3CA: <i>ethyl 3,5-dioxocyclohexanecarboxylate</i>. It should be noted that another chemical names of impurity CGA158377 have been used in the Trinexapac-ethyl RAR Volume 4CA Syngenta: <i>3-hydroxy-5-oxocyclohex-3-enecarboxylic acid ethyl ester</i> and <i>3-hydroxy-5-oxo-3-cyclohexene-1-carboxylic acid ethyl ester</i>. In view of the fact that only two options of chemical name for impurity CGA158377 are indicated in the EFSA Conclusion Appendix B Used compound codes and for the sake of clarity, the chemical name of CGA158377	The text was amended to include in section 2 only the code CGA158377.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		mentioned in Draft EFSA Conclusion Section 2 (i.e. <i>ethyl 3,5-dioxocyclohexanecarboxylate</i>) should be corrected.	
2.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, second paragraph	RMS LT: Different maximum contents of relevant impurity toluene are indicated in Draft EFSA Conclusion Section 1, Section 2 and LoEP: Draft EFSA Conclusion Section 1, LoEP section 1: 3 g/kg Draft EFSA Conclusion Section 2: 5 g/kg The different maximum amounts of toluene (5 g/kg and 3 g/kg) are proposed for the reference specification at renewal by the Applicant and the RMS LT, respectively. The maximum contents of toluene mentioned in Draft EFSA Conclusion Section 2 should be corrected.	The maximum content of impurity toluene was amended accordingly to 3 g/kg.
3.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, second paragraph	RMS LT: From a toxicological point of view the maximum content of the impurity CGA158377 in the technical specification could be accepted at the level proposed by the Applicant and EFSA (i.e. 6 g/kg) rather than the RMS LT (i.e. 3 g/kg). This can be justified by the fact that the positive LLNA study (<i>Durando J., 2017</i>) with spiked batch material (Batch No SMO5D180_ Fortified) covered the technical specification regarding the impurity CGA158377. Furthermore, this batch of trinexapac-ethyl technical was fortified with this impurity up to of the level at which it is in the technical specification proposed	The RMS agreed with applicant and EFS's proposal. Therefore there is no need to amend the EFSA's conclusion.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		by the applicant (i.e. 6 g/kg) but higher than the RMS proposed (i.e. 3 g/kg).	
4.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, second paragraph	RMS LT: From the RMS LT point of view the potentially relevance of two impurities 5 (CGA190042) and 9 (CGA252938) regarding genotoxicity is ambiguous, however it can be supported: - These two impurities triggered alert for chromosome damage <i>in vitro</i> in mammals according to the results of (Q)SAR analysis using DEREK NEXUS. - From a toxicological point of view the technical specification proposed for the impurity 5 is not comparable to the material used in genotoxicity studies regarding two old gene mutation <i>in vitro</i> and the main micronucleus <i>in vivo</i> studies since this impurity was not detected at all, while the technical specification proposed for the impurity 9 is comparable to the material used in genotoxicity studies regarding Chromosome Aberration <i>in vitro</i>, mammalian gene mutation <i>in vitro</i> and main micronucleus <i>in vivo</i> studies only taking into account acceptable limit 3 g/kg. - The applicant has submitted Ames and HPRT assays (Woods I., 2017 and Gilby B., 2017) with spiked batch material (Batch No SMO5D180_Fortified)	Noted. The text was amended to clarify the EFSA's assessment on impurities 5 and 9.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		which covered the technical specification regarding these impurities. The result of Ames assay was negative, while mammalian cell gene mutation assay was equivocal: the results in the absence of metabolic activation were contradictory and some deviations were identified in this study. - It cannot be clearly excluded that these two impurities (CGA190042 and CGA252938) could be more toxic than the parent trinexapac-ethyl regarding genotoxic potential (e.g. <i>In vitro</i> Mammalian Cell Gene Mutation, Chromosome Aberration <i>in vitro</i>). On the other hand, it should be noted that impurities 3, 9 and 12 were considered by the RMS LT to be potentially relevant impurities due to skin sensitisation potency.	
5.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, third paragraph	RMS LT: The RMS would like to add the following to the paragraph below: "...At the expert meeting, it was suggested to provide a comparative <i>in vitro</i> metabolism study between dog and human to address human relevance of dog findings and the potential role of metabolites (data gap)."	The text was amended accordingly.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
6.	Conclusion text (p. 9)	DK: One of the critical effects in short-term toxicity studies in dogs is given as "reduced body weight gain". DK finds that this should be changed to "reduced terminal body weight (in males)". It was discussed at the experts' meeting if the NOAEL should be lowered based on decreased body weight gain as this was seen at lower doses than those causing a decrease in terminal body weight, however, the majority was not in favour of basing the NOAEL on the decreased body weight gain. This should also be changed in the LoEP (point 4 below).	The text was amended accordingly.
7.	Conclusion text (p. 10)	DK: There is a misprint in the paragraph regarding the ADI. The ADI is based on a NOAEL of 31.6 mg/kg bw per day and not 0.32 mg/kg bw per day. In the same line, also the word "gain" should be deleted so that it reads "... based on reduced body weight, clinical signs,..." cf. the comments above.	The text was amended accordingly.
8.	Conclusion text (p. 11)	DK: In the section regarding metabolites, it is mentioned that the metabolite CGA300405 showed a higher acute oral toxicity than the parent. DK believes that the higher acute oral toxicity was seen for metabolite CGA275537 (tricarballic acid) not CGA300405.	The text was amended accordingly.
9.	LoEP, Section 2, Long-term	RMS LT: Regarding EFSA's inquiry does galactoceles in	The text was amended accordingly.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
	toxicity and carcinogenicity	mammary skin of rats triggering the NOAEL setting: An increase in the incidence of galactoceles in mammary skin of females at 10000 ppm (not statistically significant) as well as at 20000 ppm (statistically significant) was considered to be compound-related. The NOAEL for long-term effects was set at 3000 ppm (115.6 mg/kg bw/d) for M&F, based on an increase in the incidence of bile duct hyperplasia in the livers, renal histopathological effects (hyaline droplets) of males and galactoceles in mammary skin of females. Galactoceles are common in aging female rats; however, an increased incidence of galactoceles could be a response to hyperprolactinemia (i.e. related to prolactin-induced mammary secretory activity) too in the 2-year rat carcinogenicity study. Hence, RMS considers that galactoceles in mammary skin of rats is triggering the NOAEL setting.	
10.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, ninth paragraph	RMS LT: The following is written in the ninth paragraph: "...Parental and offspring toxicity included reduced body weight gain..." Please amend the sentence as follows: "...Parental and offspring toxicity included reduced body weight gain <u>and reduced body weight, respectively...</u>"	The text was amended accordingly.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
11.	LoEP, Section 2, Short-term toxicity, Target organ/critical effect	RMS LT: The following is written in the LoEP: "changes on the oestrus cycle & decreased absolute uterus weight ... RMS LT proposes to amend the sentence as follows: "...changes <u>in</u> oestrus <u>cyclicity</u> , decreased absolute uterus weight..."	The text was amended accordingly.
12.	LoEP, Section 2 Impact on Human and Animal Health, Short-term toxicity	DK: One of the critical effects in dogs is given as "decreased body weight gain". DK finds that this should be changed to "decreased terminal body weight in males". It was discussed at the experts' meeting if the NOAEL should be lowered based on decreased body weight gain as this was seen at lower doses than those causing a decrease in terminal body weight, however, the majority was not in favour of basing the NOAEL on the decreased body weight gain.	The text was amended accordingly.
13.	LoEP, Section 2 Impact on Human and Animal Health, studies on metabolites	DK: Regarding metabolite CGA275537: Should the data gap regarding genotoxicity and repeated exposure remain, when it is mentioned in the EFSA conclusion text that "For tricarballic acid (CGA275537) there is no sufficient data for a final conclusion on genotoxicity and no data for repeated exposure (comparison to parent or specific references values) are available. However, considering the natural occurrence of tricarballic acid, further data are not needed (see Section 3)"?	The text was amended accordingly.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		(Also, is the natural occurrence of tricarballic acid discussed in Section 3?)	
14.	LoEP, Section 2 Impact on Human and Animal Health, studies on metabolites	LoEP, Section 2 Impact on Human and Animal Health, studies on metabolites	Noted.
15.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, sixteenth paragraph, metabolite tricarballic acid (CGA275537)	RMS LT: The following is written in the sixteenth paragraph regarding metabolite tricarballic acid (CGA275537): "For tricarballic acid (CGA275537) there is no sufficient data for a final conclusion on genotoxicity and no data for repeated exposure (comparison to parent or specific references values) are available..." RMS LT suggests to amend the sentences as follows: "For tricarballic acid (CGA275537) there is no sufficient data for a final conclusion on genotoxicity and no data for repeated exposure (comparison to parent or specific references values) are available. <u>This metabolite is considered of higher acute oral toxicity than the parent compound based on acute oral toxicity study...</u>" Acute oral toxicity study is available for the metabolite CGA275537 and it is considered of higher acute oral toxicity than the parent compound. This study (<i>Sommer</i>	The text was amended accordingly.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		<i>E., 2001a; Study Report No. 20011035</i>) is summarised in the Trinexapac-ethyl RAR Volume 3CA, B.6.8.1.3.1 (365-366 pp.). It should be noted that some ambiguity remains regarding the data gap for this metabolite: possible data (on genotoxic potential and repeated exposure) need was identified at the expert meeting, the same data gap is mentioned in the LoEP but not in EFSA conclusion. If there is no need data on genotoxic potential/repeated exposure (due to the natural occurrence of tricarballic acid), perhaps there is no requirement to mention the term "data gap" in the LoEP.	
16.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, sixteenth paragraph, metabolite CGA300405 Evaluation table, Data requirement 2.11	RMS LT: Regarding EFSA's inquiry to RMS, it should be noted that the statement in EFSA Conclusion is incorrect. Please see point 9 above. The following is written in the sixteenth paragraph regarding metabolite CGA300405: "The metabolite CGA300405 is unlikely to be genotoxic. During the peer review meeting it was mentioned that the metabolite showed a higher acute oral toxicity than the parent..." Due to an error in this sentence, it should be corrected as follows:	The text was amended accordingly.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		"The metabolite CGA300405 is unlikely to be genotoxic. ~~During the peer review meeting it was mentioned that the metabolite showed a higher acute oral toxicity than the parent...~~" It should be noted that ambiguity remains regarding the data gap for this metabolite: possible data (on repeated exposure) need was identified for this metabolite at the expert meeting, data gap is mentioned in the LoEP (with error, please see point 11) but not in EFSA conclusion. If further data on repeated exposure might be not needed, perhaps there is no requirement to mention the term "data gap" in the LoEP.	
17.	LoEP, Section 2, Studies performed on metabolites or impurities, Metabolite CGA300405	RMS LT: The following is written in the LoEP: "Data gap identified for genotoxic potential and repeated exposure" Due to an error in this sentence, it should be corrected as follows: "Data gap identified for ~~genotoxic potential and repeated exposure~~"	The text was amended accordingly.
18.	LoEP, Section 2, Studies performed on metabolites or impurities,	RMS LT: The following is written in the LoEP regarding metabolite CGA224439: "Data gap identified for the repeated exposure toxicity"	The text was amended accordingly.

Mammalian toxicity			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
	metabolite CGA224439	(available 90-day rat study to JMPR)" RMS proposes to amend the sentences as follows: "Data gap identified for the repeated exposure toxicity (available 90-day rat study to JMPR) <u>and updated literature search</u> "	
19.	Draft EFSA Conclusion, Section 2 Mammalian toxicity, sixteenth paragraph, metabolite CGA313458	RMS LT: It should be noted that ambiguity remains regarding the data gap for the metabolite CGA313458: possible data (on repeated exposure) need was identified for this metabolite at the expert meeting, data gap is mentioned in the LoEP but not in EFSA conclusion. If further data on repeated exposure might be needed for the metabolite, perhaps there is requirement to mention the term "potential data gap" in the LoEP.	The text was amended accordingly.

Residues			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment

Residues			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
1.	Conclusion text, 3.1. page 11	LT: trinexapac was discussed at expert meeting and not teleconference for residue section.	Thank you noticing. The text was amended accordingly.
2.	Conclusion text, 3.1. page 11	LT: typo error – letter “p” is missing for cycloproyl, paragraph 3, line 5.	Thank you for noticing the typo. The text was amended accordingly.
3.	Conclusion text, 3.1. page 11	LT: conclusion states “Trinexapac and the metabolite CGA300405 were both present in forage and straw at comparable levels (max. 22 and 21% TRR, respectively).” If the percent mentioned is for trinexapac (free and conjugated) it should be 22 % for both commodities (trinexapac (free and conjugated) is present in wheat forage at 22.1 % TRR and grass straw at 22.36 % TRR).	There seem to be a misunderstanding on this point. The rounded percentages refer respectively to trinexapac and to CGA300405 rather than to forage and straw. For sake of clarity, the sentence has been rephrased in the conclusion.
4.	Conclusion text, 3.1. page 11	LT: it is not clear where “12% TRR, 0.66 mg/kg, grass” for Tricarballic acid (CGA275537) come from. Tricarballic acid (CGA275537, free and conjugated) is present in grass forage at 13.81 % and straw at 16.95 % TRR.	Thank you for noticing. These figures come from a typo in the expert meeting report. They have been updated to 14% TRR, 0.28 mg/kg for grass forage in the conclusion.
5.	Conclusion text, 3.1. page 11-12	LT: the wording of trinexapac acid CGA 179500 is different in Conclusion and LoEP, trinexapac (acid) in Conclusion and trinexapac in LoEP.	The text of the conclusion and the list of endpoints were aligned. The term (acid) was associated to trinexapac when referring to the residue definitions for products of plant and animal origin as currently reported in Regulation (EU) No 396/2005.

Residues			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
6.	List of End Points, table for processed commodities, page 22	LT: Names of the columns in head line are switched, it should be in the following order: Trinexapac-ethyl - CGA179500 (trinexapac) - CGA313458 - CGA224439 - CGA113745. Some values are incorrect: it should be 58.5 % instead of 58.8% and 16.1 % instead of 10.1 % for 60 min, 100°C, pH 5 values in the third study. 3.8 % instead of 17.7 % in the last line. Also there is a typo error (letter "p" is missing) for 14C-cycloproyl-trinexapac acid.	Thank you for noticing. List of endpoints updated accordingly.
7.	List of End Points	LT: Plant residue definition for monitoring (RD-Mo) page 22 and 24. RMS confirms that RO-Mo for plants and animals was agreed as definitive.	Thanks for the confirmation. Appreciated.
8.	List of End Points	LT: it is not clear why the different wording is using in definition of residue. <u>Trinexapac (acid)</u> for RD Mo plants and <u>Trinexapac</u> in all other residue definitions.	See response to comment 5.
9.	List of End Points, representative uses	LT: table on representative uses, page 26. It is not clear why HR and STMR values were deleted for barley grain NEU but not for SEU.	Thank you for noticing. The oversight has been corrected.
10.	List of End Points, representative uses	LT: table on representative uses, page 28. It is not clear how barley straw NEU values for RA (4x0.07) were calculated. As from the residue trials, trinexapac (free	1. Thank you for noticing. The oversight of the residue values for NEU in straw has been corrected.

Residues			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		and conjugated) was <u>3x<0.05</u> , <u>0.07</u> and 0.09 mg/kg. (Values in straw for which storage stability was not demonstrated are underlined). For barley straw SEU RA trinexapac (free & conj.) should be 3x<0.05 instead of 2x0.05.	2. The residue value of <0.05 mg/kg for barley straw in SEU belongs to trial NC13038-02, which is not covered by storage stability. Hence, it was excluded from the calculation (see response to comment 14). Amendment of the list of endpoints is not necessary.
11.	List of End Points, representative uses	LT: table on representative uses, page 29. For wheat straw SEU data there should be 6 x <0.05 and 1 x 0.05, instead of 7 x <0.05.	Thank you for noticing. The oversight has been corrected.
12.	List of End Points, page 33	LT: typo errors in explanation to table "Input for animal burden calculations" (a) Levels of trinexapac (free and conjugated) in straw are derived from combined dataset with major part of the samples not supported by storage stability. Contribution of metabolite CGA300405: not considered	Thank you for noticing the typos. The text was amended accordingly.
13.	Evaluation table, open point 3.13, 3.17, 3.19	LT: Vol 1 was updated in light of the outcome of Expert consultation 1 and 2 and, eventually, independency of trials (see Open point 3.16).	Noted.
14.	Evaluation table, open point 3.16	LT: RMS agrees to consider these residue trials as replicates: Barley NEU	Partial disagree. To consider the SEU trial NC13038-02 is acceptable, is not consistent with previous assessment. RMS has excluded from the assessment the

Residues			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
		- (UK) YO17 6QA(1) and YO62 7TD(2) (distance about 15 km) Barley SEU - (IT) 27010 (3) and 26866 (about 15 km) Wheat NEU - (FR) 60490(7) and 60113(8) (about 9 km). However RMS does not agree on exclusion of trial NC13038-02 (from study TK0178795) based on storage stability (stored 24.5 months). Storage stability is proven in wheat grain stored for 24 months (uncorrected recovery 79.4%) and additional 0.5 months should not make a relevant impact on degradation. As a consequence, calculation in Vol 1 (by RMS) and LoEP (by EFSA) are slightly different. However, if EFSA decides to exclude residue trials stored for 24.5 months, please also note, that samples from study TK0178795 trial NC13038-01 were analysed after 4.5 months for trinexapac (free) and after 24.5 months for trinexapac (free & conjugated). Therefore, value of 0.72 (0.69 before scaling) should also be excluded from the calculations. Additional explanations were added in Vol 3 Table B.7.3.1-2 page 164.	NEU trial on barely NC13039-01 (from study TK0178789) also stored for 24.5 months prior to analysis because not adequately covered by storage stability (refer to RAR, Vol 3, p. 142). By analogy, the SEU trial NC13038-02 shall be kept excluded. The information added to Vol 3 of the RAR is that the actual storage of the sample of the SEU trial on barely NC13038-01 is 24.5 months prior to be analysed according to the residue definition for risk assessment. Residue value of total trinexapac shall be excluded from the assessment. List of endpoints has been amended accordingly.

Residues			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
15.	RAR 09 Vol 3 CA B-7	LT: some mistakes were noticed and corrected in Vol 3 CA B-7 page 164, and table B.7.5.1-8 on page 229.	Noted.

Environmental fate and behaviour			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
1.	Conclusion text Appendix B	LT: the structure of WaterM3Photolysis metabolite could not be found in study report Adam, D., 2008a (KCA 7.2.1.2/04). It was described as structural isomer of parent only.	Therefore, a data gap was added to the conclusion for the identity of metabolite WaterM3Photolysis.

Ecotoxicology			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment

Ecotoxicology			
No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
1.	List of endpoints – section 5 ecotoxicology	LT: In the note “**** Supportive data, test perfoemd...” please correct a typo error in the word performed.	The typo in the list of endpoints was corrected. Thank you.
2.	List of endpoints – section 5 ecotoxicology	LT: in the risk assessment for non-target arthropods based on extend lab test, off-field rate should be for <i>A. rhopalosiphi</i> - 5.54 g/ha (3D), for other species - 0.554 g/ha (2D)	The list of endpoints was corrected. Thank you.
3.	List of endpoints – section 5 ecotoxicology	LT: note “ ^a NOEC estimated based...” should be deleted as irrelevant under the table “Effects on non-target soil meso- and macro fauna...”	The list of endpoints was corrected. Thank you.
4.	Evaluation table, Data requirement 5.25	LT: The RMS evaluation of the literature search was deleted and then omitted by mistake. If there is such possibility to updated RAR, the evaluation of the literature search was included in the RAR by RMS, please refer to the Vol.3, B9 AS, B.9.11.1 RMS considers the literature search comprehensive and the methodology suitable.	The data gap in the EFSA conclusion and background documents was amended considering the RMS evaluation of the literature search which was included in the RAR during the written procedure. The RMS view on the literature search was reflected in the EFSA conclusion text.

Other

Member States' comments on the draft EFSA Conclusion on Trinexapac (RMS: LT) (co-RMS: LV)
Pesticides Peer Review Written Procedure: February 2018

(23.02.2018) 22/22

No.	Reference (e.g. conclusion text, list of endpoints, evaluation table etc)	Member State comment	EFSA response to comment
5.		LT: no comments.	Noted.