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TECHNICAL REPORT

APPROVED: 21 February 2020

doi:10.2903/sp.efsa.2020.EN-1811

Outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for isopyrazam in light of confirmatory data

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) was asked by the European Commission to provide scientific assistance with respect to the risk assessment for an active substance in light of confirmatory data requested following approval in accordance with Article 6(1) of Directive 91/414/EEC and Article 6(f) of Regulation (EC) No 1107/2009. In this context EFSA's scientific views on the specific points raised during the commenting phase conducted with Member States, the applicant and EFSA on the confirmatory data and their use in the risk assessment for isopyrazam are presented. The current report summarises the outcome of the consultation process organised by the rapporteur Member State the United Kingdom and presents EFSA's scientific views and conclusions on the individual comments received.

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Keywords: isopyrazam, peer review, confirmatory data, risk assessment, pesticide, fungicide

Requestor: European Commission

Question number: EFSA-Q-2020-00099

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Suggested citation: EFSA (European Food Safety Authority), 2020. Technical report on the outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for isopyrazam in light of confirmatory data. EFSA supporting publication 2020:EN-1811. 135 pp. doi:10.2903/sp.efsa.2020.EN-1811

ISSN: 2397-8325

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Summary

Isopyrazam was approved under Regulation (EC) No 1107/2009 on 1 April 2013 by Commission Implementing Regulation (EU) No 1037/2012. It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on the relevance of the metabolites CSCD 459488 and CSCD 459489 for groundwater by 31 March 2015. The Commission Implementing Regulation (EU) No 2015/1106 had extended the deadline for the submission of the confirmatory data to 31 July 2017.

In accordance with the specific provision, the applicant, Syngenta Crop Protection UK Ltd, submitted an updated dossier in March 2015 and following the extended deadline granted for the submission of confirmatory data, a revised updated dossier was submitted in February 2018, which was evaluated by the designated rapporteur Member State (RMS), the United Kingdom, in the form of an addendum to the draft assessment report. In compliance with the guidance document SANCO 5634/2009-rev.6.1, the RMS distributed the addendum to Member States, the applicant and EFSA for comments on 18 April 2017 regarding the assessment of the environmental fate data related to the metabolite CSCD 459489 and on 30 October 2019 as regards the assessment of the toxicological assessment of the metabolite CSCD 459488 together with an updated groundwater relevance assessment. The RMS collated all comments from the two commenting rounds in the format of a combined reporting table, which was submitted to EFSA on 24 January 2020. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table.

The current report summarises the outcome of the consultation process organised by the RMS, the United Kingdom, and presents EFSA's scientific views and conclusions on the individual comments received.

Isopyrazam is the ISO common name for a mixture of 3-(difluoromethyl)-1-methyl-*N*-[(1*RS*,4*SR*,9*RS*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide [2 *syn*-isomers] and 3-(difluoromethyl)-1-methyl-*N*-[(1*RS*,4*SR*,9*SR*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]pyrazole-4-carboxamide [2 *anti*-isomers] (IUPAC). The ratio of *syn*- to *anti*-isomers is unstated. The representative uses evaluated for isopyrazam comprise foliar spray applications, as a fungicide, for control of various fungal pathogens on barley, oat, rye, wheat and triticale. The confirmatory submission provided a supporting case for the lack of epimerisation of the parent compound.

In the mammalian toxicology area, it has been previously concluded that metabolites CSCD 459488 and CSCD 459489 share the toxicological properties of the parent isopyrazam (EFSA, 2012). The toxicological relevance assessment does not have to be provided for the groundwater metabolite CSCD 459489, as the confirmatory information assessed in relation to environmental fate and behaviour was considered sufficient to conclude that the metabolite CSCD 459489 would be unlikely to reach levels in soil where they must be assessed for groundwater exposure. However, as a general rule all metabolites which are expected to occur in soil under normal use conditions should be subject to further assessments that aim to quantitatively assess their ability to contaminate groundwater (European Commission, 2003). A groundwater exposure assessment was available in the EFSA conclusion of 2012, for metabolite CSCD 459488. There was no consensus on the assessment of the toxicological relevance of the groundwater metabolite CSCD 459488. In contrast to the RMS opinion, the commenting member states (MS) and EFSA considered that the human relevance of the uterine adenocarcinomas (and according to one commenter also the liver adenomas) observed in the rat carcinogenesis study cannot be dismissed for the parent, supporting the previous EFSA conclusion (EFSA, 2012) that the criteria for classification regarding carcinogenicity may be met for isopyrazam (ECHA 2017). Consequently, the same concern exists for the metabolite CSCD 459488 that should be considered toxicologically relevant according to the guidance document on the assessment of the relevance of metabolites in groundwater (European Commission, 2003). Furthermore, the genotoxic potential of the metabolite was questioned and it was noted that the aneugenic potential of the metabolite was not addressed according to the current state-of-the-science (EFSA SC, 2011) – acknowledging that the latter concern was not raised at the time of the peer review (EFSA, 2012) and is out of the scope of this confirmatory data requirements. One MS also questioned whether a range-finding study for developmental toxicity that was part of the 2012 data package, may be sufficient to exclude a concern for the metabolite to share the developmental toxicity potential observed for the parent isopyrazam. These issues are proposed to be discussed during an

experts' meeting. Based on the above, the confirmatory data are not considered addressed since the non-relevance of metabolite CSCD 459488 cannot be established. EFSA considers a better groundwater exposure assessment (that utilises updated degradation rate information derived from investigations following guideline soil incubations) would also be desirable for CSCD 459489.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Isopyrazam was approved under Regulation (EC) No 1107/2009[1] on 1 April 2013 by Commission Implementing Regulation (EU) No 1037/2012[2]. EFSA previously finalised a Conclusion on this active substance on 29 March 2012 in the EFSA Journal (EFSA, 2012).

It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on the relevance of the metabolites CSCD 459488 and CSCD 459489 for groundwater by 31 March 2015. The Commission Implementing Regulation (EU) No 2015/1106[3] had extended the deadline for the submission of the confirmatory data to 31 July 2017.

In accordance with the specific provision, the applicant, Syngenta Crop Protection UK Ltd, submitted an updated dossier in March 2015 and following the extended deadline granted for the submission of confirmatory data, a revised updated dossier was submitted in February 2018, which was evaluated by the designated rapporteur Member State (RMS), the United Kingdom, in the form of an addendum to the draft assessment report (United Kingdom, 2017). In compliance with the guidance document SANCO 5634/2009-rev.6.1 (European Commission, 2013), the RMS distributed the addendum to Member States, the applicant and the EFSA for comments on 18 April 2017 regarding the assessment of the environmental fate data related to the metabolite CSCD 459489 and on 30 October 2019 as regards the assessment of the toxicological assessment of the metabolite CSCD 459488 together with an updated groundwater relevance assessment. The RMS collated all comments from the two commenting rounds in the format of a combined reporting table, which was submitted to EFSA on 24 January 2020. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table.

The current report summarises the outcome of the consultation process organised by the RMS, the United Kingdom, and presents EFSA's scientific views and conclusions on the individual comments received.

1.2. Interpretation of the Terms of Reference

On 22 December 2014 the European Commission requested EFSA to provide scientific assistance with respect to the risk assessment of confirmatory data following approval of an active substance in accordance with Article 6(1) of Directive 91/414/EEC[4] and Article 6(f) of Regulation (EC) No 1107/2009. EFSA's scientific views on the specific points raised during the commenting phase conducted with Member States, the applicant and EFSA on the risk assessment of confirmatory data for isopyrazam are presented.

To this end, a technical report containing the finalised reporting table is being prepared by EFSA. The deadline for providing the finalised report is 21 February 2020.

On the basis of the reporting table, the European Commission may decide to further consult EFSA to conduct a full or focused peer review and to provide its conclusions on certain specific points.

[1] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1-50.

[2] Commission Implementing Regulation (EU) No 1037/2012 of 7 November 2012 approving the active substance isopyrazam, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 308, 8.11.2012, p. 15-18.

[3] Commission Implementing Regulation (EU) No 2015/1106 of 8 July 2015 amending Implementing Regulations (EU) No 540/2011 and (EU) No 1037/2012 as regards the conditions of approval of the active substance isopyrazam. OJ L 181, 9.7.2015, p. 70-71.

[4] Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.08.1991, p.1-32. Repealed by Regulation (EC) No 1107/2009.

2. Assessment

The comments received on the pesticide risk assessment for the active substance isopyrazam in light of confirmatory data and the conclusions drawn by the EFSA are presented in the format of a reporting table.

The comments received are summarised in column 2 of the reporting table. The RMS' considerations of the comments are provided in column 3, while EFSA's scientific views and conclusions are outlined in column 4 of the table.

The finalised reporting table is provided in Appendix A of this report.

Documentation provided to EFSA

1. United Kingdom, 2017. Addendum to the assessment report on isopyrazam, confirmatory data, April 2017 revised in January 2020. Available online: www.efsa.europa.eu.

2. United Kingdom, 2020. Reporting table, comments on the pesticide risk assessment for isopyrazam in light of confirmatory data, January 2020.

References

ECHA (European Chemicals Agency), 2017. Guidance on the Application of the CLP Criteria; Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 5.0, July 2017. Reference: ECHA-17-G-21-EN; ISBN: 978-92-9020-050-5; available online: https://echa.europa.eu/guidance-documents/guidance-on-clp

EFSA Scientific Committee, 2011; Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379. [68 pp.] doi:10.2903/j.efsa.2011.2379. Available online: www.efsa.europa.eu/efsajournal

EFSA (European Food Safety Authority), 2012. Conclusion on the peer review of the pesticide risk assessment of the active substance isopyrazam. EFSA Journal 2012;10(3):2600, 110 pp., doi:10.2903/j.efsa.2012.2600

European Commission, 2003. Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 final, 25 February 2003

European Commission, 2013. Guidance document on the procedures for submission and assessment of confirmatory information following approval of an active substance in accordance with Regulation (EC) No 1107/2009. SANCO 5634/2009-rev. 6.1

Abbreviations

2-D TLC	two-dimensional thin-layer chromatography
AO	adverse outcome
AR	applied radioactivity
a.s.	active substance
CAR	constitutive androgen receptor
CLH report	Proposal for Harmonised Classification and Labelling
DAR	draft assessment report
DAT	days after treatment
DegT50	Description of time taken for 50 % of substance to disappear from a compartment as a result of degradation processes alone
EU	European Union
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
KE	Key event
LOD	limit of detection
LOQ	limit of quantification
MoA	mode of action
MS	Member State
PEC	predicted environmental concentration
PEC_{gw}	predicted environmental concentration in ground water
RAC	Risk Assessment Committee
RMS	rapporteur Member State

Appendix A – Collation of comments from Member States, applicant and EFSA on the pesticide risk assessment for the active substance isopyrazam in light of confirmatory data and the conclusions drawn by EFSA on the specific points raised

0. General

General				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
0(1)		FR (Nov 2019): No comment.	UK RMS (2019): Noted. Addressed	Addressed.

General				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
0(2)	Addendum to DAR update of October 2019 2 Overall conclusions	EFSA (2019): The sentence: 'As noted in the environmental fate section below, a 'non-relevance' assessment of the metabolite CSCD459489 is not triggered due to the levels formed in ground water' is not accurate. The sentence should have stated instead that: 'A 'groundwater non-relevance' assessment of the metabolite CSCD459489 is not triggered, due to the fact that a groundwater exposure assessment is not triggered. As noted in the environmental fate section below, the levels of CSCD459489 now demonstrated to have been formed in soil did not trigger the need for a ground water exposure assessment'.	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.

General				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
0(3)	General	EFSA (2019): An amended LoEP should be submitted according to the changes provided in the addendum.	UK RMS (2019): An amended LoEP is now available. Addressed	Addressed.

1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis

Identity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
1(1)	Conf data Addendum, B.8 Fate, Figure B.8.1, p.5	EFSA (2017): small note: in each case just one enantiomer of the compounds is represented and no mention that syn and anti are practically composed of two enantiomers. It is recognised that this information is available on p. 107.	UK RMS (2017): For clarity, an additional sentence has been included within the introduction to the section B.8. 'Environmental Fate And Behaviour' assessment, which references the information contained on page 107. Addressed	Addressed.
1(2)	Conf data Addendum, B.8 Fate, Supporting chemistry cases, p.104	EFSA (2017): In the EFSA conclusion the syn:anti ratio of the metabolites; CSCD459488 and CSCD459489 was assumed to be the same as the parent. However, confirmatory data submitted seem to indicate that the ratio of	UK RMS (2017): Appendix 3, Case 2 (beginning on page 107) provides a supporting case for the lack of epimerisation of the parent compound – the RMS considers this case to be supported and the conclusion to be scientifically justified. As noted, the deviation in the ratio between the isomers, when compared to the parent, is considered to arise from the faster degradation of -anti compared to the -syn isomer. This point is addressed within the report, for the consideration	Addressed.

Identity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		the metabolite isomers deviates from the parent isomeric ratio in favour of the syn- isomer. It is also stated that there is not likely to be any epimerisation of the parent compound. Therefore, it is assumed that the observed effect can only be explained by the faster degradation of CSCD459489 (anti) versus CSCD459488 (syn) in soil.	of the study Wyeth K and Hand L, 2014b (Report Number PM-13-259B). The RMS conclusion for this study is on page 32 of the report. Addressed	

Physical and chemical properties of the active substance				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Physical and chemical properties of the plant protection product				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Data on application and efficacy				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Further information				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Methods of analysis				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
1(3)	Conf data Addendum, B.8 Fate, Marshall, S.D. (2009), p.100	EFSA (2017): considers the re-evaluation of method T012740-05H data acceptable.	UK RMS (2017): point noted. Addressed	Addressed.
1(4)		FR (Nov 2019): No comment.	UK RMS (2019): Noted. Addressed	Addressed.
1(5)	Conf Addendum. B.5 Report No. 29473, p.15	EFSA (Dec 2019): It is not clear what is the difference between the linearity check between 0.0101 mg/mL to 0.101 mg/mL and 0.000243 mg/mL to 0.00243 mg/mL and how the LOQ was calculated from this second linearity? It is stated that for method validation 5 individual 10	UK RMS (2019): Addendum has been amended. Addressed	Addressed.

Methods of analysis				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		g amounts were prepared but in Table B.5.5 six values are inserted as recovery data. Clarification is needed.		

Other comments				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

No comments received.

2. Effects on human and animal health

Absorption, distribution, metabolism and excretion in mammals				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Acute toxicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Short-term toxicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Genotoxicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
2(1)	Confirmatory data assessment, B.6., Mammalian Toxicology, Summary	Applicant (2019): In the first paragraph on Page 25 it states the following; "*Data include further studies on the metabolite itself, but also on the parent substance (on its carcinogenic potential) as the hazard profile of isopyrazam can have a significant impact on the assessment of the relevance of CSCD459488 in groundwater.*" It is proposed that it would be more accurate to state "*Data include further studies on the metabolite itself, but also on the parent substance (to evaluate a proposed mode of action for the shift in incidence of uterine and mammary tumours in the rat) as the hazard profile of isopyrazam can have a significant impact on the assessment of the relevance of CSCD459488 in groundwater.*"	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.
2(2)	Conf Addendum. B.6 Report No. 29473, p.25 onward	EFSA (2019): It is evident that the relevance of metabolite CSCD459488 depends on the classification of the parent; therefore, EFSA understand that for the	UK RMS (2019): Thank you. The carcinogenicity hazard classification of isopyrazam will be discussed by RAC.	**Experts' consultation:**

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		assessment of the metabolite CSCD459488, classification of the parent as non-genotoxic carcinogen is the key information. The proposed mode of action is considering a deregulation of timing to senescence as the major driver leading to uterine adenocarcinoma. The mode of action is recapitulated by the applicant through a series of KEs. KE1 to KE4 are empirically supported and they show consistency in the direction that the parent substance has an impact on timing to senescence with a more persistent level of circulating PRL eventually acting by increasing the number of oestrus cycles (KE5), which is seen as a key indicator of a delay in senescence. The applicant is also proposing an increase in proliferation as part of the KE5. However, proliferation of uterine mucosal cells was not measured and the proliferative effect can only be inferred by the high incidence of uterine neoplasms observed in the	Addressed - The conclusion of the confirmatory data procedure should await the RAC Opinion	The carcinogenicity hazard classification for isopyrazam will be discussed by the ECHA RAC. In contrast to the RMS opinion, EFSA considers that the human relevance of the uterine adenocarcinoma observed in the rat carcinogenicity study cannot be dismissed for the parent and consequently the same concern exists for the metabolite CSCD 459488 that should be considered relevant according to the guidance document on assessment of the relevance of metabolites in groundwater (European Commission, 2003). This should be discussed during an experts' meeting. See also 2(5).

Long-term toxicity and carcinogenicity				
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		carcinogenicity study. Behind the lack of this critical set of data for linking the proposed KE5 to the AO (uterine adenocarcinoma), EFSA is considering that the proposed MOA is failing in describing an essential KE which is common to many mode of actions leading to uterine adenocarcinoma, namely an increase in estrogen to progesteron ratio. Measurement of the estrogen to progesteron ratio would be essential to understand the effect driven by the delay in senescence, namely the estrogen dominance, which is the likely essential KE leading to increase proliferation. EFSA also recognise that in addition of lacking measurement of the estrogen/progesteron ratio at the various time points, measurement of estrous-cycle-aware hormones measurement at different ages would have been useful to contextualize all the circumstantial		

Long-term toxicity and carcinogenicity				
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		evidences proposed in the MOA (e.g. histological changes in hormone sensitive organs) which were quantitatively limited in incidence and severity vs. control. EFSA appreciate that comparative MOA were considered and all excluded. EFSA agreed with all but MOA on modulation of estrogen metabolism via induction of CYPs. In the summary document, it is reported that the administration of isopyrazam in the diet for 14-days (500 and 3000 ppm) resulted in a significant increase in the metabolism of 17-β-estradiol to 2- and 4-estradiol in liver microsomes, however, no changes in uterine CYP 1B1 were observed. This suggests that the increase in oestrogen metabolism is a result of CYP2B/3A microsomal enzyme induction, secondary to CAR activation and that peripheral induction of estradiol hydroxylation does not occur in isopyrazam treated rats.		

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		EFSA disagree that based on these data such a MOA should be dismissed. 2- and 4-estradiol were not measured in the blood and 2- and 4-estradiol were inferred to be not produced in the uterus but were not measured. Liver hypertrophy is a clear target for the parent (and the metabolite) substance and may indicate that substance related enzyme induction occurred, including induction of enzyme hydroxylation. The applicant is also considering the circumstantial evidences that the observed shift in tumour profile is inconsistent with this MoA. Contrary to the reduction in mammary and pituitary tumours observed after isopyrazam exposure, such a MoA would be expected to cause an increase in tumours in the oestrogen sensitive mammary and pituitary tissues. EFSA is considering this observation just circumstantial as the decrease observed was not contextualized versus the		

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		historical control data and as such, the relevance of this change remains uncertain. In addition, it is difficult to make this consideration without knowing the sensitivity of the mammary gland to different hormones acting on different directions i.e. decrease in prolactin and increase in 2- and 4-hydroxyestradiol or other estradiol metabolites. Therefore, EFSA is considering that this MOA is not dismissed. This MoA is considered human relevant and should be fully dismissed by measuring the circulating level of estrogen metabolites. In summary: Although uncertainties exist for concluding on the senescence mediated MoA (lack of data on E/P ratio and uterine mucosa proliferation), EFSA agree that this MOA is unlikely to be human relevant because		

Long-term toxicity and carcinogenicity				
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		of the differences between human and rat in the physiological process of senescence and the different physiological role of PRL on maintenance of corpora lutea. However, EFSA is considering that the MoA dealing with modulation of estrogen metabolism via induction was not dismissed and considered human relevant. It is also possible that the two MoA are concomitantly occurred. In conclusion, EFSA thinks that the human relevance of the uterine adenocarcinoma observed in the rat carcinogenicity study was not dismissed and consequently the same concern exists for the metabolite CSCD459488.		
2(3)	B.6.1. Chronic Toxicity and Carcinogenicity, Table B.6.1.1-3.	Applicant (2019): Given that there was a significant decrease in mammary fibroadenoma in top dose females in the rat carcinogenicity study which has relevance to the proposed mode of	UK RMS (2019): Thank you. Addendum has been amended.	Addressed.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		action for the increased uterine tumours and that the mammary tumour incidence is presented in summary table B.6.1-1, it would be helpful to also include the incidence of mammary fibroadenoma in Table B.6.1.1-3.	Addressed	
2(4)	Confirmatory Data Assessment, B.6.1.3.1, Liver hepatocellular adenoma	DE (2019): The constitutive androgen receptor (CAR) activation seems to be a key event in liver adenoma development. It is clearly demonstrated that CAR activation induces only the proliferation of rodent hepatocytes. However, beside this MoA new data provide convincing evidence that CAR activation is also accompanied by oxidative stress that contributes to liver neoplasia (PMID: 30203046). This generation of oxidative stress is also relevant for human hepatocytes and should therefore be considered as an alternative MoA in accordance with the IPCS framework for analyzing the relevance of a cancer	UK RMS (2019): Thank you. There is no clear evidence of hepatic oxidative stress from the liver histopathology. Further consideration of this MoA does not seem justified. However, the carcinogenicity hazard classification of isopyrazam will be considered by RAC. Addressed - The conclusion of the confirmatory data procedure should await the RAC Opinion	**Experts' consultation:** In contrast to the RMS opinion, DE considers that the human relevance of the liver hepatocellular adenomas observed in the rat carcinogenicity study cannot be dismissed for the parent and consequently the same concern exists for the metabolite CSCD 459488 that should be considered relevant according to the guidance document on assessment of the relevance of metabolites in groundwater (European Commission, 2003). This should be discussed during an experts' meeting.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		mode of action for humans (Boobis et al., 2006).		
2(5)	Confirmatory Data Assessment, B.6.1.3.2, Uterine endometrial adenocarcinoma	DE (2019): In general, the provided mechanism for the development of uterine endometrial carcinoma seems plausible, but should be further discussed in the PREV meeting. Considering the involvement of progesterone and estrogen in the MoA, isopyrazam may fulfil the criteria to be relevant as an endocrine disruptor. There is also the possibility of another non-endocrine MoA which should be discussed (see further explanations).	UK RMS (2019): Thank you. The carcinogenicity hazard classification of isopyrazam will be discussed by RAC. There was no requirement to address the ED potential of isopyrazam in the confirmatory data. Addressed	See experts' consultation proposed in 2(2).
2(6)	B.6.1.3.2 Uterine endometrial adenocarcinoma (§1 p.41)	Applicant (2019): Proposes a change to the wording: There are several possible mechanisms by which the observed increase in uterine tumours could have been mediated, including genotoxicity, oestrogenicity, dopamine agonist or effects on dopamine transport, altered incidence of	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		prolactin secreting tumours in the anterior pituitary, altered oestrogen metabolism in the uterus, or a delay in age-related transition to reproductive senescence.		
2(7)	B.6.1.3.2 Uterine endometrial adenocarcinoma (p.41)	Applicant (2019): Proposes a change to the wording: The examination of transition into reproductive senescence shows differences in the patterns of changes and timing in the onset of reproductive senescence in different laboratory rat strains. In normally aging Han Wistar rats (from approximately 12-months) blood levels.	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.
2(8)	B.6.1.3.2 Uterine endometrial adenocarcinoma (p.42)	Applicant (2019): Proposes a change to the wording: To evaluate the key events of the proposed MoA, an 18-month investigative toxicity study has been conducted in which female Han Wistar rats were	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		administered isopyrazam for 13, 26, 52, 66 and 80 weeks, the doses reflecting those of the 2-year carcinogenicity study (0, 500 and 3000ppm equating to 0, 28 & 194 mg/kg bw/d). This study also included the metabolite of isopyrazam (CSCD459488), administered for the same duration (at 3000 ppm equating to 176 mg/kg bw/d) in order to evaluate its potential to cause uterine tumours via the same mode of action.		
2(9)	Table 6.1.3.2-1	Applicant (2019): Inconsistent information in sections of the document: In Table 6.1.3.2-1 it states at 3000 ppm isopyrazam, there was a decrease in food consumption for the last 4-months. This is in agreement with the study report, but it contradicts what is said on page 45 (see comment 7).	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
2(10)	B.6.1.3.2 Uterine endometrial adenocarcinoma (p.45)	Applicant (2019): Inconsistent information in sections of the document, propose a change to the wording: "*18-month investigative study food consumption, although erratic, was generally similar to controls throughout the treatment period*". Propose change to: "*18-month investigative study food consumption was eratic at 3000 ppm isopyrazam, but in the last 4 months of the study, a more consistent pattern of lower food consumption in the 3000 ppm isopyrazam group was observed.*"	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.
2(11)	B.6.1.3.2 Uterine endometrial adenocarcinoma (p.45)	Applicant (2019): Proposes a change to the wording: Although the expected age-related increases in plasma leptin occurred in animals treated with 500 ppm isopyrazam and 3000 ppm CSCD459488, plasma leptin values were still statistically significantly	UK RMS (2019): Thank you. Addendum will be amended. Addressed	Addressed.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		lower than controls at certain time-points (week 66 for the 500 ppm isopyrazam group and weeks 52 and 80 for the CSCD456488 group) in these animals, although to a lesser magnitude and duration than those observed in the 3000ppm isopyrazam animals. Adiponectin (hormone involved in fatty acid breakdown) levels between control and treated groups showed no discernible differences.		
2(12)	B.6.1.3.2 Uterine endometrial adenocarcinoma: *Key event four: suppression of age-related increase in prolactin* (p. 46).	Applicant (2019): Correction required. It states "*It was demonstrated that an age-related increase in plasma prolactin observed in the control and 500ppm isopyrazam treated animals was delayed by treatment with 3000ppm isopyrazam after 66- and 80-weeks' treatment (statistical significance was reached at week 66*)" In the 18-month study report statistically significant differences in prolactin levels	UK RMS (2019): Thank you. Addendum has been amended. Addressed	Addressed.

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		at 3000 ppm isopyrazam were only seen at the week-80 time point. This includes differences from the day 28 value at the same dose level, as well as the difference from the concurrent control.		
2(13)	B.6.1.5 Conclusion on the carcinogenic potential of isopyrazam	FR (Nov 2019): FR is of the opinion that isopyrazam should be classified for carcinogenicity based on liver and uterine tumours (please see column 3, FR comment on the CLH report, Nov 2019).	UK RMS (2019): Thank you. The carcinogenicity hazard classification of isopyrazam will be considered by RAC. Addressed - The conclusion of the confirmatory data procedure should await the RAC Opinion	**Experts' consultation:** In contrast to the RMS opinion, FR considers that the human relevance of the liver and uterine tumours observed in the rat carcinogenicity study cannot be dismissed for the parent and consequently the same concern exists for the metabolite CSCD 459488 that should be considered relevant according to the guidance document on assessment of the relevance of metabolites in groundwater (European Commission, 2003). This should be discussed during an experts' meeting. See also 2(2), 2(4) and 2(18).

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
2(14)	Confirmatory Data Assessment, B.6.1.5, Conclusion	DE (2019): The RMS should justify in this section why the reference values of the active substance are applicable for the metabolite CSCD459488.	UK RMS (2019): Thank you. The justification is in section B.6.3. Addressed	Addressed.
2(15)	Confirmatory Data Assessment, B.6.3, Information on the metabolite CSCD459488	DE (2019): In the In Vitro Mammalian Cell Gene Mutation Test (using L5178 TK+/- mouse lymphoma cells) CSCD459488 induced an increase in small mutant colonies, which was simultaneously accompanied by a decrease in large mutant colonies. These changes should be analysed statistically. Furthermore, an explanation for this uncommon effect should be provided.	UK RMS (2019): Thank you. This study was not part of this confirmatory data procedure but was evaluated in the original DAR and the conclusions agreed during the first review. Addressed	**Experts' consultation:** It is acknowledged that mutagenicity assessment has already been considered during the original peer review. It is however part of the confirmatory data procedure for the assessment of the relevance of metabolites in groundwater and it is considered, as well as the aneugenicity assessment, of such a critical nature that it should be highlighted and clarified as far as possible at any stage of the peer review. It is therefore proposed for experts' discussion during an experts' meeting. See also 2(16).

Long-term toxicity and carcinogenicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
2(16)	B.6.3 information on the metabolite CSCD459488, Ames test, in vitro chromosome aberration test, mammalian cell gene mutation assay, p. 57-60	EFSA (2019): It would be appreciated to see the results of the genotoxicity tests in a tabular format to be able to assess the results independently. The tests presented do not address the aneugenic potential of the metabolite.	UK RMS (2019): Thank you. These studies were not part of this confirmatory data procedure but were evaluated in the original DAR and the conclusions agreed during the first review. Addressed	See experts' consultation proposal in 2(15).
2(17)	B.6.3 28-day toxicity study in rats, p. 60-63	EFSA (2019): The increase in absolute spleen weight is dismissed based on historical control data, but historical control data are not presented. Please provide these data and an assessment of their reliability. Since there was no change reported on body weight, it may not be so relevant that relative spleen weight was not affected. Please provide also reliable historical control data on thyroid weight.	UK RMS (2019): Thank you. This study was not part of this confirmatory data procedure but was evaluated in the original DAR and the conclusions agreed during the first review. Addressed	**Experts' consultation:** Even if the 28-day toxicity study with metabolite CSCD 459488 was considered previously, it is of relevance to the confirmatory data requirement to assess the relevance of groundwater metabolites and its results should be agreed during an experts' meeting, in case the non-relevance of the tumours is demonstrated.

Reproductive toxicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Neurotoxicity				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Further toxicological studies				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Toxicological data on metabolites				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
2(18)	B.6.4 Non-relevance assessment of metabolite CSCD459488 in groundwater – Stage 3 of Step 3: Screening for toxicity	FR (Nov 2019): As FR considered that classification of isopyrazam as carcinogenic is warranted, it should be demonstrated that the metabolite CSCD459488 does not share its carcinogenic potential. It is noted that the MoA(s) underlying liver and uterine tumours after isopyrazam exposure are not known (postulated MoAs are not considered sufficiently substantiated). The MoA(s) should be clarified and human relevance excluded	UK RMS (2019): Thank you. Noted. The carcinogenicity hazard classification of isopyrazam will be considered by RAC. If RAC were to agree that classification is warranted, then CSCD459488 would become relevant as it shares the same tox profile as the parent. Addressed - The conclusion of the confirmatory data procedure should await the RAC Opinion	See experts' consultation proposal in 2(13).

Toxicological data on metabolites				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		before reaching a conclusion on the toxicological relevance of the metabolite. Moreover, in the available toxicity studies (28- and 90-d rat studies as well as mechanistic studies), CSCD459488 showed the same toxicity profile than isopyrazam regarding hepatic findings. Therefore, it could not be excluded that the groundwater metabolite CSCD459488 may share the same (undefined) MoA(s) leading to liver and uterine tumours and based on the available data, it should be considered relevant according to Guidance Document SANCO/221/2000.		
2(19)	Vol. 3 B.6.4 Relevance assessment of CSCD459488 p. 87	FR (2019): It is reported that "based on results from the *in planta* studies, metabolite CSCD459488 is not defined as being of comparable biological activity to target organisms relative to isopyrazam". For completeness and transparency, it would be appreciated if results from these studies for isopyrazam and	UK RMS (2019): Please see Volume 3 Annex B 3 Section B.3.1.5.2 of the DAR (April 2010) and Sections B.10.7.5-6 for information on *in planta* studies. Addressed	Addressed.

Toxicological data on metabolites				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		metabolite CSCD459488 are presented in the addendum (it seems that results are not presented in the DAR).		
2(20)	Addendum to DAR update of October 2019 B.9 – Stage 1 Step 3: biological activity	EFSA (2019): The information reported might be supportive of but is not sufficient to draw a conclusion on the relevance of the metabolite. The metabolite appears less toxic than the parent but to say that the MoA i.e. respiratory inhibition is significantly reduced, is not sufficiently proven.	UK RMS (2019): The target site is the SDH enzyme. The lack of inhibition of SDH can be considered as strong indication of reduced biological activity against a target disease. Furthermore, the *in planta* tests do provide the evidence of a significant reduction. Addressed	Addressed.
2(21)	CSCD459488-relevance assessment	AT (2019): Considering the similar toxicological profile of isopyrazam and CSCD459488 a range finding study for developmental toxicity might not be considered sufficient to exclude a concern for this metabolite, in case isopyrazam will be classified for reproductive (developmental) toxicity.	UK RMS (2019): Thank you. As microphthalmia was seen with the parent substance even in a range-finding study, we regard the negative developmental toxicity range-finding study with CSCD459488 sufficient to exclude its relevance. Addressed	**Experts' consultation:** In contrast to the RMS opinion, FR considers that the range finding study for developmental toxicity may not be sufficient to exclude a concern for the metabolite to be a developmental toxicant as observed for the parent isopyrazam. This should be discussed during an experts' meeting.

Medical data and information				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Toxicological end points: ADI, ARfD, AOEL				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Product exposure and risk assessment, including dermal absorption				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Other comments, incl comments on volume 4 (impurities, batches)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

3. Residues

Not relevant to the assessment.

4. Environmental fate and behaviour

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(1)	Addendum (Fate) B.8	Applicant (2017): For clarification, in the EFSA Conclusion the assumption was made that the formation fraction of CSCD459489 from the parent anti isomer is the same as for CSCD459488 from the parent syn isomer and that the behaviour of the two metabolite isomers in soil is the same. The new data presented by the Applicant show that these assumptions are not appropriate in this case.	UK RMS (2017): this is stated on page 3 of the Addenda. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(2)	B.8.1.2 Rate of degradation (laboratory & field)	FR (2017): Agrees with the RMS assessment. Despite some shortcomings (in particular regarding the laboratory data), the additional information provided is sufficient to show that metabolite CSCD459489 (*anti*) is expected to be minor (weight of evidence) and does not trigger a groundwater assessment.	UK RMS (2017): points noted, no further action required. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(3)	B.8.1.2 Rate of degradation (laboratory)	FR (2017): Due to the shortcomings identified, it is considered that the DT50 derived for CSCD459488 (*syn*) in these additional studies should not be considered in risk assessment and so should not be pooled for future assessments with the agreed available data reported in EFSA Journal 2012.	UK RMS (2017): the RMS agrees that the data are not of sufficient quality to be included in the LoEP; however the purpose of the study was not to derive DT_{50} values for a groundwater assessment but to demonstrate that CSCD459489 is not detected above % 5 AR and therefore groundwater modelling is not warranted. Addressed	Addressed.
4(4)	Confirmatory data assessment. Marshall S, 2009. Reassessment of the route study	EFSA (2017): In Gartenacker soil degradation of the parent was investigated over 369 days but analysis separating metabolites is only reported at 120 days. At this time point still	UK RMS (2017): agrees with EFSA that the maximum % of CSCD460260 was reached at Day 180; 19.6 %; (mean of 20 % and 19.2 % reported in the original DAR (2010); Volume 3, Annex B.8, Table 8.8); therefore the RMS requested justification from the Applicant why the data after 120 days was not re-assessed? ***Applicant response;***	Addressed.

<table>
<tr><th colspan="5">Route and rate of degradation in soil (B.8.1)</th></tr>
<tr><th>No.</th><th>Column 1

Reference to addendum to assessment report</th><th>Column 2

Comments from Member States / applicant / EFSA</th><th>Column 3

Evaluation by rapporteur Member State / response from the applicant</th><th>Column 4

EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data</th></tr>
<tr><td></td><td>submitted in the original dossier.</td><td>almost 50 % of the parent compound remains and the metabolite CSCD460260 has not yet reached a maximum level (which will be located between 120 days and 279 days). Therefore, the level reported for the anti metabolite of 1.5 % AR does not necessarily represent the maximum attained by this metabolite isomer in this soil.</td><td>In the OECD 307 guideline followed at the time (adopted 24th April, 2002), it is stated that 120 days is the normal duration for rate and pathway studies. Three of the 4 soils included in this study were incubated for up to 120 days and for the fourth soil (Gartenacker), in which there was the most degradation of isopyrazam, the incubation was extended to 365 days. Levels of CSCD460260 were maximum at 120 days for the 3 soils incubated up to 120 days. For consistency the ratio of the metabolite syn and anti isomers (CSCD459488 and CSCD459489) were assessed in the 120 DAT (days after treatment) samples for all 4 soils.

The levels of the individual metabolite isomers determined by 2-D TLC in all 4 soils at 120 DAT are shown in Table 1 below. Levels of CSCD459489 at 120 DAT were only >LOD in 2 of the 4 soils and the maximum level determined by this analytical technique was 0.3%.

Table 1: Levels of CSCD460260 isomers (determined by TLC analysis) in 4 laboratory soils at 120 days after treatment (refer to Table B.8.10 in the DAR addendum for metabolite isomer values)

CSCD460260 is comprised of syn:anti isomers CSCD459488:CSCD459489
<table>
<tr><th>Soil</th><th>CSCD459488 [% AR[a]]</th><th>CSCD459489 [% AR[a]]</th></tr>
<tr><td>18 Acres</td><td>2.5</td><td>0.3</td></tr>
</table></td><td></td></tr>
</table>

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

Pappelacker	*5.0*	*0.1*
Marsillargues	*13.7*	*<LOD*
Gartenacker	*12.6*	*<LOD*

LOD 0.1% AR

The data reported in Marshall (2009) had indicated that the levels of the isopyrazam metabolite CSCD459489 in soil were very low and were not expected to exceed 5 % AR in any of the soils investigated. During the course of this study the Gartenacker soil samples from 0 to 120 DAT has been analysed by an HPLC method that separated the CSCD460260 isomers. As levels of CSCD459489 in the 120 DAT samples had been shown by 2-D TLC to be negligible, the levels of CSCD459489 in the Gartenacker samples were not quantified by HPLC at the time. To investigate the formation of CSCD459489 further, the available HPLC data from this study was re-assessed to quantify the levels of CSCD459488 and CSCD459489 separately.

Figure 1 below shows the decline of the isopyrazam isomers and formation of CSCD460260 over 120 to 365 days in addition to the formation of the separate metabolite isomers over 0 to 120 days. Although the level of CSCD460260 in Gartenacker soil increased slightly from 17.1% at 120 days to 19.6% at 180 days (maximum observed level), this is not expected to result in maximum levels of the metabolite anti isomer

Route and rate of degradation in soil (B.8.1)				
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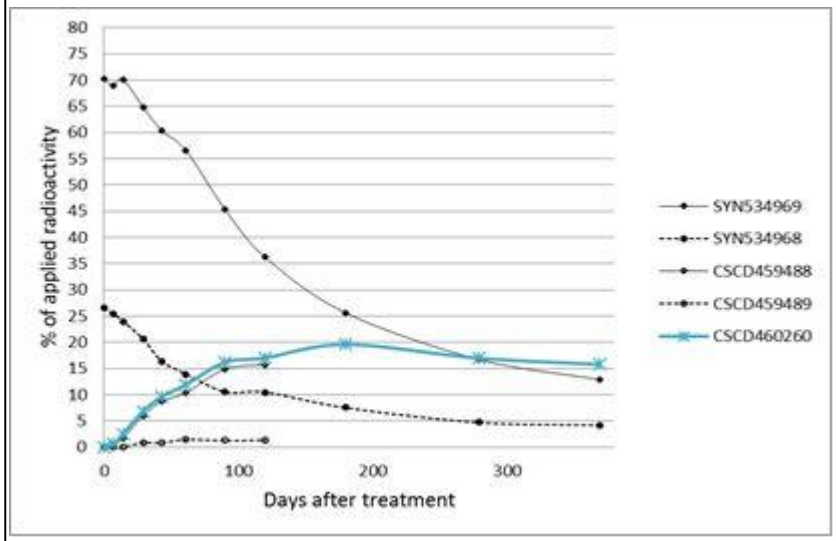
			(CSCD459489) above 5% of applied radioactivity (AR), as this would require a drastic shift in the metabolite formation fraction from the respective parent isomer in the period after 120 days compared to that over 0-120 days. Note that the % of CSCD459489 in CSCD460260 values shown in Figure 1 are conservative as quantification of levels of CSCD459489 was performed by evaluating the retention time range over which the reference standard for this isomer eluted, whether or not a discrete peak was observed. This would lead to an overestimation of radioactivity associated with the CSCD459489 peak, as is evident from comparison of the levels of CSCD459489 in Gartenacker at 120 DAT determined from the HPLC data in Table 2 below with those determined by 2-D TLC in Table 1. *The data presented in Figure 1 show the decline of the parent isomers and formation of the metabolite beyond 120 days. From 120 to 180 days the parent syn isomer declined from 36.3% AR to 25.6% AR (reduction of 35%) and the parent anti isomer declined from 10.5% AR to 7.6% AR (reduction of 28%). This was concurrent with an increase in CSCD460260 of 2.5% AR over the same period. As degradation rates of the syn and anti parent isomers were similar over 120 to 180 days, it is not conceivable that the degradation over this period would have led to an increase in the anti metabolite isomer (CSCD459489) from 1.4% AR at 120 days to >5% AR at 180 days.* *Overall the Applicant considers that assessment of the syn:anti isomer ratio in the samples at 180, 279 and 365 days for the Gartenacker soil would not change the*	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
			conclusion that levels of the anti isomer CSCD459489 formed in soil under laboratory conditions are not expected to exceed 5% AR. ***Figure 1: Degradation of isopyrazam isomers SYN534969 and SYN534968 and formation of the CSCD460260 isomers CSCD459488 and CSCD459489 in Gartenacker soil under aerobic laboratory conditions***  	

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data
			Table 2: Input values for Figure 1 from Marshall (2009). Residues determined by HPLC *(Refer to DAR addendum Table B.8.8 for CSCD460260 values, and Table B.8.11 for SYN534969, SYN534968, CSCD459488 and CSCD459489 values over 0-120 days and refer to Marshall (2009) Table 23b for additional SYN534969 and SYN534968 values over 180 to 369 days)*	

Days after treatment	*SYN534969*	*SYN534968*	*CSCD459488*	*CSCD459489*	*CSCD460260*
0	*70.2*	*26.5*	*0.0*	*0.0*	*0.0*
7	*69.0*	*25.4*	*0.6*	*0.0*	*0.7*
14	*70.2*	*24.0*	*1.7*	*0.1*	*2.6*
29	*64.9*	*20.7*	*6.0*	*0.9*	*6.9*
43	*60.4*	*16.4*	*8.8*	*0.9*	*9.7*
61	*56.6*	*14.0*	*10.4*	*1.5*	*12.0*
90	*45.4*	*10.6*	*14.9*	*1.3*	*16.2*
120	*36.3*	*10.5*	*15.7*	*1.41*	*17.1*
180	*25.6*	*7.6*	*Separate isomers not*		*19.6*

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

279	*16.8*	*4.8*	*assessed*		*17.0*
369	*12.9*	*4.3*			*15.8*

The results from re-assessment of the levels of CSCD459488 and CSCD459489 in the route and rate study (Marshall, 2009) are consistent with all the laboratory and field data provided and show that the metabolite anti-isomer is formed in much lower quantities than would be predicted from the ratio of the parent syn and anti isomers. Furthermore there is no evidence considering all of the available soil data that levels of CSCD459489 will exceed any of the criteria from 1107/2009 which trigger further assessment of its ability to contaminate groundwater.

UK RMS conclusion (2017): in light of the additional information provided by the Applicant the UK RMS considers that analysing the data up to to 120 days was sufficient to demonstrate that CSCD459489 is not formed at levels that warrant a groundwater assessment. The RMS accepts that samples from 180 DAT to 369 DAT were not reassessed as it is extremely unlikely that levels of CSCD459489 would increase from 1.41 %; which is an overestimation based on integration at the approximate time of elution, not necessarily when a discrete peak was observed at 180 DAT, to > 5 % by 369 DAT, as this would require a large increase in its formation. The microbial viability of the

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data
			Gartenacker soil was within the range recommended by OECD 307; microbial biomass > 1 % of total organic carbon for the duration of the study (Table below, Table 5 in the Marshall, 2009 study) and therefore the RMS would not anticipate a significant change in the degradative behaviour of this soil based on the data over 120 days. We would only anticipate a significant departure from behaviour seen for the first 120 days if a microbial viability declined below the level recommended by OECD 307.	

Soil Name	Microbial Biomass[1] Carbon (mg/kg soil)				Microbial Biomass as % of Soil Organic Carbon[2]			
	Before Application	134 DAT	183 DAT	End of Incubation[3]	Before Application	134 DAT	183 DAT	End of Incubation[3]
18 Acres	610.1	-	-	309.5	2.39	-	-	1.44
Pappelacker	533.4	-	-	359.1	3.68	-	-	2.48
Gartenacker	671.9	497.6	460.0	380.7	2.63	2.04	1.84	1.72
Marsillargues	482.4	-	-	398.3	3.62	-	-	2.99

1. Microbial biomass determined by the respiratory response following addition of glucose to the soil, based on the method of Anderson and Domsch (Reference 7).
2. Organic matter was calculated by applying the Van Bemmelen Factor of 1.724 to the total organic carbon content.
3. End of incubation biomass samples taken 169 DAT for 18 Acres and Pappelacker soils, 128 DAT for Marsillargues soil and 369 DAT for Gartenacker soil.

The RMS concludes that the reassesment of the Marshall (2009) study

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
			contributes to the weight of evidence that CSCD459489 is not formed at 5 % AR and therefore does not warrant a groundwater assessment. Addressed	
4(5)	Confirmatory data assessment. Marshall S, 2009. Reassessment of the route study submitted in the original dossier. (Appendix 2) p 99 - 103. TABLE A2-9	EFSA (2017): In appendix 2 data are provided also for data points previous to 120 days. From this data it is seen that ratio of *anti*/*syn* (%) isomers for metabolite CSCD460260 range from 6 % to 22 %. With an average of 13.2 % (*anti/syn* CSCD460260). The information from all available data would need to be considered in the assessment (not only the one from 120 days). Also the results for	UK RMS (2017): agrees with EFSA that the maximum % of CSCD460260 was reached at Day 180; 19.6 %; (mean of 20 % and 19.2 % reported in the original DAR (2010); Volume 3, Annex B.8, Table 8.8); therefore the RMS requested justification from the Applicant why the data after 120 days was not re-assessed? Additionally the RMS requested the Applicant to specify where the 22 % mentioned by EFSA originates from? ***Applicant response*** *As explained in 4(4), the ratio of the syn and anti isomers was examined in all 4 soils used in this laboratory study. For 3 of the 4 soils, the incubation period was 0-120 days and levels of CSCD460260 were highest at final time point. For consistency, the ratios of the syn and anti isomers of CSCD460260 (CSCD459488 and CSCD459489) were examined in 120 day samples for all 4 soils by 2-D TLC (assessment provided in the original DAR). This assessment of the 120 DAT samples by 2-D TLC (see Table 3, below) showed that the metabolite anti-isomer CSCD459489 only accounted for a maximum of 11% of the combined isomers in CSCD460260. In contrast the analysis of the parent*	Addressed.

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data
		samples corresponding to 180, 269 and 369 days should be provided (since the ones with higher amount of metabolite are the ones probably more relevant in relation to the issue of the relative levels of the isomers).	*isomers by HPLC showed that the proportion of the anti-isomer as a percentage of the combined isomers (i.e. isopyrazam) fell slightly from 27% at application to between 21 and 25% after 120 days.* ***Table 3: Proportions of CSCD460260 isomers (determined by TLC analysis) compared to the proportions of the isopyrazam isomers (determined by HPLC) in 4 laboratory soils at 120 days after treatment*** *(refer to Table B.8.10 in the DAR addendum for metabolite isomer values. SYN534969 and SYN534968 values as shown in Table 1 above)* *Isopyrazam is comprised of syn:anti isomers SYN534969:SYN534968 CSCD460260 is comprised of syn:anti isomers CSCD459488:CSCD459489*	

Soil	*SYN534969 [% AR]*	*SYN534968 [% AR]*	*SYN534968 as % of total isomers [as % isopyrazam]*	*CSCD459488 [% AR[a]]*	*CSCD459489 [% AR[a]]*	*CSCD459489 as % of total isomers [as % CSCD460260]*
18 Acres	*75.1*	*25.0*	*25.0*	*2.5*	*0.3*	*10.7*
Pappelacker	*76.3*	*23.7*	*23.7*	*5.0*	*0.1*	*2.0*

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

Marsillargues	*79.3*	*20.8*	*20.8*	*13.7*	*<LOD*	*<0.7*
Gartenacker	*36.3*	*10.5*	*22.5*	*12.6*	*<LOD*	*<0.8*

[a] Analysed by 2-D TLC. LOD 0.1% AR

For Gartenacker soil, in which the greatest level of degradation of isopyrazam was observed, the ratio of the parent isomers was determined at all sample points up to 365 days. During the course of this study reported in Marshall (2009) the Gartenacker soil samples from 0 to 120 DAT has been analysed by an HPLC method that separated the CSCD460260 isomers. As levels of CSCD459489 in the 120 DAT samples had been shown by 2-D TLC to be negligible, the levels of CSCD459489 in the Gartenacker samples were not quantified by HPLC at the time.

To provide information to support the Confirmatory Data request, the ratio of the CSCD460260 isomers was determined over 0 to 120 days, which is the normal duration for OECD 307 rate and pathway studies, from the available HPLC data from the study by Marshall (2009). The results are shown in Table 4 below. These % AR values are the average values for the two sample replicates using HPLC method T012740-05H from TABLE A2-9 in the addendum to the DAR. Note that the % of CSCD459489 in CSCD460260 values determined from HPLC data shown Table 4 are conservative as

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data
			quantification of levels of CSCD459489 was performed by evaluating the retention time range over which the reference standard for this isomer eluted, whether or not a discrete peak was observed. This would lead to an overestimation of radioactivity associated with the CSCD459489 peak. *The ratio of the parent isomers generally remained constant throughout the incubation, with the proportion of the anti-isomer (SYN534968) remaining at about 23% of the total. In contrast the metabolite anti-isomer CSCD549489 was formed at a significantly lower level, with the proportion during the majority of the period (up to 120 days) ranging from 8 to 13% of the total isomers.* *It is not clear to the Applicant how EFSA derived a maximum % for CSCD459489 in CSCD460260 of 22%.* ***Table 4: Gartenacker soil: Proportions of isopyrazam isomers over 0-365 days and CSCD460260 isomers over 0 at 120 days. All values determined by HPLC (refer to Table A2-9 in the DAR addendum)*** *Days after treatment* | *SYN534969 [% AR]* | *SYN534968 [% AR]* | *SYN534968 as % of total isomers (isopyrazam)* | *CSCD459488 [% AR[a]]* | *CSCD459489 [% AR[a]]* | *CSCD459489 as % of total isomers*	

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

							(CSCD460260)
0	*70.2*	*26.5*	*27.4*	*0.0*	*0.0*		*-*
7	*69*	*25.4*	*26.9*	*0.6*	*0.0*		*-*
14	*70.2*	*24*	*25.5*	*1.7*	*0.1*		*5.6*
29	*64.9*	*20.6*	*24.1*	*6.0*	*0.9*		*13.0*
43	*60.4*	*16.4*	*21.4*	*8.8*	*0.9*		*9.3*
61	*56.6*	*14*	*19.8*	*10.4*	*1.5*		*12.6*
90	*45.4*	*10.6*	*18.9*	*14.9*	*1.3*		*8.0*
120	*36.25*	*10.5*	*22.5*	*15.7*	*1.41*		*8.2*
180	*25.6*	*7.55*	*22.8*	*average 0-120 days*			*9.45*
279	*16.75*	*4.75*	*22.1*				
369	*12.9*	*4.25*	*24.8*				

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

	average 0-120 days	*23.3*	
	average 0-369 days	*23.3*	
	average 180-369 days	*23.2*	

The ratio of the isopyrazam syn and anti isomers in the soil over the period 120 to 365 days was relatively constant. Considering that there is no indication that there was proportionally more degradation of the parent anti isomer beyond 120 days, i.e. no enrichment of the syn isomer in the remaining isopyrazam, it is not conceivable that that the proportion of the anti isomer CSCD459489 in metabolite CSCD460260 would have increased significantly over the incubation period 120 to 365 days.

Overall the Applicant considers that information provided in the DAR addendum on the syn:anti isomer ratios of isopyrazam and metabolite CSCD460260 in the laboratory soil samples support the conclusion that the anti isomer CSCD459489 is formed in soil in a much lower proportion of CSCD460260 than that of the isopyrazam anti isomer in the parent material and that levels of CSCD459489 are not expected to exceed 5% AR in laboratory soil.

Route and rate of degradation in soil (B.8.1)				
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			The results from re-assessment of proportion of the metabolite anti-isomer CSCD459489 in the route and rate study (Marshall, 2009) are consistent with all the laboratory and field data provided and show that the proportion of the metabolite anti-isomer in soil is much lower than would be predicted from the ratio of the parent syn and anti isomers. Furthermore there is no evidence considering all of the available soil data that levels of CSCD459489 will exceed any of the criteria from 1107/2009 which trigger further assessment of its ability to contaminate groundwater. **UK RMS conclusion (2017):** the RMS considers that the ratio of the metabolite isomers is very unlikely to increase in favour of the *anti* isomer (CSCD459489) after 120 days. Over the 120 days that were measured the ratio of the anti:syn isomers remained at between 5.6 % to 13 % so even if the maximum proportion (13 %) of CSCD459489 formed the ratio, when the total metabolite isomers were at there greatest (19.6 %) then only 2.55 % AR would be CSCD459489. The RMS concludes that this study contributes to the weight of evidence that CSCD459489 is not formed at 5 % AR and therefore does not warrant a groundwater assessment. Additionally the RMS considers that this study demonstrates that a much lower proportion of the –*anti* isomer (CSCD489489) contributes to the metabolite isomeric ratio (e.g; metabolite isomeric ratio (syn:anti) ~ 90:10), compared to the parent isomeric ratio; which has a greater	

Route and rate of degradation in soil (B.8.1)				
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			proportion of the *-anti* isomer, e.g; parent isomeric ratio (syn:anti) ~ 77:23 (Table 4, above). Addressed	
4(6)	Addendum (Fate) B.8.1.1 and B.8.1.2 Degradation of Isopyrazam in Five European Soils (Wyeth & Hand, 2014a)	Applicant (2017): The RMS noted that compared to the original study, relative reduction in the maximum level of CSCD459489 (0.08% of applied parent vs 1.9% AR) was apparently greater than reduction in the relative amount of the parent *anti* isomer applied (isopyrazam *syn:anti* 80:20 vs 73.4:26.6). The difference in *syn:anti* ratio of applied parent was not expected to affect the comparison of the	UK RMS (2017): proposes to add the following text; "*the Applicant has highlighted that the syn:anti isomer of the parent was not expected to affect the comparison of the formation of the -syn and -anti metabolites. It should be pointed out that the 80:20 ratio is closer to the current specification for isopyrazam (85:15 to 89:11). In addition quantification of CSCD459489 in the original Marshall (2009) study was overly conservative so the 24 times difference if likely to be lower. The LOQ of both isomers is 0.05 µg/kg which equates to 0.013 % of applied isopyrazam".* Addressed	Addressed. The text was added.

Route and rate of degradation in soil (B.8.1)				
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		formation of the *syn* and *anti* metabolites from the respective parent isomers in the new study. Quantrification of CSCD45989 in the orignal study was very conservative and 1.9% is an over-estimate. The IZM *syn:anti* ratio of 80:20 is closer to the current specification (range 85:15 to 89:11) than 70:30. The purpose of the study was to compare the formation of the *syn* and *anti* metabolites from the respective parent isomers. The LOQ for both isomers was 0.05 µg/kg (which		

Route and rate of degradation in soil (B.8.1)				
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		equates to 0.013% of applied IZM, based on the average initial concentration of 356.7 µg a.s./kg) and is considered to be sufficiently sensitive to examine the formation of both the *syn* and *anti* metabolites under these laboratory soil conditions. Furthermore, the discrepancy between the levels of CSCD459489 in this study and the Marshall (2009) is likely to be significantly less than the 24x indicated by the RMS. This is because the reported 1.9% formation in the Marshall study is based on a quantification		

Route and rate of degradation in soil (B.8.1)				
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		of radioactivity within the retention time range for the CSCD459489 even where no discrete peak was observed. As acknowledged by the RMS, this value is likely to be a significant over-estimate for the purposes of conservatism.		
4(7)	Addendum (Fate) B.8.1.1 and B.8.1.2 Degradation of Isopyrazam in Five European Soils (Wyeth &	Applicant (2017): The RMS noted that the soil physico-chemical properties were not re-analysed in the field soil samples collected for this new study. Repeat assessment of these properties was not considered to be critical to the objective of the study	UK RMS (2017): considers that the soil properties would have changed dependent on the local environment e.g., addition of organic matter, crops grown etc, which have impacted microbial activity and subsequent degradation rates. However as pointed out on page 17 of the Addenda the RMS considers this deviation from a typical OECD 307 study did not invalidate the study. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	Hand, 2014a)	which was to compare relative formation of CSCD459488 and CSCD459489 from isopyrazam under identical laboratory conditions. The five field soil samples used for this study, were collected in 2013 from locations where some of the isopyrazam EU field dissipation trials had been conducted. The original soil characterisations for soils sampled in 2007 were done to GLP and included in the reports reviewed in the DAR. In the intervening 6 years, these fields had continued		

Route and rate of degradation in soil (B.8.1)				
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		to be managed for agricultural use and extensive changes to the soil properties were not expected. Given that there was no intention to draw correlations between degradation behaviour and physico-chemical properties, further characterisation was not considered to be essential. The purpose of the study was to compare the formation of CSCD459488 and CSCD459489 from isopyrazam, side by side under identical conditions, in five different soils.		

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(8)	Addendum (Fate) B.8.1.1 and B.8.1.2 Degradation of Isopyrazam in Five European Soils (Wyeth & Hand, 2014a)	Applicant (2017): The RMS noted that microbial activity was not measured in the field soil samples collected for this new study. This assessment was not considered to be critical for assessment of the study findings in this case. The field soils collected for this study were treated with isopyrazam only 3 weeks after sampling, therefore it is unlikely that the microbial biomass would have depleted over such a short time. The levels of appied	UK RMS (2017): the RMS accepts the Applicants' justification for not measuring microbial activity and considers that this deviation from a typical OECD 307 study did not invalidate the study, as highlighted in the study summary. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		isopyrazam in the test soils declined over the study period. As isopyrazam is stable to hydrolysis at pH 5-9, the observed decline in levels of isopyrazam is considered to have been microbially mediated and therefore evidence that the soils were microbially active. As the RMS has pointed out, the isopyrazam SFO DT_{50} values obtained from the study data are within the range for aerobic soil degradation reported in the EFSA Conclusion (2012).		

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(9)	Addendum (Fate) B.8.1.1 and B.8.1.2 Degradation of Isopyrazam in Five European Soils (Wyeth & Hand, 2014a)	Applicant (2017): The RMS noted that soil moisture during the test was not maintained at between pF2.5 – pF2 for some of the soils. The formation of CSCD459488 and CSCD459489 in soil was compared side by side, so any effects of soil moisture on degradation are expected to have impacted formation of both metabolite isomers similarly. The observation that the ratio of CSCD459488 to CSCD45989 formed in soil was close to 100:0 was consistent for all test soils	UK RMS (2017): agrees that the deviation of the soil moisture from pF2 did not invalidate the study, as detailed on page 18. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(10)	Addendum (Fate) B.8.1.1 and B.8.1.2 Degradation of Isopyrazam in Five European Soils (Wyeth & Hand, 2014a)	Applicant (2017): The RMS noted that methanol was present at 6.5 % in the application solution. However, once added to the test soils the amount of methanol was < 0.2% of the soil mass. The addition of such small amount of additional methanol is not expected to significantly affect the microbial community. If there were any effects of the methanol on the microbial degradation of IZM in soil, these would have impacted the formation of CSCD459488 and CSCD459489 similarly.	UK RMS (2017): agrees that the presence of methanol in the soil did not invalidate the results of the study. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		It is of note that, methanol occurs naturally in soil (formed from degradation of plant material).		
4(11)	Addendum (Fate) B.8.1.1 and B.8.1.2 Degradation of Isopyrazam in Five European Soils (Wyeth & Hand, 2014a)	Applicant (2017): The RMS noted that one replicate treated soil sample was analysed at some time points. Two replicates were not included at every time point for all soils done to constraints on incubation space running the five test systems concurrently. However each soil was sampled on 4 to 5 occasions up to 56 DAT	UK RMS (2017): accepts the Applicants' justification for deviating from the 5 time points required in the FOCUS kinetics guidance (2009) and as detailed on page 18, the RMS considered the data valid and had used the residues to estimate DT_{50} values. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		and consistently levels of CSCD459489 were extremely low and the ratio of CSCD459488 to CSCD45989 was close to 100:0.		

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(12)	Confirmatory data assessment. Degradation of isopyrazam in five EU soils. Wyeth and Hand 2014a p16 and p17	EFSA (2017): The issues identified by the RMS as drawbacks in this study are agreed. In addition, not being performed under GLP the study may be considered a preliminary investigation that would need proper confirmation with experiments performed under GLP	UK RMS (2017): despite the issues identified the RMS considers that this study is suitable to be used in a 'weight of evidence' approach to demonstrate that the *–anti* isomer of the metabolite (CSCD459489) was formed in low amounts and does not warrant a groundwater exposure assessment. The RMS does not consider that an OECD 307 to GLP is necessary when the 'weight of evidence' is considered. Addressed	EFSA view does not concur with that of the RMS. Our consideration remains that the study may be considered a preliminary investigation that according to our understanding of data requirements regulations, would need proper confirmation with experiments performed under GLP. Alternatively, the study might be submitted for publication in a peer reviewed scientific journal, which would make the results challengeable / repeatable by other researchers. This is an issue of transparency / confidence that might be placed in the applicants' investigations.
4(13)	Confirmatory data assessment. Degradation of	EFSA (2017): One of the main drawbacks of the study in relation to the point discussed for the confirmatory data is the short duration to the	UK RMS (2017): acknowledges the short duration of the study and there asked the Applicant to justify why a study run for 56 days was considered sufficient when a large portion of isopyrazam remained. ***Applicant response***	Addressed.

<table>
<tr><th colspan="5">Route and rate of degradation in soil (B.8.1)</th></tr>
<tr><th>No.</th><th>Column 1

Reference to addendum to assessment report</th><th>Column 2

Comments from Member States / applicant / EFSA</th><th>Column 3

Evaluation by rapporteur Member State / response from the applicant</th><th>Column 4

EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data</th></tr>
<tr><td></td><td>isopyrazam in five EU soils. Wyeth and Hand 2014a p16 and p17</td><td>study 56 days in relation to the half-life of the parent (102 – 364 days) in these experiments. Levels of metabolites generated over this initial period of degradation are low and no meaningful conclusion on their proportion can be derived.</td><td>The purpose of the study by Wyeth and Hand (2014a) was to investigate the formation of the metabolite isomers CSCD459488 and CSCD459489 from their respective parent isomers side-by-side in 5 different soils under laboratory conditions.The degradation of isopyrazam and formation of CSCD459488 and CSCD459489 observed in these soils are shown graphically in Figure 2 below. From these graphs it can be seen that the concentrations of CSCD459488 in the treated soils increased significantly, reaching levels equivalent to 5.6 to 35.7 µg/kg on average after 56 days (maximum level 9.78% molar formation of metabolite in Polish soil at 49 DAT). In contrast concentrations of CSCD459489 were generally <LOD (<0.00001 µg/mL in sample extracts) in all 5 soils over the period 0-56 days. The study therefore reached its intended aim of demonstrating that the overall levels of the anti-isomer CSCD459489 formed are much lower proportionally than the theoretical amounts expected if the parent anti-isomer behaved the same as the syn-isomer. A longer incubation time was therefore unnecessary.

Figure 2: Levels of isopyrazam and the metabolites CSCD459488 and CSCD459489 in the soil sample extracts during the laboratory incubation at 20oC in five soils

<table><tr><th>Decline of isopyrazam concentration in the sample extracts during the incubation</th><th>Concentrations of CSCD59488 and CSCD459489 in the sample extracts during the incubation</th></tr></table></td><td></td></tr>
</table>

Route and rate of degradation in soil (B.8.1)				
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			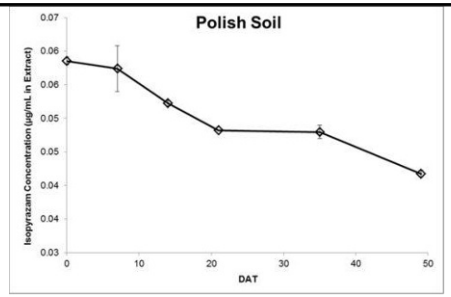 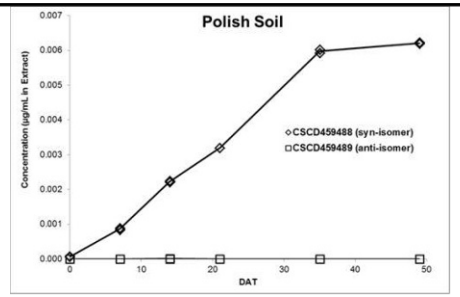	

Route and rate of degradation in soil (B.8.1)				
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			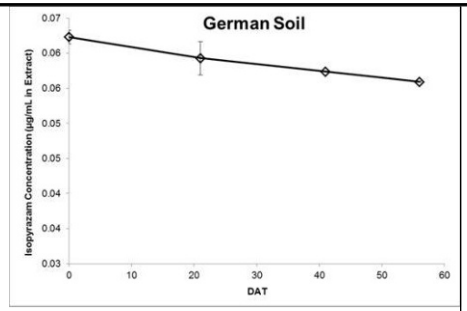 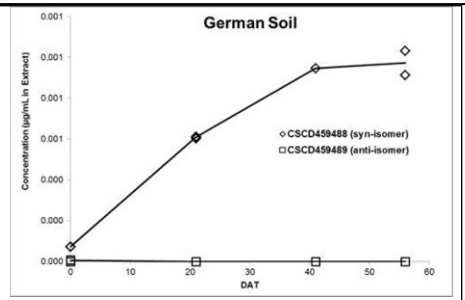	

Route and rate of degradation in soil (B.8.1)				
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			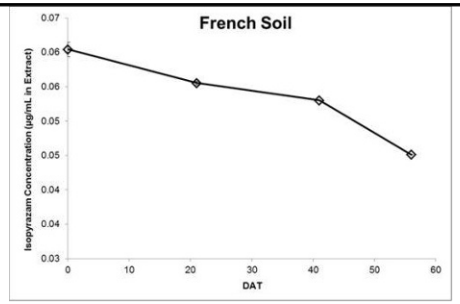 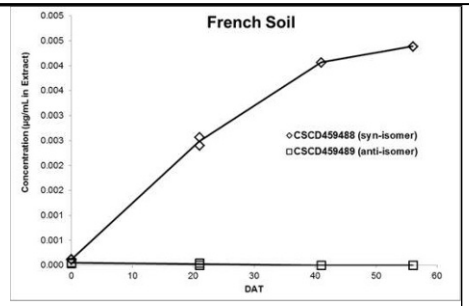	

Route and rate of degradation in soil (B.8.1)				
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			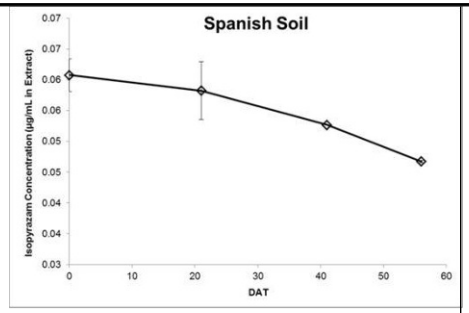 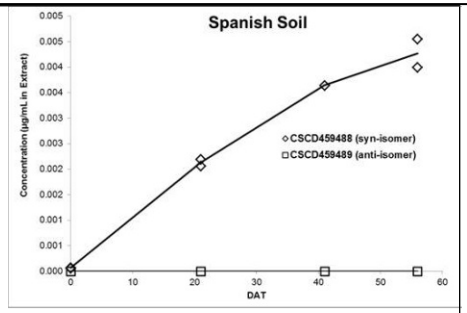	

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			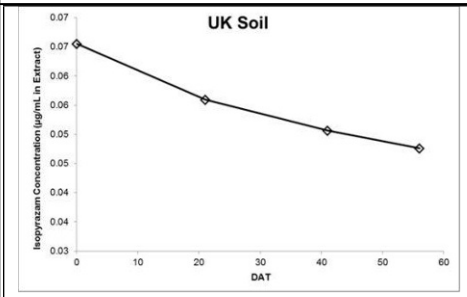 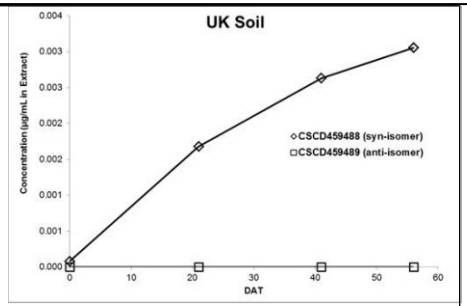 *The Applicant considers that the duration of the study (up to 56 days) was sufficient to demonstrate in 5 additional soils to those used in the regulatory study by Marshall (2009) that levels of CSCD459489 in soil are well below those expected in theory and support the overall findings that the amounts of the anti-isomer CSCD459489 formed in soil are trivial.* *Furthermore there is no evidence considering all of the available soil data that levels of CSCD459489 will exceed any of the criteria from 1107/2009 which trigger further assessment of its ability to contaminate groundwater.*	

Route and rate of degradation in soil (B.8.1)				
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			UK RMS conclusion (2017): the purpose of this study was to demonstrate that the metabolite isomeric ratio differed from the parent isomeric ratio and not to determine the transformation route and or rate of isopyrazam. The RMS considers that the study duration was sufficient to demonstrate that the anti-isomer of the metabolite (CSCD459489) was formed in much lower amounts compared to metabolite -syn isomer (CSCD459488) and to show that the amounts of CSCD459489 formed were lower than theoretically expected from the formation of the parent *anti-* isomer. In addition it is very unlikely that if the study was extended beyond 56 days that the amount of CSCD459489 formed would significantly increase, as demonstrated in the re-assessment of the Marshall (2009) study the maximum amount of CSCD459489 detected was < 1.5 % AR. The RMS therefore considers that this study contributes to the weight of evidence that CSCD459489 is formed at levels < 5 % AR and does not warrant a groundwater modelling assessment. Addressed	
4(14)	Confirmatory data assessment. Degradatio	EFSA (2017): According the study report analytical method GRM006-05A was used in this study (Wyeth and Hand 2014a) to	UK RMS (2017): the fate evaluation received clarification from the chemistry specialist that the LOQ of 0.5 mg/kg would apply to this study as additional validation had not been provided to support the lower LOQ. Therefore the RMS proposes to replace the ratios based on the LOQ of 0.5 µg/kg. As a result the new average ratio of CSCD459488 to CSCD459489 is 86:14, which is an overestimate of the *anti-* metabolite isomer due to the assumption that the	Addressed. The updated LOQ and compound ratios have been added to the amended addendum.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	n of isopyrazam in five EU soils. Wyeth and Hand 2014a p29 Table B.8.14.	analyse metabolites of isopyrazam and its metabolite. For the metabolite CSCD460260 isomers a LOQ = 0.0005 mg /kg is reported (see table A2-2 in p 93). This corresponds to LOQ = 0.5 micro g / kg not to 0.05 micro g / kg as stated in table B.8.14 (p29). Ratios of isomers would need to be recalculated based on the validated LOQ. It is noted that the LOQ = 0.5 micro g/ g for metabolite isomers is the only one reported as validated in the study *GRM006.05A. SYN520453*	residue of 0.0 µg/kg is equivalent to the LOQ of 0.5 µg/kg, when it is likely to be much lower. Addressed	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		- Analytical Method for the Determination of Residues of SYN520453 as SYN534968 and SYN534969 and the Metabolites CSCD459489 and CSCD459488 in Soil. Final Determination by LC-MS/MS S.L. Hargreaves. Additional *ad hoc* validation data seem to have been provided in the context of Garrigue 2015 reanalysis of field dissipation studies but this is not transferable to the Wyeth and Hand 2014a study since, as specified in Garrigue 2015, to lower the LOQ for *anti* metabolite requires an updated		

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		procedure (e.g. increased injection volume) that was clearly not available and validated in 2014.		
4(15)	Confirmatory data assessment. Degradation of isopyrazam in five EU soils. Wyeth and Hand 2014a p29 Table B.8.14.	EFSA (2017): Table B.8.14 seems to be derived from table 4 in the study report. In the study report the results are given as micro g/mL (soil?). In the table it seems the values have been transformed to micro g/kg dry weight. How has this transformation being done? e.g. how does 6.22 micro g/L become 35.6 micro g/kg dry weight?	UK RMS (2017): as detailed on page 23 the RMS requested that the Applicant convert the analyte concentrations from µg/L to µg/kg of soil to enable comparison with the LOQ given in mg/kg. The Applicant supplied the new values and provided an explanation of the values used to convert the concentrations. Briefly for each replicate the total mass of analyte recovered (µg) was calculated by multiplying the concentration of the analyte (µg/mL) by the total volume of the extract (mL). The total mass of analyte recovered (µg) was then divided by the total mass of soil extracted per replicate sample (kg) to determine the concentration of the analyte (µg/kg). The concentration of the analyte was then converted from a wet weight basis to the equivalent concentration based on dry weight, considering the moisture content of the soil.	Addressed. The amended addendum has included the clarifications discussed in column 3.

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data
		In addition if the values are directly measured as micro g/mL the LOQ should also be expressed in these units. If a LOQ = 0.5 micro g /L was assumed, then most of the values of the metabolite *syn* isomer (the major one) would already be below of the LOQ and the study would not provide any information on the ratio of isomers of the metabolite.	The RMS proposes to include details of how the conversion was conducted using the summary below which was supplied by the Applicant; Calculation Method 1. The reported concentrations are in µg/mL in the analyzed extract. The total volume of each extract was 50 mL Therefore, $$Total\ mass\ analyte\ recovered\ (\mu g) = \frac{\mu g}{ml}\ x\ 50\ mL$$ 2. The total mass of soil extracted per replicate sample was 10 g (wet weight), i.e. 0.01 kg. Therefore, $$\frac{\mu g}{kg}\ (wet\ weight) = \frac{Total\ mass\ analyte\ recovered\ (\mu g)}{0.01\ kg}$$ 3. The equivalent dry weight concentration was calculated as below.	

Soil	Moisture content during incubation (g water/100g	Conversion factor for dry to wet weight.	Mass (g dry weight) equivalent to 10 g wet	Mass dry weight analysed (kg)

Route and rate of degradation in soil (B.8.1)

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	dry weight soil)		weight $\left(\frac{10\ g}{Conversion}\right.$	
Polish Soil	15	1.15	8.70	0.00870
German Soil	14	1.14	8.77	0.00877
French Soil	19	1.19	8.40	0.00840
Spanish Soil	17	1.17	8.55	0.00855
UK Soil	21	1.21	8.26	0.00826

$$\frac{\mu g}{kg}\,(dry\ weight) = \frac{Total\ mass\ analyte\ recovered\ (\mu g)}{Mass\ dry\ weight\ analysed\ (kg) - See\ Table}$$

Addressed

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(16)	Addendum (Fate) B.8.1.1 and B.8.1.2 Comparative Degradation of Isopyrazam Metabolites CSCD459488 and CSCD459489 in Five European Soils (Wyeth & Hand, 2014b)	Applicant (2017): The RMS noted that one replicate treated soil sample was analysed at some time points and that the total number of sample points was 4 or 5 for each soil. The Applicant considers that the data obtained were sufficient to assess the relative degradation rates of CSCD459488 and CSCD459489 in soil and agrees with the RMS's conclusion that collectively the data from this study show that the minor metabolite isomer, CSCD459489 degrades faster than the *syn* isomer, CSCD459488,	UK RMS (2017): calculated DegT50 values despite the reduced number of time points and stated on page 31 that CSCD459489 degraded faster than CSCD459488. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		under identical test conditions. The purpose of the study was to compare the soil degradation rates for the two metabolite isomers and to assess if differential degradation could in part explain the observation that the ratio of CSCD459488 to CSCD459489 formed in soil is not the same as the *syn:anti* isomer ratio of the parent isopyrazam. The soil degradation rates observed in this study for CSCD459488 were at the quicker end of the range reported in the EFSA Conclusion (2012).		

Route and rate of degradation in soil (B.8.1)				
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		However, under identical test conditions and consistently in five different soils, the minor metabolite isomer, CSCD459489 degraded faster than the *syn* isomer, CSCD459488.		
4(17)	Confirmatory data assessment. Comparative degradation of isomers of soil metabolite CSCD460260 of	EFSA (2017): Main drawbacks of the study are: - Not performed under GLP - Only one replicate for most of the samples. - Insufficient number of data points for deriving reliable kinetic parameters for all soils but the Polish one. Nevertheless, degradation	UK RMS (2017): this study was designed to contribute to the 'weight of evidence' that CSCD459489 does not warrant a groundwater assessment. This study demonstrated that CSCD459489 degraded faster than CSCD459488, which is evident in the isomeric ratio of the metabolite isomers. In addition compared to the proportion of the CSCD459489 (*–anti*) metabolite in the ratio of the parent isomers, the proportion of the *–anti* isomer in the metabolite isomeric ratio is much lower. Furthermore the greater amount of CSCD459488 is not a consequence of a high leaching potential of CSCD459489 as the Lewis study showed the Kfoc values of the metabolite isomers were only moderately mobile (Kfoc range; 152 - 214). The RMS therefore concludes that the issues identified with this study are not sufficient to exclude it from the 'weight of evidence'.	Addressed.

Route and rate of degradation in soil (B.8.1)				
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	isopyrazam. Wyeth and Hand 2014b.	of both isomers in five soils was preliminary investigated giving a plausible indication that the degradation of *anti* isomer of metabolite CSCD460260 is faster than degradation of *syn* isomer. Half-lives obtained in this investigation could be used in a preliminary refined estimation of PEC GW for both isomers (as alternative to the default of 1000d). Half-life values could be later confirmed by a proper GLP study in three soils. Also in the case of the parent isopyrazam it seems that degradation of	Addressed	

Route and rate of degradation in soil (B.8.1)				
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		anti isomer may be faster than *syn* isomer according results of study Marshall S, 2009 but the difference seems on the rates seems to be less important than for the metabolite.		
4(18)	Addendum (Fate) B.8.1.2.2. Field studies	Applicant (2017): The RMS noted (page 48) that the isomeric ratio of the isopyrazam applied in the Italy (Zeiger, 2009e) and Poland (Zeiger, 2009a) studies was not specified. In all six field trials initiated in 2007, the same batch of isopyrazam formulation A15149AC was applied. This was batch reference J8045/13, containing isopyrazam	UK RMS (2017): was not privy to this information, when compiling the Addenda and the batch number is only detailed in 2 of the 6 studies. The RMS therefore proposes to add the additional text; "*The Applicant has informed the RMS that the same batch of isopyrazam formulation A15149AC was applied in all of the field studies, which had a syn:anti ratio of 72:28 w/w*". Addressed	Addressed The amended addendum has included the clarification discussed in column 3.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		with a *syn:anti* isomer ratio of 72:28 w/w. The batch number was stated in the Zeiger (2009[e]) and (2009a) study reports.		
4(19)	Confirmatory data assessment. B.8.1.2.2. Field studies. Reassessment of chromatograms from EU field dissipation trials to determine levels of CSCD45948	EFSA (2017): Only selected samples on the 0-10 cm horizon in the field dissipation trials (Simmon 2009, Zeiger 2009a,b,c,d,e) were considered (as reported by the RMS and also in the study report). Since both the parent isopyrazam and the metabolite CSCD460260 have the potential for leaching is doubtful the upper layer of field dissipation studies is	UK RMS (2017): acknowledges the comment from EFSA regarding the detections of CSCD459488 below 0 - 10 cm at a maximum of 0.0031 mg/kg (3.1 µg/kg) which is within the range of residues detected in the 0-10 cm horizon. The conclusions for the horizons below 10 cm for each individual study report are included below; **Spain**: No measurable residues of CSCD459488 were determined below the 0-10 cm soil horizons at any analysis interval except for an isolated residue of 0.0008 mg/kg dry soil in the 10-20 cm soil horizon at 370 DAA. **France**: Residues of CSCD459488 were below the LOQ in the 10-20 cm soil horizon at 14 and 28 DAA. Residues then increased from 0.0010 mg/kg dry soil at 62 DAA to a maximum of 0.0031 mg/kg dry soil at 357 DAA. No measurable residues of CSCD459488 were determined below the 10-20 cm soil horizons, at any analysis interval.	Addressed.

Route and rate of degradation in soil (B.8.1)				
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	9. Garrigue 2015a P 48.	sufficient to capture the levels of metabolites formed. In addition, only two samples were selected not necessarily being the ones that will capture highest residues of *anti* metabolite.	**UK**: Residues of CSCD459488 were 0.0016 mg/kg dry soil in the 10-20 cm soil horizon at 14 DAA. These residues then decreased to below the LOQ between 28 DAA to 180 DAA and were at 0.0018 mg/kg dry soil at 366. **Italy**: No measurable residues of CSCD459488 were determined below the 0-10 cm soil horizon at any analysis interval except for an isolated residue at 0.0008 mg/kg dry soil in the 10-20 cm soil horizon at 369 DAA and 0.0022 mg/kg dry soil in the 20-30 cm soil horizon at 369 DAA. **Poland**: No measurable residues of CSCD459488 (LOQ was 0.0005 mg/kg) were determined below the 0-10 cm soil horizon. **Germany**: No measurable residues of CSCD459488 were determined below the 0-10 cm soil horizon at any analysis interval except for isolated residues of 0.0018 and 0.0016 mg/kg dry soil at 355 and 553 DAA in the 10-20 cm soil horizon. The RMS therefore requested justification from the Applicant why residues below 10 cm were not examined. ***Applicant response*** *The original field study data showed that in the majority of cases levels of the syn metabolite isomer (CSCD459488) in samples from below the 0-10 cm horizon were <LOQ (<0.0005 mg/kg). As the analytical method LOQ for CSCD459489 was also 0.0005 mg/kg*	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
			and levels of this metabolite isomer were shown in the laboratory studies to be very much lower than those of CSCD459488, it was considered very likely that the concentrations of CSCD459489 in samples from 10-30 cm horizon would be too low to quantify. This is why the residues below 10 cm were not reanalysed. *This approach is also justified by the expectation that the anti-metabolite isomer (CSCD459489) is not more mobile in soil than the syn metabolite isomer (CSCD459488). This prediction is based on the available information to compare the mobility of CSCD459488 and CSCD459489 in soil, Soil sorption coefficients for the two metabolite isomers are similar (CSCD459488 K_{FOC} = 124 (arithmetic mean EFSA, 2012) and CSCD459489 K_{FOC} = 193 (arithmetic mean, Lewis, 2014) and the data from Wyeth & Hand (2014b, DAR addendum, page 31) showing that CSCD459489 degrades faster in soil than CSCD459488 under identical aerobic laboratory conditions.* *The rationale for this approach to assess the residues of CSCD459489 in the 0-10 cm horizon is supported by the findings of the re-assessment of the metabolite isomers in field soil. Information on the levels of CSCD459488 and CSCD459489 form the six 2007 field trials is summarised in Tables 5 to 10 below. In these trials isopyrazam with a nominal syn:anti ratio of 72:28 was applied in a single application at a nominal rate of 200 g a.s./ha. The maximum residue of CSCD459488 observed below 10 cm was 0.0031 mg/kg in the 357 days-after-application sample in the trial in France 2007 (Table 6). Both the assessment of the original chromatogram for the 0-10 cm sample at this time point and the reanalysis of this sample indicated that the ratio of CSCD459488 to*	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
			CSCD459489 was 99:1 (Table 6 below and DAR addendum Table B.8.22). The corresponding calculated concentration of CSCD459489 in this 10-20 cm sample is 0.00003 mg/kg, which is below the LOQ for the analytical method of the original study (0.0005 mg/kg) and below the revised analytical method used for re-analysis of the samples for CSCD459489 (Garrigue (2015) LOQ 0.00005 mg/kg). *It should be noted that **all** the available chromatograms for samples for the 0-10 cm horizon were considered in the first part of the re-assessment of the field soil samples for residues of CSCD459489. Two samples were selected from each of the six 2007 field soil trials for re-analysis to confirm the assessment based on the original chromatograms. The assessment of the residues of CSCD459489 and the ratio of CSCD459488 to CSCD459489 in field soil samples was done in two steps; step 1 – examination of all the original study chromatograms and quantification of CSCD459489, based on the reported concentrations of CSCD459488 in the same analyses (Braid & Warinton, 2015) and step 2 – re-analysis of selected samples to confirm the assessment based on the original study chromatograms (Garrigue, 2015).* *At step 1 it was considered that reliable estimation of CSCD459489 concentrations from the original chromatograms could be made where peak heights were >3x base line noise (BLN). Therefore concentrations of CSCD459489 and the metabolite syn:anti isomer ratio were not reported in those cases where CSCD459489 was not detectable or levels were <3x BLN (designated "NQ" in Tables 5 to 10 below). Step 2 involved reanalysis of two samples from each of the 6 trials to confirm the findings at step 1. The first sample*	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
			was selected by considering the first time point when residues of CSCD458489 were expected to be quantifiable and the last sample. The intention was to take two samples with a relatively wide time span to check for a change in the metabolite isomer ratio with time. *The summary information in Tables 5 to 10 below has been compiled for this response to check for the highest residues of CSCD459489 in the field soil samples, considering all sample points and residues below 10 cm. This assessment shows that the maximum total residues of CSCD459489 (based on the concentration of CSCD459488 in 0-30 cm soil horizon and the measured ratio of CSCD459488 to CSCD459489 in the field soils) range from 0.000013 mg/kg to 0.000036 mg/kg and equate to 0.029% to 0.104% of the maximum concentration of parent (% molar formation of metabolite).* *Overall the field soil data are consistent with the laboratory data and show that levels of the metabolite anti isomer CSCD459489 formed in soil are very low and below the original study analytical method LOQ of 0.0005 mg/kg (equivalent to 0.17% to 0.37% molar formation fraction of CSCD459489, DAR addendum Table B.8.20) in all soils and at all time points. There is no evidence considering all of the available soil data that levels of CSCD459489 will exceed any of the criteria from 1107/2009 which trigger further assessment of its ability to contaminate groundwater.* ***Table 5: Spain 2007 – Residues of CSCD459488 and CSCD459489 (rate 200 g a.s./ha, Reference IIA 7.3.1/09)***	

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

	Data in original study report (Zeiger, 2009b)			*Refer to DAR addendum Table B.8.22*		
Days after Last Application (DALA)	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*Total CSCD459488 (mg kg^{-1} dry weight)[a]*	*CSCD459488:CSCE459489[b] based on original chromatograms*	*CSCD459488:CSCE459489[b] from re-analysis*	*Max. calculated level of CSCD459489 (mg kg^{-1} dry weight)[c] % molar formation[d] in brackets*
Horizon	*0-10 cm*	*10-20 cm*	*0-30 cm*			
0	*<0.0005*	*NA*	*<0.0005*	*NQ*	*-*	
14	*<0.0005*	*<0.0005*	*<0.0005*	*NQ*	*-*	
27	*<0.0005*	*<0.0005*	*<0.0005*	*NQ*	*-*	
61	*0.0010*	*<0.0005*	*0.00042*	*NQ*	*-*	
94	*0.0019*	*<0.0005*	*0.00072*	*97:3*	*97:3*	
119	*0.0028*	*<0.0005*	*0.00102*	*98:2*	*-*	
180	*0.0017*	*<0.0005*	*0.00065*	*97:3*	*97:3*	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

370	*0.0025*	*0.0008*	***0.00118***	*NQ*	*-*	*0.000036 (0.069%)*

[a] No residues >LOD (>0.0005 mg/kg) in 20-30 cm horizon. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is <LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + (0.5 x 0.0005) mg/kg + 0 mg/kg] ÷ 3. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is >LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + 10-20 cm residue mg/kg + (0.5 x 0.0005) mg/kg]/3

[b] For comparison the nominal syn:anti ratio of the parent isomers was 72:28

[c] CSCD459489 residue calculated based on CSCD459488 total residue and CSCD459488:CSCD459489 ratio of 97:3

[d] See DAR addendum page 53 for calculation of % molar formation. Maximum concentration of parent in 0-30 cm calculated as 0.15 mg/kg ÷ 3 and molar ratio factor for metabolite is 0.9573

NQ – not quantifiable

Table 6: France 2007 – Residues of CSCD459488 and CSCD459489 (rate 200 g a.s./ha, Reference IIA 7.3.1/11)

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

	Data in original study report (Zeiger, 2009d)			*Refer to DAR addendum Table B.8.22*		
Days after Last Application (DALA)	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*Total CSCD459488 (mg kg^{-1} dry weight)[a]*	*CSD459488:CSCE459489[b] based on original chromatograms*	*CSCD459488:CSCE459489[b] from re-analysis*	*Max. calculated level of CSCD459489 (mg kg^{-1} dry weight)[c] % molar formation[d] in brackets*
Horizon	*0-10 cm*	*10-20 cm*	*0-30 cm*			
0	*<0.0005*	*NA*	*<0.0005*	*NQ*	*-*	
14	*0.0012*	*<0.0005*	*0.00048*	*NQ*	*-*	
28	*0.0035*	*<0.0005*	*0.00125*	*97:3*	*98:2*	
62	*0.0041*	*0.0010*	*0.00178*	*97:3*	*-*	

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

91	*0.0046*	*0.0011*	*0.00198*	*99:1*	*-*	
119	*0.0067*	*0.0016*	*0.00285*	*99:1*	*-*	
180	*0.0097*	*0.0019*	***0.00395***	*NQ*	*-*	*0.00004 (0.104%)*
357	*0.0055*	*0.0031*	*0.00295*	*99:1*	*99:1*	

[a] No residues >LOD (>0.0005 mg/kg) in 20-30 cm horizon. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is <LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + (0.5 x 0.0005) mg/kg + 0 mg/kg] ÷ 3. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is >LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + 10-20 cm residue mg/kg + (0.5 x 0.0005) mg/kg]/3

[b] For comparison the nominal syn:anti ratio of the parent isomers was 72:28

[c] CSCD459489 residue calculated based on CSCD459488 total residue and CSCD459488:CSCD459489 ratio of 99:1

[d] See DAR addendum page 53 for calculation of % molar formation. Maximum concentration of parent in 0-30 cm calculated as 0.110 mg/kg ÷ 3 and molar ratio factor for metabolite is 0.9573

NQ – not quantifiable

Table 7: UK 2007 – Residues of CSCD459488 and CSCD459489 (rate 200 g a.s./ha, Reference IIA 7.3.1/10)

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

	Data in original study report (Zeiger, 2009c)			*Refer to DAR addendum Table B.8.22*		
Days after Last Application (DALA)	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*Total CSCD459488 (mg kg^{-1} dry weight)[a]*	*CSCD459488:CSCE459489[b] based on original chromatograms*	*CSCD459488:CSCE459489[b] from re-analysis*	*Max. calculated level of CSCD459489 (mg kg^{-1} dry weight)[c] % molar formation[d] in brackets*
Horizon	*0-10 cm*	*10-20 cm*	*0-30 cm*			
0	*<0.0005*	*NA*	*<0.0005*	*NQ*		
14	*0.0010*	*0.0016*	*0.00095*	*NQ*	*-*	
28	*<0.0005*	*<0.0005*	*<0.0005*	*NQ*	*-*	
60	*0.0017*	*<0.0005*	*0.00065*	*NQ*	*-*	
90	*0.0043*	*<0.0005*	*0.00152*	*97:3*	*98:2*	
119	*0.0032*	*<0.0005*	*0.00115*	*98:2*	*99:1*	
180	*0.0049*	*<0.0005*	*0.00172*	*98:2*	*-*	

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

366	*0.0078*	*0.0018*	*0.00328*	*99:1*	*-*	
545	*0.0081*	*0.0017*	***0.00335***	*99:1*	*-*	*0.000034 (0.051%)*

[a] No residues >LOD (>0.0005 mg/kg) in 20-30 cm horizon. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is <LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + (0.5 x 0.0005) mg/kg + 0 mg/kg] ÷ 3. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is >LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + 10-20 cm residue mg/kg + (0.5 x 0.0005) mg/kg]/3

[b] For comparison the nominal syn:anti ratio of the parent isomers was 72:28

[c] CSCD459489 residue calculated based on CSCD459488 total residue and CSCD459488:CSCD459489 ratio of 99:1

[d] See DAR addendum page 53 for calculation of % molar formation. Maximum concentration of parent in 0-30 cm calculated as 0.190 mg/kg ÷ 3 and molar ratio factor for metabolite is 0.9573

NQ – not quantifiable

Table 8: Italy 2007 – Residues of CSCD459488 and CSCD459489 (rate 200 g a.s./ha, Reference IIA 7.3.1/13)

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

	Data in original study report (Zeiger, 2009e)			*Refer to DAR addendum Table B.8.22*		
Days after Last Application (DALA)	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*Total CSCD459488 (mg kg^{-1} dry weight)[a]*	*CSCD459488:CSCE459489[b] based on original chromatograms*	*CSCD459488:CSCE459489[b] from re-analysis*	*Max. calculated level of CSCD459489 (mg kg^{-1} dry weight)[c] % molar formation[d] in brackets*
Horizon	*0-10 cm*	*10-20 cm*	*0-30 cm*			
0	*<0.0005*	*NA*	*<0.0005*	*NQ*	*-*	
17	*0.0028*	*<0.0005*	*0.00102*	*95:5*	*94:6*	
27	*0.0035*	*<0.0005*	*0.00125*	*95:5*	*-*	
60	*0.0030*	*<0.0005*	*0.00108*	*96:4*	*-*	
92	*0.0026*	*<0.0005*	*0.00095*	*96:4*	*-*	
119	*0.0035*	*<0.0005*	*0.00125*	*97:3*	*-*	
180	*0.0041*	*<0.0005*	*0.00145*	*NQ*	*-*	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

369	*0.0066*	*0.0008*	***0.0032***	*99:1*	*99:1*	*0.000032 (0.032%)*

[a] Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is <LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + (0.5 x 0.0005) mg/kg + 0 mg/kg] ÷ 3. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is >LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + 10-20 cm residue mg/kg + (0.5 x 0.0005) mg/kg]/3. Residues only detected in the 20-30 cm horizon at 369 d (0.0022 mg/kg) and total residue at 369 days calculated as (0.0066 + 0.0008 + 0.0022)/3 mg/kg

[b] For comparison the nominal syn:anti ratio of the parent isomers was 72:28

[c] CSCD459489 residue calculated based on CSCD459488 total residue and CSCD459488:CSCD459489 ratio of 99:1

[d] See DAR addendum page 53 for calculation of % molar formation. Maximum concentration of parent in 0-30 cm calculated as 0.290 mg/kg ÷ 3 and molar ratio factor for metabolite is 0.9573

NQ – not quantifiable

Table 9: Poland, 2007 – Residues of CSCD459488 and CSCD459489 (rate 200 g a.s./ha, Reference IIA 7.3.1/08)

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

	Data in original study report (Zeiger, 2009e)			*Refer to DAR addendum Table B.8.22*		
Days after Last Application (DALA)	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*Total CSCD459488 (mg kg^{-1} dry weight)[a]*	*CSCD459488:CSCE459489[b] based on original chromatograms*	*CSCD459488:CSCE459489[b] from re-analysis*	*Max. calculated level of CSCD459489 (mg kg^{-1} dry weight)[c]* *% molar formation[d] in brackets*
Horizon	*0-10 cm*	*10-20 cm*	*0-30 cm*			
0	*<0.0005*	*NA*	*<0.0005*	*NQ*	*-*	
13	*0.0007*	*<0.0005*	*0.00032*	*93:7*	*-*	
28	*0.0006*	*<0.0005*	*0.00028*	*92:8*	*93:7*	
61	*0.0014*	*<0.0005*	*0.00055*	*97:3*	*-*	
91	*0.0027*	*<0.0005*	*0.00098*	*98:2*	*-*	

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

119	*0.0027*	*<0.0005*	*0.00098*	*97:3*	*98:2*	
179	*0.0028*	*<0.0005*	*0.00102*	*NQ*	*-*	
340	***0.0035***	*<0.0005*	***0.00125***	*99:1*	*-*	*0.000013 (0.029%)*

[a] No residues >LOD (>0.0005 mg/kg) in 20-30 cm horizon. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is <LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + (0.5 x 0.0005) mg/kg + 0 mg/kg] ÷ 3.

[b] For comparison the nominal syn:anti ratio of the parent isomers was 72:28

[c] CSCD459489 residue calculated based on CSCD459488 total residue and CSCD459488:CSCD459489 ratio of 99:1

[d] See DAR addendum page 53 for calculation of % molar formation. Maximum concentration of parent in 0-30 cm calculated as 0.130 mg/kg ÷ 3 and molar ratio factor for metabolite is 0.9573

NQ – not quantifiable

Table 10: Germany 2007 – Residues of CSCD459488 and CSCD459489 (rate 200 g a.s./ha, Reference IIA 7.3.1/12)

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

Data in original study report (Zeiger, 2009a) — *Refer to DAR addendum Table B.8.22*

Days after Last Application (DALA)	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*CSCD459488 Residue (mg kg^{-1} dry weight)*	*Total CSCD459488 (mg kg^{-1} dry weight)[a]*	*CSCD459488:CSCE459489[b] based on original chromatograms*	*CSCD459488:CSCE459489[b] from re-analysis*	*Max. calculated level of CSCD459489 (mg kg^{-1} dry weight)[c] % molar formation[d] in brackets*
Horizon	*0-10 cm*	*10-20 cm*	*0-30 cm*			
0	*<0.0005*	*NA*	*<0.0005*	*NQ*	*-*	
3	*<0.0005*	*<0.0005*	*<0.0005*	*NQ*	*-*	
7	*<0.0005*	*<0.0005*	*<0.0005*	*NQ*	*-*	
13	*<0.0005*	*<0.0005*	*<0.0005*	*NQ*	*-*	
20	*0.0008*	*<0.0005*	*0.00035*	*NQ*	*-*	
27	*0.0010*	*<0.0005*	*0.00042*	*95:5*	*95:5*	

Route and rate of degradation in soil (B.8.1)

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State / response from the applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data

56	*0.0019*	*<0.0005*	*0.00072*	*NQ*	*-*	
83	*0.0029*	*<0.0005*	*0.00105*	*98:2*	*-*	
115	*0.0035*	*<0.0005*	*0.00125*	*98:2*	*-*	
167	*0.0034*	*<0.0005*	*0.00122*	*98:2*	*-*	
355	*0.0030*	*0.0018*	*0.00168*	*98:2*	*-*	
553	*0.0034*	*0.0016*	***0.00175***	*98:2*	*98:2*	*0.000036 (0.061%)*

[a] No residues >LOD (>0.0005 mg/kg) in 20-30 cm horizon. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is <LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + (0.5 x 0.0005) mg/kg + 0 mg/kg] ÷ 3. Where residue in 0-10 cm is >LOQ and residue in 10-20 cm is >LOQ, total residue in 0-30 cm is calculated as [0-10 cm residue mg/kg + 10-20 cm residue mg/kg + (0.5 x 0.0005) mg/kg]/3.

[b] For comparison the nominal syn:anti ratio of the parent isomers was 72:28

[c] CSCD459489 residue calculated based on CSCD459488 total residue and CSCD459488:CSCD459489 ratio of 98:2

[d] See DAR addendum page 53 for calculation of % molar formation. Maximum concentration of parent in 0-30 cm calculated as 0.170 mg/kg ÷ 3 and molar ratio factor for metabolite is 0.9573

NQ – not quantifiable

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
			UK RMS conclusion (2017): the Applicant has highlighted that all of the available chromatographic samples for the 0-10 cm horizon were examined initially to check whether CSCD459489 would be quantifiable based on the peak heights > 3 x base line noise (BLN) and two chromatograms selected for reassessment to confirm the findings from the original chromatographic assessment. The RMS considers that this was sufficient. Regarding the detection of residues below 10 cm based on the additional tables submitted by the Applicant the RMS is satisfied that CSCD459489 will be not detected in levels that warrant a groundwater assessment. Additionally the Lewis (2014) study demonstrated that CSCD459489 is less mobile than CSCD459488 so if CSCD459488 was not identified at detectable levels below 10 cm then CSCD459489 will not be detected there either as it was consistently detected in much lower amounts than the -syn (CSCD459488) metabolite isomer. The RMS concludes that the examination of residues in the 0 – 10 cm horizons was sufficient to demonstrate that CSCD459489 is not detected at > 5 % AR and therefore it does not warrant a groundwater assessment. Addressed	
4(20)	Addendum (Fate)	Applicant (2017): For clarity the following	UK RMS (2017): agrees with the wording provided by the Applicant and proposes to replace the RMS text with the text suggested by the Applicant;	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	B.8.1.2.2. Field studies Braid and Warinton (2015)	sentence (1st sentence, page 50) could be re-worded: Chromatographic re-analysis demonstrated that CSCD459489 was not detectable in all samples and when CSCD459489 was detectable were low; ranging from not quantifiable (LOQ 0.05 µg/kg) to 0.063 % on a molar basis (see Table B.8.21 for calculation). Suggested re-wording: Chromatographic re-analysis demonstrated that CSCD459489 was not	*"Chromatographic re-analysis demonstrated that CSCD459489 was not quantifiable in all samples (based on study method LOQ of 0.5 µg/kg) and when CSCD459489 was detectable (LOD defined as 3 x baseline noise) levels were low; maximum 0.056% on a molar basis (see Table B.8.21 for calculation)".* Addressed	The amended Addendum included the update indicated in column 3.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		quantifiable in all samples (based on study method LOQ of 0.5 µg/kg) and when CSCD459489 was detectable (LOD defined as 3 x baseline noise) levels were low; maximum 0.056% on a molar basis (see Table B.8.21 for calculation).		
4(21)	Addendum (Fate) B.8.1.2.2. Field studies Braid and Warinton (2015)	Applicant (2017): For clarity the following sentence (last paragraph, page 50) could be re-worded: The RMS also changed values reported below the LOQ of 0.05 µg/kg to the value of; 0.05 µg/kg (discussed in the Garrigue	UK RMS (2017): agrees with the wording provided by the Applicant and proposes to replace the RMS paragraph with the Applicants' text; *"Where CSCD459489 residues were determined from the original study chromatograms to be lower than the new LOQ for the re-analysis of selected field soil samples (LOQ 0.05 µg/kg, see Garrigue 2015a), the RMS changed the residue value for Table B.8.19 to "< 0.05 µg/kg" and 0.05 µg/kg was used to calculate the CSCD459488:CSCD459489 ratio in the sample."* Addressed	Addressed. The amended Addendum included the update indicated in column 3.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		2015a study) Suggested re-wording: Where CSCD459489 residues were determined from the original study chromatograms to be lower than the new LOQ for the re-analysis of selected field soil samples (LOQ 0.05 µg/kg, see Garrigue 2015a), the RMS changed the residue value for Table B.8.19 to "< 0.05 µg/kg" and 0.05 µg/kg was used to calculate the CSCD459488:CSCD459489 ratio in the sample.		

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(22)	Addendum (Fate) B.8.1.2.2. Field studies Braid and Warinton (2015)	Applicant (2017): Table B.8.19 typo – the header for the 4th column should be "CSCD459489" (peak height), not "CSCD459488:CSCD459489".	UK RMS (2017): agrees with the wording provided by the Applicant and proposes to replace the title header. Addressed	Addressed. The amended Addendum included the update indicated in column 3.
4(23)	Confirmatory data assessment. B.8.1.2.2. Field studies. Reassessment of chromatograms from EU field dissipation trials to	EFSA (2017): It is noted that, in field dissipation and accumulation trials samples reanalysed, chromatographic peak of *anti*-metabolite has not being directly identified, but only indirectly assumed to be the peak before the main peak identified as CSCD460260 (assumed now to represent the *syn*	UK RMS (2017): the points raised by the EFSA are acknowledged, however under the scope of this confirmatory data assessment, it is considered that the case (Appendix 3) provides sufficient confidence to allay concerns regarding the identity of the –*anti* metabolite within the previous studies. Should it be deemed necessary by the Commission that further data to address the unequivocal determination of the *anti*- metabolite chromatographic peaks is required, then the RMS would consider it prudent to delay further consideration until the active renewal, to allow the Applicant sufficient time to address this point. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	determine levels of CSCD459489. Braid, S. and Warinton, J. 2015.	metabolite). Retention time changes experiment to experiment and sample chromatogram showing separation of the peaks is provided only for a 50:50 mixture. Coalescence of peaks in all or some of the reanalysed samples, where proportion of metabolite isomers is expected to be of at least 3:1, cannot be completely ruled out from the information provided.		
4(24)	Confirmatory data assessment. B.8.1.2.2. Field studies.	EFSA (2017): As already pointed out by the RMS, stability of the residues for 6 years, under the storage conditions, would need to be demonstrated	UK RMS (2017): noted and as mentioned this issue has been highlighted on page 55 of the Addenda. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	Reassessment of chromatograms from EU field dissipation trials to determine levels of CSCD459489. Garrigue 2015a	in order to validate the result of the reanalysis of the field dissipation studies samples.		
4(25)	Addendum (Fate) B.8.1.3. Adsorption and desorption in soil,	Applicant (2017): The applicant considers that data from Lewis (2014) provide relevant information in support of the the confirmatory information requirement for CSCD459489. By providing robust	UK RMS (2017): proposes to add the additional sentence to page 59 "*the similarity in the Kfoc values of the isopyrazam metabolite isomers suggests that their degradation is not a consequence of differential downwards movement, but truly related to the different degradation rate of the isomers*". Addressed	Addressed. The amended Addendum included the update indicated in column 3.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	Lewis (2014)	information on the soil partiction coefficients for CSCD459489, the relative mobility of the two metabolite isomers in field soil may be considered. Adsoption K_{FOC} values for CSCD459488 and CSCD459489 are similar (on average 124 for CSCD459488 and 193, for CSCD459489). These data, coupled with information on comparative formation and degradation of CSCD459488 and CSCD459489, indicate that the observed change in metabolite *syn:anti* isomer ratio in field soil		

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		(close to 100:0 in all soil samples) compared to parent isopyrazam *syn:anti* ratio (approximately 70:30 for isopyrazam used in the field studies) is not due to differential downward movement of the metabolites in soil.		
4(26)	Addendum (Fate) B.8.5: Groundwater monitoring, Liss and Naeb (2016)	Applicant (2017): The RMS commented that that bromide tracers should have been used to show hydrological connectivity between the points of application to the GMW. Considering the hydrology at the monitoring sites (21 sites in 5 regions of Germany), all sites are	UK RMS (2017): considers that hydrological connectivity is a key issue in groundwater monitoring studies and does not accept that the Applicant can be certain that the fields where isopyrazam is applied are connected to the groundwater monitoring wells; the concerns of the RMS are provided in quality criteria 2 on page 68 and copied below for clarity; *"FOCUSgw II guidance, (2014) clearly indicates that monitoring studies must prove hydrological connectivity of the treated areas to the sampling sites. In this study there is no reference made to how hydrological connectivity has been determined apart from the following statement in Liss & Naeb (2016); "the dominant groundwater flow direction was determined based on topographical and hydrogeological parameters of each individual monitoring site. The up-gradient area, relevant to the groundwater monitoring well, was defined by a*	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		considered to be vulnerable for leaching and there is good documented evidence of ispoyrazam use in the up-gradient land segements. The study monitoring sites are predominantly on permeable, sandy soils, with no evidence of confining layers and a shallow groundwater table. Isopyrazam containing products were applied to fields upgradient of the wells along the dominant flow direction up to a distance of 1 km from the GMW. Applications of isopyrazam	*45° circle segment. This opening angle was used to allow for a potential seasonal deviation in the dominant groundwater flow direction and to take into account for dispersion of solutes within the aquifer. The length of segment sides is 1 km."* *The Notifier has assumed hydrological connectivity due to the treated fields being "up-gradient" of the GMW and within the 45° segment (an example is shown in Figure B.8.23). However the RMS considers that the Notifier has not demonstrated the assumed hydrological connectivity thus it is uncertain that water from the treated areas will flow into the borehole.* *Additionally, several of the isopyrazam treated fields were outside the segment where groundwater is presumed to flow to the borehole, e.g; had 0.0 hectares within the segment (see **Appendix 6** and Figure B.8.23). Therefore the residues from these fields may not reach the GMW, potentially leading to false negatives, as shown in fields 2.2, 2.4 and 2.5. Although the absence of isopyrazam detection in the GMW fed from these fields is unlikely to be a direct result of the up-gradient field being outside the segment, several fields being connected to each GMW, it could reduce the amount of isopyrazam reaching and being detected in the GMW.* *The lack of evidence for hydrological connectivity means that when isopyrazam is applied to a field it cannot be guaranteed that it will reach the GWM, as there are no data to show where the residues will travel to. The RMS considers that bromide tracers should have been used to show hydrological connectivity between the points of application to the GMW."*	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		within the upgradient segments are proactively arranged for this monitoring study and significant amounts of isopyrazam have been applied to cereal fields at 1 x 125 g a.s./ha per year in these areas. Application records from the participating farms show that significant amounts of isopyrazam are being applied to the segemnts (0.1 to 4.5 kg per year) and to most fields in the segments, in most years.	Addressed	
4(27)	Addendum (Fate) B.8.5:	Applicant (2017): The RMS noted that some isopyrazam treated fields	UK RMS (2017): acknowledges the Applicants' justification for some fields being outside of the segment, but considers that the concerns about the	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	Groundwater monitoring, Liss and Naeb (2016)	were outside the segment where groundwater is presumed to flow to the borehole. The study involved prospective applications of isopyrazam containing products to cereal fields in a defined sector upgradient of the monitoring wells. In a very few instances, this was not possible and the treated fields were outside of the defined sector. This is an ongoing study and whenever possible, prospective applications will be made to the fields within the sector.	likelihood of isopyrazam applied in these fields reaching the groundwater monitoring wells is still valid and has been highlighted on page 68. Addressed	
4(28)	Addendum (Fate)	Applicant (2017): The RMS commented on the	UK RMS (2017): considers that the Applicant needs to provide evidence that a travel time of 3-5 years is the maximum for groundwater and can show that it	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	B.8.5: Groundwater monitoring, Liss and Naeb (2016)	travel time for isopyrazam and its metabolites. The Applicant acknowledges that the properties these compunds will affect their movement to groundwater and that the time taken for them to move through the unsaturated (vadose) zone could take several years. The calculated flow velocity presented in the interim groundwater monitoring report, "travel distance" is, as stated on page 137, "that for groundwater and no allowance was made for sorption processes or the	does not extended beyond 5 years when the sorption properties of isopyrazam are considered. Addressed	

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		time required for a substance to leach through the unsaturated zone". It should be noted that the 3-5 years travel time for groundwater in the saturated zone is the maximum time and in most instances should be a lot shorter since the treated areas are a lot closer to the wells than the maximum length of the segment (1 km).		
4(29)	Addendum (Fate) B.8.5: Groundwater monitoring, Liss and	Applicant (2017): The RMS commented on the monitoring frequency (2-4 times per year). As this monitroing study involves prospective applications on multiple fields along 1	UK RMS (2017): notes the point of the Applicant but cannot accept that the sampling effort is sufficient without evidence on the travel time of isopyrazam. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
	Naeb (2016)	km segment lengths, over multiple years the Applicant considers that this frequency of sampling is sufficient to determine representative concentrations in groundwater.		
4(30)	Addendum to DAR update of October 2019 B.8	EFSA (2019): Thank you for the updates that have clearly addressed the comments made by EFSA on the earlier assessment of April 2017. Following the clarifications made now, EFSA can agree the RMS assessment and conclusions regarding environmental fate and behaviour (addendum to	UK RMS (2019): Thank you. Noted. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		B.8).		
4(31)	Missing section of the DAR update	EFSA (2019): The addendum section B.8 has evaluated new information that has been provided since the EFSA conclusion was published but no updates have been made to the list of agreed endpoints consequent to the evaluation of this extra information. Where the information was assessed as providing reliable information by the RMS this needs to be reflected in an update to the list of agreed endpoints. New DT50 values and adsorption values have been derived	UK RMS (2019): The LoEP has been amended. Addressed	Addressed.

Route and rate of degradation in soil (B.8.1)				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		from new studies. Some updated entry in the list of endpoints regarding groundwater monitoring information should be considered.		

Adsorption,desorption and mobility in soil				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(32)	Vol. 3, B.8.5 Groundwater Monitoring	DE (2017): Regarding the groundwater monitoring in Germany, we have to remark the assessment of the monitoring study is not finalised at this time point. The decision is still open.	UK RMS (2017): notes Germanys point and will edit the final paragraph in the box on page 70 as follows (under-lining indicates changes to the original text); *"Finally the RMS considers there is currently insufficient information to fully understand how this assessment would relate to other EU situations. The EFSA PPR Panel (2013) expressed the opinion that "current knowledge on groundwater hydrology at the European level is insufficient as a basis for authorisation decisions. Tier 4 is therefore not recommended to demonstrate safe use at the EU level". Therefore the RMS has not relied on this study, at this time for this confirmatory data requirement as the absence of residues cannot assume an absence of leaching. However currently the study has not been finalised".* Addressed	Addressed. The amended Addendum included the update indicated in column 3.
4(33)	Confirmatory data assessment. B.8.5 Groundwater monitoring.	EFSA (2017): The assessment on these studies performed by the RMS is agreed. The different uncertainties identified by the RMS (including available duration of the studies in relation of presumed	UK RMS (2017): the agreement of EFSA has been noted. Addressed	Addressed.

Fate and behaviour in water and sediment and effect of water treatment procedures on the nature of residues				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		traveling time of isopyrazam and its metabolite) prevent to use this data to exclude the leaching of the metabolite.		

Fate and behaviour in air				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

PEC in soil				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

PEC in surface water and ground water				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

PEC from airborne transport and other routes of exposure				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Definition of the residues				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**

Not relevant to the assessment.

Other comments incl. available monitoring data				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
4(34)	Overall conclusions	DE (2017): Regarding the overall conclusions in the addendum we followed the assessment by RMS UK and applied the outcome to the zonal registration. Metabolite CSCD459489 was not considered for PECgw. Relevance assessment was not triggered.	UK RMS (2017): DE position has been noted. Addressed	Addressed. Please note a different reading / interpretation of the groundwater relevance guidance by EFSA in the column 4 entry at comment 4(35).
4(35)	Confirmatory data assessment. Overall conclusion.	EFSA (2017): The information provided cannot be considered sufficient to rule out the need to address the potential ground water contamination by the hydroxylated metabolite resulting from the transformation of the *anti* isomer of the parent compound (30 % of the applied active substance). However, some plausible indication has been provided that the maximum levels attained in soil by the *anti* isomer of metabolite CSCD460260 in relation to the *syn* isomer may be lower than what would be expected if the proportion in the parent was conserved. Since epimerisation of the molecule framework seems to be chemically excluded, the lower levels attained by the *anti* isomer	UK RMS (2017): notes the position of EFSA and agrees that the Applicants' case would have been strengthened by conducting all of their studies to GLP and extending the duration of some studies, however the RMS does not consider any of the deviations from standard soil degradation studies to have invalidated the studies. Overall the RMS considers that based on a 'weight of evidence' approach despite the deficiencies in the some studies, the information supplied by the Applicant is sufficient to demonstrate that CSCD459489	EFSA agrees that it might be considered that the information supplied by the applicant is sufficient to demonstrate that CSCD459489 does not form in soil at levels > 5 % AR and so according to the relevant groundwater metabolites guidance CSCD459489 did not reach levels in soil where it must be assessed. However we also note that the relevant groundwater metabolites guidance also states that 'As a general rule all metabolites which are expected to occur in soil under normal use conditions on the basis of results from soil degradation studies

Other comments incl. available monitoring data				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		of the metabolite could be only explained by a faster degradation of this isomer with respect to the *syn* metabolite. A **non GLP** study seems to confirm this hypothesis showing consistent lower soil half lives for the *anti* isomer than for the *syn* one. In addition, a GLP study is available were adsorption / desorption of *anti* isomer of metabolite is measured. Therefore, data have been provided that allow to refine the PEC GW for *anti* isomer of metabolite CSCD460260 by using the geometric mean DT_{50} = 44.7 days and a geomean Kfoc = 190.6 mL/g (1/n = 0.9). In addition a 0.3 formation fraction from the total parent (or ff = 1 from the *anti* metabolite of the parent) can be assumed (exclusion of epimerisation). These new PEC GW should allow to preliminary refine the values calculated for the EFSA conclusion based on assumed worst case end points. The refinement could be considered definitive when the shorted half	does not form in soil at levels > 5 % AR and therefore conclude that a groundwater exposure assessment is not required. Addressed	should be subject to further assessments…..with the aim of quantitatively assessing their ability to contaminate groundwater.' Note: EFSA previous responses eg. at comment 4(12) regarding the requirement for GLP for investigation not published in the peer reviewed scientific literature.

Other comments incl. available monitoring data				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State / response from the applicant**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
		life of the *anti* isomer is confirmed by rate degradation studies performed under GLP.		

5. Ecotoxicology

Not relevant to the assessment.

Appendix B – List of end points – updated endpoints

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

Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	CSCD460260 (CSCD459488 and CSCD459489) – 4.2 – 23.6 % AR at 45 - 195 d (n= 5) CSCD459488 – 16.5% AR at 120 d (n=1) CSCD459489 – 1.9% AR at 61 d (n=1) Non-GLP, non-OECD guideline, non-radiolabelled laboratory study of 49 – 56 days duration on five soils indicated maximum % formation of CSCD459489 was 0.08% on molar basis vs 9.78% molar formation of CSCD459488. By 7-21 days, CSCD459488 compared to CSCD459489 (syn:anti-isomer) ratio 99:1; parent syn:anti-isomer ratio 80:20. Note that on weight of evidence basis, CSCD459489 is considered to not trigger inclusion in environmental exposure assessment as a soil metabolite. In addition, the ratio of CSCD459488 to CSCD459489 is not considered to reflect that of the syn- and anti-isomers comprising parent isopyrazam, with a very much higher proportion of CSCD459488 compared to CSCD459489. CSCD465008 – 11.5 % AR at 150 d (n= 1) [^{14}C-phenyl] & [^{14}C-pyrazole] labels

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

Laboratory studies ‡

Non-GLP, non-OECD guideline, non-radiolabelled aerobic soil incubations of 49 – 56 days duration on five soils comparing degradation rate of CSCD459488 and CSCD459489 (metabolites added as starting material). CSCD459488 SFO DT50 geomean 158.5 days (106 – 278 days); CSCD459489 SFO DT50 geomean 44.7 days (31.6 – 62.9 days). Study suggests that CSCD459489 degrades more quickly than CSCD459488 resulting in low observed formation of CSCD459489. Adds to weight of evidence that CSCD459489 does not trigger inclusion in environmental exposure assessment as a soil metabolite.

Field studies ‡

Field studies CSCD459488 – generally did not demonstrate clear decline in residues. Compartment modelling derived kinetic values not considered reliable. In modelling, default DT50 of 1000 days with 'conservative' formation fraction of 0.15 used. SFO decline from peak at CH06 site, DT50 299 days, DT90 993 days, χ^2 10.8.

Field studies CSCD465008 – residues often low and insufficient sample points after peak to calculate decline. Calculation of kinetic parameters was not possible due to unreliability of kinetic parameters for precursor metabolite. SFO decline from peak at DE06 site, DT50 65 days, DT90 223 days, χ^2 24.1.

Site[1]	Max molar % CSCD459488	Max molar % CSCD459489[2]	Max molar % CSCD465008
nFR06	4.2 (362 DAT)		4.9 (63 DAT)
CH06	6.1 (28 DAT)		3.9 (59 DAT)
IT06	8.6 (358 DAT)		1.8 (120 DAT)
DE06	7.1 (351 DAT)		6.9 (14 DAT)
PO07	2.7 (340 DAT)	0.029 (340 DAT)	3.7 (340 DAT)
ES07	2.1 (370 DAT)	0.069 (370 DAT)	17.3 (119 DAT)
UK07	5.0 (545 DAT)	0.051 (545 DAT)	0.9 (28 DAT)
sFR07	10.1 (180 DAT)	0.104 (180 DAT)	6.2 (91 DAT)
DE07	2.8 (553 DAT)	0.061 (553 DAT)	1.1 (27 DAT)
IT07	2.6 (369 DAT)	0.032 (369 DAT)	2.2 (119 DAT)

[1] Codes for location refer to the country and year, e.g. CH06 = Switzerland 2006.

[2]Re-inspection of field study chromatograms from the six field dissipation studies in 2007 indicated that % molar formation of CSCD459489 ranged from 0.029 – 0.104% at 180 – 553 DAT. Re-analysis of samples indicated maximum molar fraction of CSCD459489 was 0.063% compared to 5.83% for CSCD459488.

Soil adsorption/desorption (Annex IIA, point 7.1.2)

CSCD459489 ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	K_F (mL/g)	K_{Foc} (mL/g)	1/n
Sandy Clay Loam	4.2	5.5			6.39	152	0.9151
Loam	1.8	7.1			3.84	213	0.8798
Silty Clay	0.9	7.5			1.93	214	0.9002
Arithmetic mean					4.05	193	0.8984
pH dependence (yes or no)			No				

Note that adsorption coefficients of CSCD459488 and CSCD459489 are similar. This suggests that changes in isomeric ratio of the metabolites in field dissipations studies compared to isomeric ratio of the parent substance might be considered unlikely to be due to differences in leaching potential but rather different degradation rates of the two metabolites.

Residues requiring further assessment

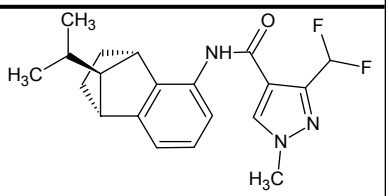
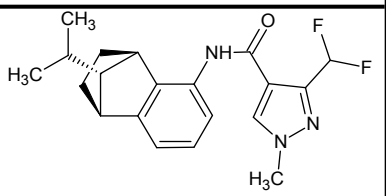
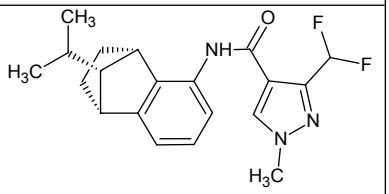
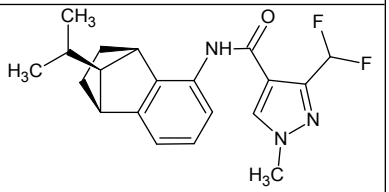
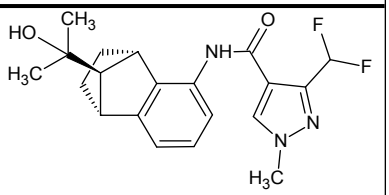
Environmental occurring metabolite requiring further assessment by other disciplines (toxicology	Soil: parent isopyrazam and metabolites CSCD459488 and CSCD465008.

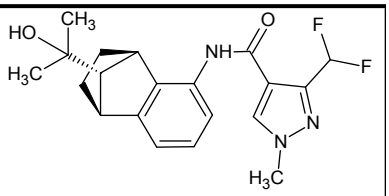
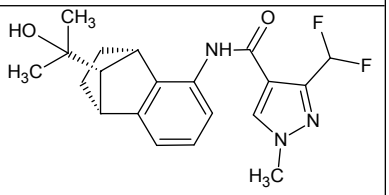
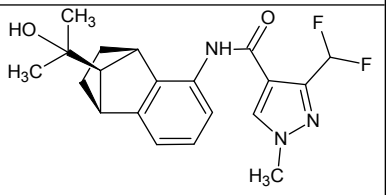
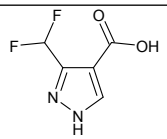
and ecotoxicology) and or triggering groundwater exposure assessment.	Surface water: parent isopyrazam, soil metabolites CSCD459488 and CSCD465008. Sediment: parent isopyrazam. Groundwater: parent isopyrazam and metabolites CSCD459488, CSCD459489 and CSCD465008. Air: parent isopyrazam.

Monitoring data, if available (Annex IIA, point 7.4)

Ground water (indicate location and type of study)	Interim data from a monitoring study in five regions in Germany. Analysis for isopyrazam, CSCD459488 and CSCD459489. Concentrations all <LOQ (0.05 µg/L). Results not relied upon due to uncertainty over adequacy of the study.

Appendix C – Used compound codes

Code/trivial name[a]		IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
isopyrazam (mixture of isomers)	*syn*-isomers	3-(difluoromethyl)-1-methyl-*N*-[(1*R*,4*S*,9*R*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@@H]3CC[C@@H]([C@@H]3C(C)C)c21 XTDZGXBTXBEZDN-HEHGZKQESA-N	
		3-(difluoromethyl)-1-methyl-*N*-[(1*S*,4*R*,9*S*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@H]3CC[C@H]([C@H]3C(C)C)c21 XTDZGXBTXBEZDN-IOASZLSFSA-N	
	anti-isomers	3-(difluoromethyl)-1-methyl-*N*-[(1*R*,4*S*,9*S*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@@H]3CC[C@@H]([C@H]3C(C)C)c21 XTDZGXBTXBEZDN-XEZPLFJOSA-N	
		3-(difluoromethyl)-1-methyl-*N*-[(1*S*,4*R*,9*R*)-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalen-5-yl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@H]3CC[C@H]([C@@H]3C(C)C)c21 XTDZGXBTXBEZDN-XJKCOSOUSA-N	
CSCD460260 hydroxy-isopyrazam (mixture of isomers)	**CSCD459488** hydroxy-isopyrazam (*syn*-isomers)	3-(difluoromethyl)-*N*-[(1*R*,4*S*,9*R*)-9-(2-hydroxypropan-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-1-methyl-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@@H]3CC[C@@H]([C@@H]3C(C)(C)O)c21 HCWDTMPDJPLLNY-HWWQOWPSSA-N	

		3-(difluoromethyl)-*N*-[(1*S*,4*R*,9*S*)-9-(2-hydroxypropan-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-1-methyl-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@H]3CC[C@H]([C@H]3C(C)(C)O)c21 HCWDTMPDJPLLNY-WQGACYEGSA-N	
	CSCD459489 hydroxy-isopyrazam (*anti*-isomers)	3-(difluoromethyl)-*N*-[(1*R*,4*S*,9*S*)-9-(2-hydroxypropan-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-1-methyl-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@@H]3CC[C@@H]([C@H]3C(C)(C)O)c21 HCWDTMPDJPLLNY-OZVIIMIRSA-N	
		3-(difluoromethyl)-*N*-[(1*S*,4*R*,9*R*)-9-(2-hydroxypropan-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-1-methyl-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)Nc1cccc2[C@H]3CC[C@H]([C@@H]3C(C)(C)O)c21 HCWDTMPDJPLLNY-BFQNTYOBSA-N	
CSCD465008		3-(difluoromethyl)-1*H*-pyrazole-4-carboxylic acid OC(=O)c1c[NH]nc1C(F)F IGQNDARULCASRN-UHFFFAOYSA-N	

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2019.1.1 ACD/Labs 2019 Release (File version N05E41, Build 110555, 18 Jul 2019)
(c): ACD/ChemSketch 2019.1.1 ACD/Labs 2019 Release (File version C05H41, Build 110712, 24 Jul 2019)