Technical Report

efsa SUPPORTING PUBLICATIONS

APPROVED: 24 January 2024
doi: 10.2903/sp.efsa.2024.EN-8587

Outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for pinoxaden 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 pinoxaden are presented. The current report summarises the outcome of the consultation process organised by the rapporteur Member State Austria and presents EFSA's scientific views and conclusions on the individual comments received.

Key words: pinoxaden, peer review, confirmatory data, risk assessment, pesticide, herbicide

Requestor: European Commission
Question number: EFSA-Q-2023-00458
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Suggested citation: EFSA (European Food Safety Authority), 2024. Technical report on the outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for pinoxaden in light of confirmatory data. EFSA supporting publication 2024:EN-8587. 223 pp. doi:10.2903/sp.efsa.2024.EN-8587

ISSN: 2397-8325

Summary

Pinoxaden was included in Annex I to Directive 91/414/EEC on 1st July 2016 by Commission Directive (EU 2016/370) and has been deemed to be approved under Regulation (EC) No 1107/2009, in accordance with Commission Implementing Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011. It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on:

1. a validated method of analysis of metabolites M11, M52, M54, M55 and M56 in ground water;
2. the relevance of the metabolites M3, M11, M52, M54, M55 and M56, and the corresponding groundwater risk assessment, if pinoxaden is classified under Regulation (EC) No 1272/2008 as H361d (suspected of damaging the unborn child).

The applicant should provide to the Commission, the Member States and EFSA the information referred to point 1 by 30 June 2018 and information referred to point 2 within six months from the notification of the classification decision under Regulation (EC) No 1272/2008 of the European Parliament and of the Council[1] (2) concerning pinoxaden.

In accordance with the specific provision, the applicant, Sygenta, submitted an updated dossier in August 2018 (addressing confirmatory data under point 1)) and in April 2019 (addressing confirmatory data under point 2)), which was evaluated by the designated rapporteur Member State (RMS), Austria, in the form of two addenda to the draft assessment report. In compliance with guidance document SANCO 5634/2009-rev.6.1, the RMS distributed the addenda to Member States, the applicant and EFSA for comments on 16 November 2018[2] and on 17 May 2022[3]. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 30 June 2023. 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, Austria, and presents EFSA's scientific views and conclusions on the individual comments received.

Pinoxaden is the ISO common name of 8-(2,6-diethyl-4-methylphenyl)-7-oxo-1,2,4,5-tetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-9-yl 2,2-dimethylpropanoate (IUPAC). Based on the information in the GAP table in the latest list of endpoints update provided by the RMS (see Appendix C), the formulation for the representative uses evaluated in the course of the confirmatory data submission (A13814D) is a different formulation to the one previously peer reviewed. Detailed information on its composition has not been included in an updated volume 4 to the DAR. Validated analytical methods for analysis of metabolites M11, M52, M54, M55 and M56 in ground and surface water were provided.

In the area of **mammalian toxicology**, confirmatory data may address point 2 of data requirements. However further peer review is proposed to discuss whether the general approach to consider data from metabolite M3 to address the relevance of metabolites M11, M54, M55 and M56 is acceptable (as proposed by the RMS) and whether metabolite M3 is not relevant since divergent views were expressed by Member States on the outcome of the developmental toxicity study in rabbits. EFSA notes that if metabolites M2 and M52 exceed 0.1 µg/L, they should be considered relevant metabolites following the EC guidance document[4] on the assessment of

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).

[2] Addendum 1 containing the RMS assessment of the confirmatory data set under point 1 (Austria, 2018)

[3] Addendum 2 containing the RMS assessment of the confirmatory data set under point 2 (Austria, 2022 and 2023)

[4] Sanco/221/2000 –rev.10- final: https://food.ec.europa.eu/system/files/2016-10/pesticides_ppp_app-proc_guide_fate_metabolites-groundwtr.pdf

the relevance of groundwater metabolites since data are not available to show that M2 and M52 does not share the toxicological properties of pinoxaden (harmonised classification as Repr. 2 (H361d, *suspected of damaging the unborn child*)). In addition, M2 showed biological activity and its genotoxic potential should be clarified. EFSA also notes that if metabolite M55 exceed 0.1 µg/L it should be considered a relevant metabolite following the EC guidance document on the assessment of the relevance of groundwater metabolites since M55 showed positive results in the Ames Test and equivocal /positive results in the *in vivo* Comet assay.

An assessment of the potential exposure for consumers to metabolites through sources other than drinking water was not provided and further action may be needed in line with the pertinent guidance document Sanco/221/2000 – rev.10 pending the conclusions of the proposed peer review in the section on environmental fate and behaviour (notably on groundwater exposure assessment).

Regarding environmental fate and behaviour, a MS had some diverging views to EFSA and the RMS on substance properties to be used in groundwater exposure modelling for metabolite M55 degradation, including possible pH dependence and kinetic formation fractions between metabolites M2 and M3, plus the approach for deriving KFoc values in particular for the Marsillargues soil and metabolite M52. Regarding the use of groundwater monitoring data, the RMS proposed and EFSA agrees that an expert meeting discussion would be appropriate to discuss the RMS proposed approach, noting that a MS had a diverging view on the approach of scaling GW concentrations measured in the monitoring studies to account for differences between farmer practice at monitored sites and the intended uses that need to be assessed. The need for discussion on what might be considered as appropriate practice regarding temporal sampling and temporal practice for expressing concentrations when using them to compare to parametric limits, in the context of edge of field sampling wells, for samples from the saturated zone, is also concluded as having utility.

Lastly it is also noted that the designated RMS for Pinoxaden under AIR VI EU renewal programme, is currently working on the renewal dossier of Pinoxaden. The identified areas for which an experts' consultation is recommended may be addressed in the context of the renewal of approval of Pinoxaden for which the peer review will start upon submission of the renewal assessment report by the designated RMS.

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1 Introduction

1.1 Background and terms of reference as provided by the requestor

Pinoxaden was included in Annex I to Directive 91/414/EEC[5] on 1 July 2016 by Commission Directive (EU 2016/370)[6], and has been deemed to be approved under Regulation (EC) No 1107/2009[7], in accordance with Commission Implementing Regulation (EU) No 540/2011[8], as amended by Commission Implementing Regulation (EU) No 541/2011[9]. EFSA previously finalised a Conclusion on this active substance on 14 June 2013 (EFSA, 2013).

It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on:

1. a validated method of analysis of metabolites M11, M52, M54, M55 and M56 in ground water;
2. the relevance of the metabolites M3, M11, M52, M54, M55 and M56, and the corresponding groundwater risk assessment, if pinoxaden is classified under Regulation (EC) No 1272/2008 as H361d (suspected of damaging the unborn child).

The applicant should provide to the Commission, the Member States and EFSA the information referred to point 1 by 30 June 2018 and information referred to point 2 within six months from the notification of the classification decision under Regulation (EC) No 1272/2008 of the European Parliament and of the Council[10] (2) concerning pinoxaden.

In accordance with the specific provision, the applicant, Sygenta, submitted an updated dossier in April 2019, which was evaluated by the designated rapporteur Member State (RMS), Austria, in the form of an addendum to the draft assessment report (Austria, 2018 and 2022). In compliance with 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 17 May 2022. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 30 June 2023. 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, Austria, 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 and Article 6(f) of Regulation

[5] 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.

[6] Commission Implementing Regulation (EU) 2016/370 of 15 March 2016 approving the active substance pinoxaden, 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 70, 16.3.2016, p. 7–11.

[7] 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.

[8] Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p.1-186.

[9] Commission Implementing Regulation (EU) No 541/2011 of 1 June 2011 amending Implementing Regulation (EU) No 540/2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p.187-188.

[10] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).

(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 pinoxaden are presented.

To this end, a technical report containing the finalised reporting table is being prepared by EFSA.

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.

2 Assessment

Documentation provided to EFSA

1. Austria, 2018. Addendum to the assessment report on Pinoxaden, confirmatory data (point 1), November 2018. Available online: https://open.efsa.europa.eu/questions/EFSA-Q-2023-00458?search=pinoxaden
2. Austria, 2019. Revised addendum to the assessment report on Pinoxaden, confirmatory data (point 1), January 2019. Available online: https://open.efsa.europa.eu/questions/EFSA-Q-2023-00458?search=pinoxaden
3. Austria, 2022. Addendum to the assessment report on Pinoxaden, confirmatory data (point 2), May 2022. Available online: https://open.efsa.europa.eu/questions/EFSA-Q-2023-00458?search=pinoxaden
4. Austria, 2023. Revised addendum to the assessment report on Pinoxaden, confirmatory data (point 2), June 2023. Available online: https://open.efsa.europa.eu/questions/EFSA-Q-2023-00458?search=pinoxaden
5. Austria, 2023a. Reporting table, comments on the pesticide risk assessment for Pinoxaden in light of confirmatory data, June 2023. Available online: https://open.efsa.europa.eu/questions/EFSA-Q-2023-00458?search=pinoxaden

References

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

European Food Safety Authority, 2013. Conclusion on the peer review of the pesticide risk assessment of the active substance pinoxaden. *EFSA Journal* 2013; 11 (8):3269, 112 pp. doi:10.2903/j.efsa.2013.3269.

Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under regulation (EC) No 1107/2009 (Commission Document Sanco/221/2000 –rev.10- final dated 25 February 2003).

Abbreviations

a.s.	active substance
DAR	draft assessment report
GAP	good agricultural practice
DG SANCO	European Commission Directorate General Health and Consumers
EU	European Union
LC50	lethal concentration, median
LD50	lethal dose, median; dosis letalis media
MS	Member State
PEC	predicted environmental concentration
PECsed	predicted environmental concentration in sediment
PECsoil	predicted environmental concentration in soil
PECsw	predicted environmental concentration in surface water
PRIMo	Pesticide Residue Intake Model
RMS	rapporteur Member State

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

Confirmatory data a – a validated method of analysis of metabolites M11, M52, M54, M55 and M56 in ground water

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

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**	**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)	Addendum to RAR, Vol.3CA, Conclusion, p.10	EFSA agrees that the evaluated method meets the guideline criteria and can be used for monitoring residues of M11, M52, M54, M55 and M56 in ground and surface water at a LOQ of 0.05 µg/L.	RMS: Agreed.	Provided method (GRM017.06A, Langridge, 2015) can be considered as validated for analysis of M11, M52, M54, M55 and M56 in ground and surface water at a LOQ of 0.05 µg/L. Provided method (Watson, 2017) can be considered as validated for analysis of M11, M52, M54, M55 and M56 in ground and surface water at a LOQ of 0.025 µg/L. In addition, the method (Watson, 2017) can be considered as an ILV of the method GRM017.06A for metabolites M11, M52, M54, M55 but not acceptable as an ILV for M56 (due to a difference in the conditions used in the primary and ILV methods). However, it is noted that the residue definition for monitoring in groundwater is still open, pending evaluation of toxicological relevance of some of the metabolites. See comments related to Confirmatory data b, section 2.

1(2)	Vol. 3, B.5.3, Confirmatory data B5 – analytical method for water (Langridge G., 2015, report CEMR-6750-REG NOA407855_10320 and Watson G., 2017, report RES-00108 NOA407855_10417)	FR: Method for analysis, together with ILV for all substances included in the residue definition for monitoring purposes have been reported in the addendum 1 and are considered as fully validated according to SANCO/825/00 rev.8.1. However, RMS should indicate if data to confirm the specificity and linearity of the method (calibration curves, chromatograms for calibration standards, control and fortified samples) have been provided for all both mass transitions.	RMS: Information on linearity and specificity will been added to the addendum.	Addressed.
1(3)	Addendum 1 to Vol. 3, B.5.3.2, Residues in water	DE: The analytical methods are accepted to address the confirmatory information required in Reg (EU) 2016/370. Sufficiently validated methods for the determination of the metabolites M11, M52, M54, M55 and M56 in ground water are available. However, the presented method by Watson, 2017 (Method GRM017.06**B**) cannot be accepted as ILV for the primary method by Langridge, 2015 (Method GRM017.06**A**). Significant differences regarding the extraction of residues of pinoxaden and the metabolites M2, M3 and M56 have to be considered. Please correct. The statement regarding the reproducibility (ILV) should be amended since the ILV (Watson, 2017) uses **not** the same conditions and **not** the same fortification levels as the primary method.	RMS: Reference to an ILV is removed and method GRM07.06B is presented as a "stand alone" method. No ILV is present for either method. However, no ILV is required in the confirmatory information.	See point (1) above.

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**	**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(4)	Addendum to RAR, Vol.3CA, Conclusion, p.10	EFSA: It should be noted that the method uses a reversed phase column and the optical isomers of the metabolites containing a chiral centre would not be resolved, if both present.	RMS: Agreed.	See 2(4).
1(5)	Vol. 3, B.5.2, Confirmatory data B5 – analytical method for treated plants, plant products, foodstuffs of plant and animal origin and feedingstuffs	FR: A confirmatory methods for the determination of free and conjugated metabolites M4 and M6 in high water content and dry matrices and a complete validation for the determination of free and conjugated metabolites M4 and M6 in high oil and high acid content commodities of plant origin are always required to fill the EFSA data gap.	RMS: The addendum was prepared to address the requirements of the confirmatory information. *The applicant shall submit confirmatory information as regards: (a) a validated method of analysis of metabolites M11, M52, M54, M55 and M56 in ground water;* It is not intended to fill in any other data gaps identified by EFSA.	EFSA agrees with RMS' reply.

Confirmatory data b – the relevance of the metabolites M3, M11, M52, M54, M55 and M56, and the corresponding groundwater risk assessment, if pinoxaden is classified under Regulation (EC) No 1272/2008 as H361d (suspected of damaging the unborn child)

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

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**	**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)	Analytical Methods (Addendum 2_Volume_3CA_B-5)	FR: Please detail, for all analytical methods, which typical chromatograms have been provided to assess the specificity of the methods for the determination of analyte.	Applicant (SYN): Spcificty has been addressed in terms of the analytical technique used within each method. Control chromatograms are presented within methods and studies to demonstrate specificity. RMS: RMS consideres more detailed information as not necessary as it should be clear that chromatograms according to the analytical technique used in the method were presented.	Addressed.
1(2)	Volume 3 CA B.5, general.	NL: It is not fully clear if the EFSA Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances (2019) should apply on this data package for the confirmatory data of pinoxaden which is included in Volume 3 CA B.5, nonetheless the following comment(s) is(are) made in relation to this issue. An overview table should be included according to 3.8 of the EFSA Administrative guidance (as stated in Appendix D) for all pre-registration analytical methods presented for fate	Applicant (SYN): Noted – the data provided here is confirmatory data requested linked to the pinoxaden approval from 2016 (Reg. 2016/370). The submission was done in 2018 before the publication of the EFSA Administrative guidance. RMS shall decide if the DAR Addendum shall be updated accordingly. RMS: As the submission was done before the implementation of the EFSA Administrative guidance, RMS considered it not necessary to update the DAR Addendum 2 accordingly. The conclusion for each method	Addressed. Confirmatory data are processed according to SANCO 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)

		(p. 6-25) and toxicology (p. 26-39). The studies should be presented as stated in 3.16 of the EFSA Administrative guidance (according to Appendix E), this is currently not the case. It should be made clear what the conclusion of the study is from the applicant and that from the RMS, this is not clear now. According to 3.1 of the EFSA Administrative guidance *'The views and conclusions of the RMS should always be clearly and transparently reported to differentiate the view of the applicant from that of their own.'*.	always contains the conclusion of the RMS.	
1(3)	Volume 3 CA B.5, all summaries of the analytical methods presented.	NL: Missing is data on the extract stability, in case samples extract are stored for a period longer than 24 hours. In addition a linear relationship could be included for completeness purposes to see if the correlation of the signal vs concentration is linear, now only a Correlation coefficient is stated.	Applicant (SYN): Noted – additional information is available in study and method reports. RMS shall decide if those information needs to be added to the DAR Addendum. RMS: According to SANCO/3029/99 rev 4, the method description in the submitted method must include information on the reagent stability information. The summary in the DAR Addendum only contains a summary of the method validation see chapter 3 of SANCO/3029/99 rev 4). In addition, it is mentioned in the summary whether the detector response was linear or not.	Addressed. Information on the extract stability was not reported. Information on linearity was reported. EFSA agrees with the evaluation done by RMS, the methods although not fully validated according to SANCO/3029/99 rev 4 can be considered as fit for purpose.
1(4)	Vol. 3, B.5.1.2.1, Robinson, 2012 (KIIA7.2.3/01, p. 6)	DE: Please check the LOQ and the LOD. For the LOQ 0.0005 **µ**g/kg and for the LOD as ½ LOQ 0.00025 **mg**/kg is stated.	Applicant (SYN): LOQ is quoted as corresponding to the lowest calibration point of 0.0005 µg/mL, which is equivalent to 0.0026 mg/kg dry soil. The LOD is quoted as half of this value – this appears to be a typo and should be 0.0013 mg/kg. RMS is kindly requested to update the DAR addendum accordingly.	Addressed.

			RMS: Amended.	
1(5)	Vol. 3, B.5.1.2.1, Fingern, 2016 & Fingern, 2016a & Fingern, 2016 b (KIIA7.3.1/01 & /02 & 03, p. 13, p. 15 & p. 16)	DE: Please check and correct the 1st MS/MS transition for M3 (m/z 333.325→**2149**.200 is mentioned).	Applicant (SYN): Typo – correct MS/MS transition is 333.325 →149.200. RMS is kindly requested to update the DAR addendum accordingly. RMS: Amended.	Addressed.
1(6)	Addendum. Vol 3 CA B.5.1.2.1. Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate studies, KIIA7.2.3/01, KIIA7.2.3/02	EFSA: LOQ of 0.0005 µg/kg was reported, a clarification is needed how this LOQ was set.	Applicant (SYN): Please check reply to comment 1(4) for detailed response. RMS: Amended accordingly.	Addressed.
1(7)	Addendum. Vol 3 CA B.5.1.2.1. Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate studies,	EFSA: LOQs of the methods were set at the lowest calibration point. Please note that according to SANCO/3029/99 rev.4 LOQ is defined as the lowest concentration tested, at which an acceptable mean recovery (70-110%), with an acceptable RSD (<20%) is obtained	Applicant (SYN): Noted – agreed that the definition of LOQ within SANCO/3029/99 rev. 4 was not used to define the LOQ within this study. In some studies it is clear that reliable quantification is achievable below the lowest fortification level (e.g. Robinson, 2012, KIIA7.2.3/01) where 0.008 mg/kg/10% of applied chemical was the lowest fortified recovery level). However, calibration lines were plotted below this value to account for potential lower soil degradation values, so a lower LOQ was stated e.g. 0.0026 mg/kg. The study is considered fit-for-purpose. RMS: Agreed with answer of applicant. In addition, for some methods, only one determination at each recovery level was made and therefore, no mean and RSD could be determined at the lowest concentration tested.	Addressed. According to SANCO/3029/99 rev. 4, LOQ should be defined at the lowest concentration tested, at which an acceptable mean recovery, with an acceptable RSD is obtained. It is noted the applicant's and RMS' proposals - LOQ to be set at the lowest calibration level and supporting explanation. EFSA considers the proposal as acceptable, however amounts measured below the lowest fortification levels should be considered with an uncertainty.

1(8)	Addendum. Vol 3 CA B.5.1.2.1. Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate studies Simmons, D., Burns, G., McLean, N. (2009)(KIIA7.3.1/05, report No T001309-02, 08SYN122.REP, NOA407855_50087)	EFSA: RMS concluded that the two methods are validated according to guideline SANCO/3029/99 rev 4. However, some of the important validation parameters are not reported e.g. calibration range for each of the metabolites, information at which level recoveries for each metabolite were investigated and the value of these recoveries. In addition, LOQ of 0.05 µg/kg for all analytes is reported. A clarification is needed how this LOQ was set.	Applicant (SYN): The study was analysed using analytical method 35-01 which has been fully validated to SANTE/2020/12830 and is therefore demonstrated to be fit-for-purpose. The study presents a good level of validation data although it is acknowledged that it is not all presented in detail within the report. The study and associated validation are considered fit-for-purpose. The method LOQ is stated as 0.5 ppb = 0.5 µg/kg which is the same as the LOQ in the method used (35-01). Syngenta has conducted a new validation for method 35-01 that also confirms the full validityof the mothod 35-01 (Watson, 2022; Report No. RES-00370) according to SANTE/2020/12830. The new validation will be part of upcoming AIR6 submission and can be submitted upon request. RMS: As indicated in the DAR Addendum 2, full validation is provided in method M35-01 in the DAR of pinoxaden.	Addressed. Method was validated with a LOQ of 0.5 µg/kg in the original DAR.
1(9)	Volume 3 CA B.5, B.5.1.2.1. Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate studies, KIIA7.2.3/01-05, p. 6-13.	NL: The following is concluded (by the RMS? See above point) for these five analytical method summaries *"Matrix effects were not assessed, only one determination at each recovery level and therefore no RSDs/ repeatability available. Therefore, the method is not fully validated according to guideline SANCO/3029/99 rev 4 but considered fit for purpose."*. However if the validation criteria are not met, correctly the analytical method is not validated according to SANCO/3029/99 rev. 4, nonetheless	Applicant (SYN): The applicant agrees with the RMS conclusion that the method is fit-for-purpose. Although the recovery data was not generated to the SANCO/3029/99 rev 4 guidance (i.e. 5 recoveries at duplicate levels), 21 recoveries across 3 soil types at 7 different levels have been analyesed. RSDs <5 for each soil. Calibration plots are presented R > 0.99, and controls samples analysed. The methodology has been validated to a good level and can be considered fit-for-purpose.	Addressed. EFSA agrees with RMS assessment of the methods.

		the AM is still considered to be fit for the intended purpose without any further substantiation. Therefore the RMS is requested to state in more detail the reason for acceptability, why is the AM considered fit for the intended purpose. Furthermore, the linear range is expressed in µg/mL, whereas the recoveries/LOQ are expressed in mg/kg, please state the linear range also in mg/kg. In addition the fortification levels are also stated to be between 10-100% of the initial amount, however no information is presented on the initial amount, please specify.	The calibration range is 0.0005 µg/ml to 0.5 µg/mL which is equivalent to 0.0026 mg/kg dry soil to 2.6 mg/kg dry soil. Fortification levels are 90% - 10% of the applied amount (equivalent to 0.08 mg/kg). RMS: Information is amended in the DAR Addendum 2. As explained by the applicant, the methods are considered as fit for purpose as linearity and specificity were acceptable, and the recoveries for each fortification level were good (even though not determined 5 times). A more detailed conclusion is amended.	
1(10)	Volume 3 CA B.5, B.5.1.2.1. Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate studies, KIIA7.3.1/01-05	NL: The linear range is expressed in ng/mL, whereas the recoveries/LOQ are expressed in mg/kg, please state the linear range also in mg/kg. Furthermore, the linear range of KII7.3.1/05 is not stated at all and no recovery/fortification levels are mentioned.	Applicant (SYN): KIIA7.3.1/01: Range = 1.5 - 200 µg/kg (0.0015 – 0.2 mg/kg) KIIA7.3.1/02 – As above KIIA7.3.1/03 – As above Appears to be a numbering error as there is no KIIA7.3.1/04 KIIA7.3.1/05 – Procedural recoveries are assumed to be at the same level as the storage stability samples (5 ng/g). Agreed that this is not made clear in the report. RMS is kindly requested to update the DAR addendum accordingly. RMS: Amended accordingly. Full validation for KIIA 7.3.1/05 is provided under method M35-01 in the DAR of pinoxaden.	Addressed.
1(11)	Volume 3 CA B.5, B.5.1.2.1. Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate	NL: The linear range is expressed in µg/mL, whereas the recoveries/LOQ are expressed in mg/kg, please state the linear range also in mg/kg (at least as soils are used the recovery is assumed to be expressed in mg/kg, rather than µg/mL). Furthermore, no recovery/fortification levels are	Applicant (SYN): The applicant agrees with the RMS that the studies are fit for purpose. It is agreed that the definition of LOQ within the study is not as described in SANCO/3029/99 rev. 4. However, from the chromatograms presented it is noted that 0.0001 µg/mL is clearly	Addressed. For LOQs see EFSA reply in 1(7).

	studies, KIIA7.4.2/01-05, p. 19-26.	mentioned. In addition the LOQ is based on the signal/noise ratio which is not in agreement with SANCO/3029/99 rev. 4. In case of KIIA7.4.2/01 the LOQ is below the lowest calibration level. Also in all these summaries the conclusion is that the validation does not meet the requirements of SANCO/3029/99 rev. 4, but it is considered fit for the intended purpose without further substantiation. Therefore the RMS is requested to state in more detail the reason for acceptability, why is the AM considered fit for the intended purpose.	quantifiable and significantly above background noise. For KIIA 7.4.2/01 the lowest measured concentration is 0.0033 µg/ml; the lowest point in the calibration line is 0.0005 µg/ml. LOQ is stated as 0.0001 µg/mL taken from the lowest concentration chromatogram presented. Studies KIIA7.4.2/01-05 are adsorption/desorption studies and concentrations are those measured in the aqueous supernatant, thus calibration units are appropriate to be expressed in µg/ml. RMS: The conclusion is amended. RMS agrees with the applicant that for the adsorption/desorption studies, the calibration concentration in µg/mL is acceptable.	
1(12)	Vol. 3, B.5.1.2.2, Olangua, 2019 (KIIA 5.8/05, p. 26)	DE: In the study summary, no information about extraction and clean-up is given. It should be added as basic method information. For the analyte, a quantification transition as well as two confirmatory transitions are mentioned. Please state if recovery and precision data, calibration data as well as chromatograms were provided for all transitions.	Applicant (SYN): In the final report all required information are stated. In Appendix 1, page 52 of the full report following is stated: Blank matrix (20 µL) was fortified with recovery working solution (10 µL) in the appropriate wells of a 96 well plate and diluted with acetonitrile (170 µL), vortex mixed for 5 minutes at 1000 rpm, and centrifuged at 4°C and 3000 g for 10 minutes. 100 µL of supernatant was transferred to a clean 96 well plate and diluted with 375 µL of mobile phase A [Water/Formic acid/1M Ammonium Formate (aq) (100/0.2/0.2, v/v/v)] and 25 µL of MeOH/DMSO (50/50, v/v), followed by vortex mixing at 700 rpm for 5 minutes.	Addressed. Part of the missing information has been included in the updated addendum, although some mismatching between the information provided by the applicant and reported by RMS is noted. However, all needed information to conclude that the method is acceptable has been provided in column 3 of comments 1(12) and 1(19) of this table.

			For the purposes of confirmatory analyte response quantitation, the two confirmatory mass transitions were summed. Confirmatory recovery and precision data is provided in Table 5, page 27 and Table 7, page 29 of the full report. At a fortification level of 0.05 mg/L, individual sample recoveries ranged 96 – 101%, with a mean of 99% and RSD of 1.9%. At a fortification level of 0.5 mg/L, individual sample recoveries ranged 97 – 105%, with a mean of 101% and RSD of 3.0%. Confirmatory transition calibration data is provided in Table 3, page 25 and Figure 2, page 40 of the full report, showing a linear function of y = 124484.345x + 55.1644680 and R^2 of 0.9985 using $1/x^2$ weighting. Summed confirmatory transition chromatograms for the matrix blank, LOD standard, ULOQ standard (highest concentration calibration standard), LOQ fortified sample and 10 x LOQ fortified sample are presented in Figures 8 – 12, pages 46 – 50 of the full report. RMS is kindly requested to update the study summary accordingly. For upcoming AIR6 submission the study summary will be amended to include this information and clarify the summing of confirmatory transitions for confirmatory analyte quantitation. RMS: Information is amended.	
1(13)	Vol. 3, B.5.1.2.2., Shah, 2019 (KIIA5.8/09, p. 29)	DE: In the study summary, no information about extraction and clean-up is given. It should be added as basic method information.	Applicant (SYN): In the final report all required information are stated. Appendix 1, page 51 of the full report states following: Blank matrix (20 µL) was fortified with recovery working solution (10 µL) in the appropriate	Addressed.

			wells of a 96 well plate and diluted with acetonitrile (70 µL), vortex mixed for 5 minutes at 1000 rpm, and centrifuged at 4°C and 3000 g for 10 minutes. An aliquot of supernatant (50 µL) was transferred to a clean 96 well plate and diluted with 125 µL of mobile phase A [Water/Formic acid/1M aqueous Ammonium Formate (100/0.2/0.2, v/v/v)] and 25 µL of MeOH/DMSO (50/50, v/v), followed by vortex mixing at 1000 rpm for 5 minutes. RMS is kindly requested to update the study summary accordingly. For upcoming AIR6 submission the study summary will be amended accordingly. RMS: Information is amended.	
1(14)	Vol. 3, B.5.1.2.2.; Shah, 2019a (KIIA5.8/11, p. 31)	DE: Please check and correct the MS/MS transitions. In the method description of the study the transitions m/z 359.1→203.2 & 359.1→159.2 are given.	Applicant (SYN): Mass transitions of 359.1 → 203.2 (Quantitative) and 359.1 → 159.2 (Confirmatory) confirmed from study report. Mass transitions given in the study summary appear to have been a typographical error. RMS is kindly requested to update the study summary accordingly. For upcoming AIR6 submission the study summary will be amended accordingly. RMS: Amended.	Addressed.
1(15)	Vol. 3, B.5.1.2.2., Shah, 2019b (KIIA5.8/13, p. 33-34)	DE: The study title refers to SYN546106 but in the complete section, SYN546105 is mentioned as analyte. Please check and correct the section. Different MS/MS transitions are given in the method description of the study (m/z 361.0→173.1 & 361.0→217.1). Please check and correct.	Applicant (SYN): Analyte confirmed as SYN546106 from study report; no analysis of SYN546105 took place as part of this study. This appears to have been a typographical error. RMS is kindly requested to update the study summary accordingly. For upcoming AIR6 submission the study	

			summary will be amended accordingly. RMS: Amended.	
1(16)	Vol. 3, B.5.1.2.2., Mustchin, 2019 (KIIA5.8/21, p. 37)	DE: Please correct the analyte name in the section "principle of the method". Additionally, details on extraction and clean-up procedure are missing and should be added as important method information.	Applicant (SYN): Analyte confirmed as SYN546108 from study report; no analysis of SYN546105 took place as part of this study. This appears to have been a typographical error. RMS is kindly requested to update the study summary accordingly. Appendix 1, page 54 of the full report states following: Blank matrix (20 µL) was fortified with recovery working solution (10 µL) in the appropriate wells of a 96 well plate and diluted with acetonitrile (170 µL), vortex mixed for 5 minutes at 1000 rpm, and centrifuged at 4°C and 3000 g for 10 minutes. An aliquot of supernatant (100 µL) was transferred to a clean 96 well plate and diluted with 375 µL of mobile phase A [Water/Formic acid/1M aqueous Ammonium Formate (100/0.2/0.2, v/v/v)] and 25 µL of MeOH/DMSO (50/50, v/v), followed by vortex mixing at 700 rpm for 5 minutes. RMS is kindly requested to update the study summary accordingly. For upcoming AIR6 submission the study summary will be amended accordingly. RMS: Amended.	Addressed.
1(17)	Addendum. Vol 3 CA B.5.1.2.2. Methods in feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies, Davies, I., Castle, B.,	EFSA: A clarification on the LOQ of the method is needed. LOQ of 0.25 ng/mL, however the lowest fortification level reported is 25 ng/mL	Applicant (SYN): Lowest fortification level for the recovery assessment confirmed at 25.0 ng/mL from study report. This appears to have been a typographical error. RMS is kindly requested to update the study summary accordingly.	Addressed.

	(2018)(KIIA 5.8/15, report No BFI0729)		RMS: Amended.	
1(18)	Addendum. Vol 3 CA B.5.1.2.2. Methods in feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies, Davies, I., Castle, B., (2018)(KIIA 5.8/19, report No BFI0728)	EFSA: It is stated that recovery was investigated at two fortification levels, however only one value for recovery is reported (75.37 %). Is this the recovery at 25.0 ng/mL? In addition, LOQ of 0.25 ng/mL, however the lowest fortification level reported is 25 ng/mL, a clarification is needed	Applicant (SYN): The mean recovery value quoted in the study summary is the lower of the two mean recoveries generated (hence ≥ 75.37%). The 3200 ng/mL fortification level had a mean recovery of 82.74%. In this case, the 75.37% value is the mean recovery at the 25.0 ng/mL level. This statement does not specify, however, that both recoveries were within the 70 – 110% acceptable range, in accordance with the guidance in force at the time of submission. RMS is kindly requested to update the study summary accordingly. Lowest fortification level for the recovery assessment (and therefore LOQ of the method) confirmed at 25.0 ng/mL from study report. This appears to have been a typographical error. RMS is kindly requested to update the study summary accordingly. For upcoming AIR6 submission the study summary will be amended accordingly. RMS: Amended.	Addressed.
1(19)	Volume 3 CA B.5, B.5.1.2.2. Methods in feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies, KII5.8/05, p. 26-27.	NL: No data on the recovery and RSD are stated in the summary, although it is mentioned that the recovery is within 70-100% and the RSD is <20%, no data is presented to support this claim.	Applicant (SYN): Recovery and precision data for fortified samples at the 0.05 mg/L level are presented in Table 4, page 26 (Quantitative transition) and Table 5, page 27 (Summed confirmatory transitions) of the full report. The individual recoveries ranged from 91 – 103% with a mean of 98 % and RSD of 4.5% for the quantitative transition, and ranged 96 – 101% with a mean of 99% and RSD of 1.9% for the	See 1(12)

			summed confirmatory transitions. Data for fortified samples at the 0.5 mg/L level are presented in Table 7, page 29 of the full report (for both the quantitative transition and summed confirmatory transitions). The individual recoveries ranged from 97 – 103% with a mean of 100 % and RSD of 2.6% for the quantitative transition, and ranged 97 – 105% with a mean of 101% and RSD of 3.0% for the summed confirmatory transitions. RMS is kindly requested to update the study summary accordingly. For upcoming AIR6 submission the study summary will be amended accordingly to include the range of individual sample recovery values, and mean recovery and RSD values, for both fortification levels and both the quantitative transition and summed confirmatory mass transitions. RMS: Missing information is amended.	
1(20)	Volume 3 CA B.5, B.5.1.2.2. Methods in feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies, KII5.8/06, p. 27-29.	NL: Also in all this summary the conclusion is that the validation does not meet the requirements of SANCO/3029/99 rev. 4, but it is considered fit for the intended purpose without further substantiation. Therefore the RMS is requested to state in more detail the reason for acceptability, why is the AM considered fit for the intended purpose.	Applicant (SYN): The conclusion of non-compliance with the validation requirements under SANCO/3029/99 rev. 4 are based upon the fact that there were no efforts towards a determination of an LOQ of the method performed as part of the method validation. However, as detailed in Section 3.2.4, page 11 and Section 4.4, page 12 of the study report, the acceptance criterion for the validation of specificity were that any interfering peaks detected at the established retention time of the analyte in both diluted vehicle and diluent samples were to have a peak	Addressed.

			area of no greater than 2% of that of the lowest concentration standard, and no interfering peaks were detected in either sample. This is confirmed by the representative chromatograms of the diluent and diluted vehicle samples displayed in Figure 4, page 22 and figure 5, page 23 of the study report, respectively, along with the representative chromatogram of the lowest concentration calibration standard displayed in Figure 2, page 20 of the study report. As such, the stated criteria for specificity and results of the specificity validation, along with the other acceptable validation data, effectively show the method is fit for the intended purpose despite lacking any definition of, or method of determination for, the LOQ of the method. RMS: Conclusion is amended.	
1(21)	Volume 3 CA B.5, B.5.1.2.2. Methods in feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies, KII5.8/15-19, p. 34-37.	NL: Data on the RSD for each fortification level (repeatability) is missing, it is only stated that the RSD is < 20%, therefore this claim is not fully supported. Furthermore, the LOQ is stated to be 0.25 ng/mL, however the lowest recovery was measured at 25.0 ng/mL, please clarify this contradiction.	Applicant (SYN): RSDs of the recoveries were not reported but may be calculated from the peak area data reported and are given below. For KII5.8/15, the calculated RSDs for SYN546107 are 5.11% at 25.0 ng/mL and 2.77% at 3200 ng/mL for SYN546107. The calculated RSDs for tolbutamide range from 1.80% to 3.38%. For KII5.8/19, the calculated RSDs for SYN546107 are 4.40% at 25 ng/mL and 7.92% at 3200 ng/mL. The calculated RSDs for tolbutamide range from 2.96% to 7.03%. Study summaries will be amended to include calculated RSD values. Amended study summaries will be	Addressed.

			submitted in course of AIR6 dossier and can be provided upon request. Lowest fortification level for the recovery assessment (and therefore LOQ of the method) confirmed at 25.0 ng/mL from both study reports. This appears to have been a typographical error. Study summaries will be amended for AIR6 submission to correct this information and can be provided upon request. RMS: Amended.	
1(22)	Vol. 3, B.8, Langridge, 2019 (KIIA 7.12/18 & KIIA 7.12/42, p. 366)	DE: It is stated, that the analytical method GRM017.06B is used for the analysis of water samples. However, the description of the method and presentation of validation data are missing in Vol. 3, B.5. If it has not been presented in previous addenda of the DAR, the method should be added and evaluated in Vol. 3, B.5.	Applicant (SYN): A description of analytical method GRM017.06B together with an ILV is given in the DAR Addendum 1 to Volume 3 – B.5, which has been evaluated already in 2019 by the RMS. RMS: Noted.	In the DAR Addendum 1 (2019) description and validation data for method GRM017.06**A** and an ILV of method GRM017.06**B** were reported. It has been clarified by RMS that both methods should be considered as standalone methods (different conditions are used for M56) and none of them has an ILV (see RMS reply in column 3 of comment 1(3) of commenting table for confirmatory data a). It remains unclear whether method GRM017.06B is identical with Watson, 2017 (indicated as an ILV for GRM017.06B).

Section 2 – Effects on human and animal health

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**	**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)	Missing documentation	EFSA: an overview table on the toxicological profile of metabolites would be useful to have an overall picture of the previous assessment	Applicant (SYN): Thanks a lot for the comment. In case RMS intends to add such an overview, Syngenta can	Addressed. Overview table of metabolites M3, M11, M54, M55 and M56 added to section 5.8. of the addendum.

		complemented by the current assessment. The applicant/RMS is suggested to compile the template: IUCLID templates for PPP Risk Assessment - Template 5.4 - Template summary table on the assessment of the toxicological profile of metabolites https://doi.org/10.5281/zenodo.4557353	support the RMS in the generation of the table upon request. RMS: provided overview table of metabolites M3, M11, M54, M55 and M56 from applicant was added at the beginning of the section 5.8. of the addendum.	
2(2)	Addendum Vol. 1, Table 1.1-2 and 1.2 Relevance assessment of pinoxaden metabolite M2	DE: As stated, M2 (NOA 407854) is a major rat metabolite of pinoxaden in the metabolism of rats (more than 94 % of radioactivity was found in urine). However, the conclusion that M2 is non-genotoxic by analogy with the parent pinoxaden is not considered sufficiently robust for several reasons (please see column 3).	Applicant (SYN): Thank you for the feedback. Syngenta can confirm that a new Ames assay, new in vitro micronucleus assay and a new HPRT assay have been conducted with M2. All results are negative. The reports will be made available at AIR6 and can be submitted upon request. RMS: please refer to answer provided by applicant. _____ - It is not clear, whether M2 is also formed under *in vitro* conditions and has therefore been sufficiently investigated in the Ames test, the chromosomal aberration test and the MLA test with the parent pinoxaden. - A possible genotoxic potential of M2 without metabolic activation cannot be excluded, as this condition was not investigated in the studies conducted with pinoxaden. However, this condition must be addressed. - The micronucleus assay *in vivo* with pinoxaden was performed with mice. Is there evidence,	Addressed. Additional genotoxicity studies on **M2** to be considered under additional peer review process. If M2 exceeds 0.1 µg/L, it should be considered a relevant metabolite according to the EC guidance since it contributes to the toxicological profile of the active substance and it has comparable biological activity to pinoxaden. See also 2 (12)

			that M2 is also formed in the metabolism of mice and reaches the bone marrow? According to EFSA's clarification of some aspects related to genotoxicity assessment by (EFSA Journal 2017;15(12):5113), *"a rationale (substantiated by data) for considering this data representative of the species used in the genotoxicity study must be presented."* - The only genotoxicity test that can be used to determine with certainty that M2 has been formed is the UDS *in vivo* with pinoxaden. However, this test is no longer recommended due to its low sensitivity (EFSA Journal 2017;15(12):5113) and can therefore only be considered as supporting information in this context. According to SANCO/221/2000 – rev.11, metabolites exceeding 0.1 µg/L in groundwater must be tested for genotoxicity by an Ames test, an *in vitro* Mammalian Cell Gene Mutation Test (tk or hprt locus) and an *in vitro* micronucleus test. If the genotoxicity data of the parent substance are to be used for the metabolite, further information is required (see above).	
2(3)	Addendum Vol. 1, 1.3.5 Conclusion on relevance of the pinoxaden metabolite M3	DE: The reduction of the NOAEL for developmental effects (variant cartilage findings) and maternal effects to 30 mg/kg bw per day is supported. The maternal NOAEL is also supported by the decreased food intake by -14 % and -23 %, respectively. However, the toxic	Applicant (SYN): Thank you for the feedback. Syngenta agrees with the reported NOAEL for maternal toxicity (100 mg/kg/day). At doses of 300 mg/kg/day, absolute bodyweight loss was observed at the beginning of the study which persisted through to Day 9 of gestation and, bodyweight gain lagging beyond day 9 for the	**Peer review proposed** to discuss NOAEL setting in the developmental toxicity study on **M3** in rabbits and its relevance as a groundwater metabolite. See also 2(10, 15, 16, 17, 18, 19, 32).

		maternal effects are considered to be only slight.	remainder of gestation compared to other dose groups. Animals in dose group 5 (300 mg/kg/day) had a mean absolute bodyweight loss of 115 grams (-3.3%) over 8 days of dosing (day 6 – 13). In contrast, the control group, who had a net gain in mean body weight of 72.5 grams (~2.5%). Absolute bodyweight loss at 300 mg/kg/day was accompanied by decreased food intake -23 %. Food consumption is a strong indicator of toxicity in rabbits. An absolute bodyweight loss in combination with reduced food consumption at 300 mh/kg/day is considered adverse. RMS: thank you.	
2(4)	Addendum Vol. 1, 1.4.3.3 & 1.4.5; 1.6.3.3 & 1.6.5; 1.7.3.3 & 1.7.5; 1.8.3.3 & 1.8.5; 2.4, 2.5 Screening for Toxicity for M11, M54, M55 and M56	DE: Based on the present information DE has doubts to conclude that the metabolites M11, M54, M55 and M56 are not developmentally toxic (see further explanations).	Applicant (SYN): Thank you for the feedback. The need to assess the relevance of metabolites is not dictated by structural similarity or *in vivo* metabolism, it is purely based on the hazard classification of the parent molecule alone. Taking this into consideration, M3 is the environmental parent molecule to M11, M54, M55 and M56 and therefore the hazard profile of M3 can be used to determine the relevance of metabolites which form from M3 (M11, M54, M55 and M56). In agreement with EFSA, the relevance of metabolites formed from another metabolite would be covered by the toxicity profile of the precursor and, providing a lack of developmental toxicity is demonstrated for M3 metabolite, this should reasonably be applicable to metabolites proven to be degradation products of M3 in the environment in line with the guidance	**Peer review proposed** to discuss general approach to consider data from M3 for relevance assessment of the downstream metabolites (grouping approach for the non-relevance assessment of M3, M11, M54, M55 and M56; as well as of the comparison to a threshold of concern of 0.02 µg/kg body weight per day at groundwater relevance assessment Step 4.). EFSA notes that if metabolite M55 exceed 0.1 µg/L; it should be already considered a relevant metabolite following the EC guidance document on the assessment of the relevance of groundwater metabolites since and M55 showed equivocal /positive results in the *in vivo* Comet assay (see 2(6)). The discussion should also consider potential differences on toxicity for those groundwater metabolites

			document on the assessment of groundwater metabolites (stage 3 of step 3 of the assessment of the relevance of metabolites). To summarise, we couldn't (and still cannot) synthesise these metabolites in kilogram quantities required, hence we proposed testing with M3 and grouping approach which was accepted by EFSA in 2016. In addition, we conducted a pan-European groundwater monitoring study to establish realistic levels of these metabolites in the groundwater. The developmental toxicity study with M3 was negative and the monitoring study demonstrated that the metabolites are not found at levels above 0.1µg/L in the groundwater. Further to this the metabolites have been demonstrated not to have ACCase inhibition properties – see reply to comment in point 2(9) below for further details. For a more detailed answer on the grouping approach, reference is made to reply to comment 2(7) RMS: Noted. Due to BREXIT RMS changed from UK to AT in 2019/2020. Grouping approach was discussed between former RMS UK, applicant and EFSA. _____ The use of a grouping approach is appreciated. However, in our opinion, validation of the grouping approach as presented in Appendix 1 of the Addendum to Volume 1 is still lacking. The argument that M3 is the	containing a chiral centre (i.e. all of them except M3 and M11). See also 1 (4), 2(7, 8, 36) and 4(49).

			precursor metabolite in soil/environment does not justify the assumptions concerning the potential mammalian toxicity of down-stream metabolites. Such an approach could only be supported if M11, M54, M55 and M56 were also major metabolites identified in animal metabolism studies (in this case in rabbits), not as environmental breakdown products. A read-across assessment for these metabolites that is in accordance with the requirements of the ECHA (RAAF, ECHA-17-R-01-EN) and/or the OECD Guidance on Grouping on Chemicals (ENV/JM/MONO(2014)4) is needed. Based on the available data, metabolites M11, M54, M55 and M56 are not considered acceptable in concentrations above 0.1 µg/L in groundwater.	
2(5)	Addendum Vol. 1, 1.5.5 Conclusion on relevance of the pinoxaden metabolite M52	DE: The opinion of RMS is supported, a possible developmental toxicity of M52 is not clarified. A read-across assessment for M52 consistent with ECHA (RAAF, ECHA-17-R-01-EN) and/or OECD guidance on grouping of chemicals (ENV/JM/MONO(2014)4) is required.	Applicant (SYN): Thank you for the feedback. If M52 exceeds 0.1 µg/L then it would be considered a relevant metabolite. However, following the endpoint parameter set proposed by RMS AT, M52 is below 0.1 µg/L in 7 out of 9 scenarios in the Tier-1 FOCUS modelling, whereas only one scenario pass is required for EU approval. The Tier-1 modelling provided by the applicant, considering the field DT50 of the precursor metabolite M2 shows maximum concentrations of 0.002 µg/L for M52, far below the trigger of 0.1 µg/L. In addition, the Tier-4 groundwater modelling shows that M52 is below 0.1 µg/L considering the 90th percentile annual maximum	Addressed. If M52 exceeds 0.1 µg/L, it should be considered a relevant metabolite according to the EC guidance since data are not available to show that M52 does not share the toxicological properties of pinoxaden. See also 2(13, 38).

			concentration. With this, M52 is not considered a relevant metabolite. RMS: Thank you.	
2(6)	Addendum Vol. 1, 1.7.3.2 STEP 3, Stage 2: screening for genotoxicity for M55	DE: The RMS conclusion for metabolite M55 is supported. The comet assay is considered equivocal due to the occurrence of numerous hedgehog cells. As no indications of cytotoxicity were reported, the aetiology of these cells remains unclear and the OECD TG does not provide guidance interpreting such results. As such, a genotoxic potential of M55 cannot be excluded and the metabolite is considered relevant according to the SANCO/221/2000 guidance document.	Applicant (SYN): Thank you for the comments. Syngenta agree that the *in vivo* rat alkaline comet assay in the duodenum is equivocal after SYN546107 oral administration of male Crl:CD (SD) rats due to the confounding presence of hedgehog cells. Syngenta disagree that BMD cannot be used for a genotoxic endpoint and refers to detailed comment in section 2 (27). RMS: Thank you. _____ In accordance with the RMS, it must be noted that an *in vivo* comet assay is not appropriate for deriving an ADI. No mechanistic data are available that clearly show a threshold mechanism leading to genotoxicity. In general, no threshold value is assumed for genotoxicity and therefore no reference values can be used, even if using a BMD approach.	Addressed. If **M55** exceeds 0.1 µg/L, it should be considered relevant based on hazard assessment, Stage 2 of Step 3: Screening for genotoxicity, based on positive results in the Ames Test and equivocal results in the *in vivo* Comet assay. See also 2(11, 26, 27, 28, 33, 34, 39, 40).
2(7)	Addendum. B.6. Page 9 Comments of RMS:	EFSA: According to the RMS the rabbit developmental toxicity study (OECD 414) conducted with M3 (as precursor in the environment of the other metabolites) may be used to address the relevance of groundwater metabolites M11, M54, M55 and M56. However, this is not totally in line with the European Commission Guidance, on which the comparison of each metabolite is normally done against the parent, i.e. active substance. This approach to consider the precursor, instead of the active	Applicant (SYN): Thank you for the comments. Syngenta is surprised about EFSA's comment because ahead of the submission of the Confirmatory Data EFSA expressed its opinion about the submitted "grouping" approach. In 2016, Syngenta presented its strategy regarding the grouping approach to EFSA via the (pre-Brexit) RMS (UK) and received the following response from EFSA: "*According to applicant's claim above, M3 is the precursor of metabolites*	See 2(4).

		substance, should be further discussed and agreed by Member States. Please noted that it would be better to conduct a formal grouping and read-across approach for the different metabolites from the toxicological point of view, currently missing.	*M11, M54, M55 and M56 in the environment, but not M52. On this basis, provided that adequate evidence is given that the M3 is their precursor and having into consideration the "general concept" of the guidance document on the relevance of groundwater metabolites for PPPs, we would agree that in terms of toxicity screening according to stage 3 of step 3, the relevance of metabolites formed from another metabolite would be covered by the toxicity profile of the precursor."* Again in 2017, Syngenta approached EFSA with the following question "Do EFSA agree that with the above justifications a developmental toxicity study with M3 will be sufficient to establish the non-relevance of pinoxaden groundwater metabolites M3, M11, M54, M55 and M56?". The following response was received from EFSA: "*Provided that a lack of developmental toxicity is demonstrated for M3 metabolite, as already answered in 2016, we agree that this should reasonably be applicable to metabolites proven to be its degradation products in the environment in line with the guidance document on the assessment of groundwater metabolites (stage 3 of step 3 of the assessment of the relevance of metabolites).*" Therefore, in agreement with EFSA and the RMS the "grouping" strategy was followed. The applicant conducted a developmental toxicity study according to OECD 414 in the rabbit

			with M3, in addition to a dose range finding study and a toxicokinetic study. The OECD 414 study results do not warrant a developmental toxicity classification for metabolite M3. The relevance of metabolites which formed from another metabolite are therefore covered by the toxicity profile of the precursor. Syngenta expects that EFSA's input prior the submission of the confirmatory data is still valid and should be followed in the further assessment of the Pinoxaden Confirmatory Data. In addition, Syngenta is of the firm opinion that conducting a developmental toxicity study with M3 only is a technically robust and conservative approach to addressing the hazard potential of pinoxaden groundwater metabolites. Despite all metabolites being below 0.1 µg/L in the monitoring data, M3 has the highest predicted exposure of all groundwater metabolites in the tier 1 PECgw modelling data and has the highest frequency and concentrations of all the groundwater metabolites in GW monitoring. This approach also greatly reduces the potential number of animals required to establish the non-relevance of pinoxaden groundwater metabolites in line with Commission Regulation (EU) No 283/2013: Conducting 5x OECD 414 guideline studies with rabbits will require approximately 400 adult female rabbits (5 studies x 4 groups/study x 20 adult female rabbits/group). This

			estimate does not include animals used in dose range finding studies and approximately 10 times this number of pups. To summarise, we couldn't (and still cannot) synthesise these metabolites in kilogram quantities required, hence we proposed testing with M3 and grouping approach which was accepted by EFSA in 2016. In addition, we conducted a pan-European groundwater monitoring study to establish realistic levels of these metabolites in the groundwater. The developmental toxicity study with M3 was negative and the monitoring study demonstrated that the metabolites are not found at levels above 0.1µg/L in the groundwater. Further to this the metabolites have been demonstrated not to have ACCase inhibition properties – see comment in point 2(9) below for further details. RMS: Please refer to answer of applicant. Due to BREXIT RMS changed from UK to AT in 2019/2020. Grouping approach was discussed between former RMS UK, applicant and EFSA.	
2(8)	Addendum. B.6. Page 9 M11, M54, M55 and M56	EFSA: If the approach to consider M3 data for metabolites M11, M54, M55 and M56 is not agreed by Member States (or if M3 is considered relevant), metabolites M11, M54, M55 and M56 should be considered relevant metabolites according to the EC guidance since data are not available to show that M11, M54, M55 and M56 does not share the toxicological properties of pinoxaden.	Applicant (SYN): Thank you for the feedback. Syngenta agrees that if M3 is considered relevant, metabolites M11, M54, M55 and M56 could be considered relevant if they exceed 0.1 µg/L. However, Syngenta's grouping strategy was agreed with EFSA via past RMS (UK) in 2016/2017 communication as a pragmatic way of addressing if metabolites M3, M11, M54, M55 and	See 2(4).

			M56 have the same toxicological properties as pinoxaden. Indeed, M3 was tested to 300 mg/kg/day (3x the top dose of pinoxaden) and did not reveal any relevant developmental findings which would warrant a classification for developmental toxicity. A detailed answer on the grouping approach can be found in 2 (7) above. RMS: please refer to answer at 2(7). However, we agree with comment made by EFSA.	
2(9)	Addendum. B.6. Page 9	EFSA: acknowledged the difficulty to synthesise in high amount some of the metabolites, as well as avoiding vertebrate testing. The pesticide mode of action of pinoxaden is inhibition of acetyl CoA carboxylase. This mechanism has been associated with malformation in rats and rabbits (Catlin et al. 2021; doi: 10.1093/toxsci/kfaa169) and may explain the developmental toxicity of pinoxaden, although there is not experimental data to demonstrate it. The applicant could explore to conduct a comparative *in vitro* mechanistic studies (as the alternative methods described in Catlin et al. 2021) with the parent compound and the groundwater metabolites in order to conclude on hazard identification for the metabolites.	Applicant (SYN): Thank you for the comment and sharing the publication. Syngenta refers to reply to comment 2(7) and reiterates that EFSA agreed that the relevance of metabolites formed from another metabolite would be covered by the toxicity profile of the precursor. M3 is precursor and "parent" to downstream metabolites and therefore, the relevance of downstream metabolites has been addressed by testing M3. In the study by Catlin et al. (2021) the author demonstrated that an Acetyl-CoA carboxylase (ACC) inhibitor, when administered orally to Sprague Dawley rats and New Zealand White rabbits, caused developmental toxicity. The author reported that some, but not all, of the invitro alternative screening assays also gave a positive signal, namely the murine embryonic stem cell [MESC] assay and rat whole embryo culture were able to predict the *in vivo* outcome in the rat and rabbit.	Peer review proposed to consider additional ACCase activity in pinoxaden metabolites.

			Although the paper claims to be indictive of hazard identification, the true goal of the paper was to inform risk assessment by identifying the dose at which near-complete inhibition of de novo lipogenesis (DNL) is achieved; at which point developmental toxicity is likely to occur. Doses below this point would not induce developmental toxicity and could be considered safe. The applicant does not believe that this paper would be a suitable model to address developmental toxicity of pinoxaden metabolites without in vivo testing, as the authors have used whole embryo culture, which required vertebrates and the outcome is predicable based on significant comparative work using knock-out mice and the use of rats and rabbits to confirm results. Syngenta acknowledge the link between Acetyl-CoA carboxylase (ACCase) inhibition and developmental toxicity, and that pinoxaden mechanism of action is ACCase inhibition. Biological activity data are already available for metabolites M11, M52, M54, M55 and M56. These data demonstrate that pinoxaden metabolites do not possess ACCase inhibition activity equivalent to pinoxaden (Pinoxaden – Biochemistry: In vitro Acetyl CoA Carboxylase enzyme assay to investigate the inhibitory effects of the metabolites of Pinoxaden, 2012).

			The absence of ACCase activity in pinoxaden metabolites is considered as sufficient additional weight of evidence and the data will be provided in course of AIR6 submission and can also be provided upon request. Although ACCase activity was assessed using enzymes extracted from chloroplasts of Poacease grass, ACCase activity is biologically conserved and plays a fundamental role in de novo long-chain fatty acid synthesis in both plant and animals. Therefore, the lack of ACCase inhibition activity in the biological activity studies are applicable to mammalian cells. RMS: please refer to answer provided by applicant.	
2(10)	Addendum. B.6. Britton L, 2017. [redacted] - Oral (Gavage) Prenatal Developmental Toxicity Study in the Rabbit. Laboratory Report No. [redacted] Page 17, 18.	EFSA: developmental toxicity effects were observed with M3, namely "foetal and litter incidence of thoracic vertebrae: one or more centra: dumbbell ossification in the 300 mg/kg/day dose group was statistically identified as higher than in Controls and was outside the historical control range". On this basis M3 could qualify of having a toxicological hazard of concern. According to the RMS as all ossification effects were observed in presence of maternal toxicity, there is no need to classify M3 for developmental toxicity. However, it should be further justified whether maternal toxicity can cause the ossification effects seen.	Applicant (SYN): Thank you for the feedback. Syngenta disagrees that the incident of dumbell ossification at 300 mg/kg/day is a toxicological hazard of concern. The conclusion of the toxicology report stated: "The foetal and litter incidence of thoracic vertebrae: one or more centra: dumbbell ossification in the 300 mg/kg/day dose group was statistically identified as higher than in controls and was outside the historical control range. However, given the lack of effects on any other measures of foetal development, this was considered a spontaneous change unrelated to treatment." Syngenta has extracted additional HCD data for 'Thoracic vertebrae: one or more centra: dumbell ossification' from another report which was conducted at the same CRO. At the	Peer review proposed to consider the additional Historical Control Data. See also 2(3).

time that the report was finalised, the HCD placed this occurrence at:

No. Of foetuses effected (0.4-0.7%)
No. Of Litters effected (4.4-5.8%)

The updated HCD now places this occurrence at:
No. Of fetuses effected (0.4-1.1%)
No. Of Litters effected (4.4-9.5%)

Although the occurrence of 3 fetuses (1.8%) from 3 litters (14.3%) is outside of HCD, it is only marginally outside of HCD: 1.8% vs 1.1% & 9.5% vs 14.3%.

Updated HCD will be submitted in course of AIR6 and can be provided to RMS upon request.

Ossification of vertebral bodies:
Ossification centers on each side of the vertebral body. With continued growth, the ossification centers touch each other (forming a dumbbell-shaped profile). The ossification centers then continue to expand throughout the vertebral body (DeSesso and Scialli, 2018). These findings (incomplete, bipartite and dumbbell ossification) are normal stages in skeletal development and are transient findings (Chahoud *et al*., 2015; Hofmann *et al*., 2016) that may indicate a slightly delayed schedule of events but do not indicate disrupted development (DeSesso and Scialli, 2018). Changes in the size, shape, or symmetry of sternebrae or vertebral centra are transient and have no implications for the health or survival of the offspring (DeSesso and

Scialli, 2018). In most circumstances, Thoracic vertebral ossification is completely resolved within days of birth and is not a permanent effect on the animal. Therefore, the higher incidences of the observations discussed above should be considered to be non-adverse. The small number of fetuses affected, lack of an affect (delay) on the incidence of other ossification parameters and minor difference between study incidence of top of the HCD is highly indicative of normal biological variability, of no toxicological significance.

References:

DeSesso JM, Scialli AR (2018) Bone development in laboratory mammals used in developmental toxicity studies. Birth Defects Res.; 110(15):1157-1187. doi: 10.1002/bdr2.1350.

Chahoud I, Talsness CE, Walter A, Grote K (2015) Postnatal investigation of prenatally induced effects on the vertebral column of rats reduces the uncertainty of classification of anomalies. Reprod Toxicol.; 58:15-23. doi: 10.1016/j.reprotox.2015.07.078.

Hofmann T, Buesen R, Schneider S, van Ravenzwaay B (2016) Postnatal fate of prenatal-induced fetal alterations in laboratory animals. Reprod Toxicol.; 61:177-85. doi: 10.1016/j.reprotox.2016.04.010

RMS: please refer to answer provided by applicant regarding provided new HCD.

			HCD data and assessment of body weight and body weight gain was included. RMS is still of the opinion that the initial body weight loss (days 6 to 7 of gestation) and the resulting lagging behind in body weight at 300 mg/kg bw/day and 100 mg/kg bw/day dosing groups compared to control should be considered in evaluation. The NOAEL for maternal toxicity was therefore set at 30 mg/kg bw/day.	
2(11)	Addendum. B.6. [redacted] (2018) SYN546107 – Crl:CD(SD) Rat In Vivo Comet Test. Laboratory Report No. [redacted] Page 95.	EFSA: If M55 exceeds 0.1 µg/L, it should be considered relevant based on hazard assessment, Stage 2 of Step 3: Screening for genotoxicity, based on positive results in the Ames Test and equivocal results in the *in vivo* Comet assay.	Applicant (SYN): Thank you for the feedback. Syngenta agrees with EFSA. If M55 exceeds 0.1 µg/L then it would be considered a relevant metabolite. However, following the endpoint parameter proposed by RMS AT, the Tier-4 groundwater monitoring shows that M55 is below 0.1 µg/L considering the 90th percentile annual maximum concentration (0.030 µg/L) or the maximum annual average concentration (0.018 µg/L, c.f. Vol 1). With this, M55 is not considered a relevant metabolite. Syngenta is conducting a transgentic rodent assay (OECD 488) in the rat with SYN546107 to understand the equivocal results in the duodenum. This study has been commissioned and will be submitted in course of AIR 6. RMS: agree with comment from EFSA.	See 2(6).
2(12)	Addendum. B.6 / Volume 1. M2	EFSA: If M2 exceeds 0.1 µg/L, it should be considered a relevant metabolite according to the EC guidance since it contributes to the toxicological profile of the active	Applicant (SYN): Thank you for the feedback. Syngenta agrees with EFSA, M2 contributes to the toxicology profile of pinoxaden and if it did exceed 0.1 µg/L then it would be considered a relevant metabolite.	See 2(2).

		substance and it has comparable biological activity to pinoxaden.	However, M2 concentrations are below 0.1 µg/L in the Tier-1 FOCUS modelling as well as the Tier-4 considering the 90th percentile annual maximum concentration and therefore M2 is not considered a relevant metabolite. RMS: agree with comment from EFSA.	
2(13)	Addendum. B.6. / Volume 1. M52	EFSA: If M52 exceeds 0.1 µg/L, it should be considered a relevant metabolite according to the EC guidance since data are not available to show that M52 does not share the toxicological properties of pinoxaden.	Applicant (SYN): Thank you for the feedback. Syngenta agrees with EFSA. If M52 exceeds 0.1 µg/L then it would be considered a relevant metabolite. However, following the endpoint parameter set proposed by RMS AT, M52 is below 0.1 µg/L in 7 out of 9 scenarios in the Tier-1 FOCUS modelling, whereas only one scenario pass is required for EU approval. The Tier-1 modelling provided by the applicant, considering the field DT50 of the precursor metabolite M2 shows maximum concentrations of 0.002 µg/L for M52, far below the trigger of 0.1 µg/L. In addition, the Tier-4 groundwater modelling shows that M52 is below 0.1 µg/L considering the 90th percentile annual maximum concentration. With this, M52 is not considered a relevant metabolite. RMS: agree with comment from EFSA.	See 2(5).
2(14)	Missing documentation	EFSA: RMS has not provided an updated list of endpoints that incorporates the new endpoints coming from their assessment of what was submitted against confirmatory data. Such a document is needed that should as the starting point for its preparation, use the	Applicant (SYN): RMS is kindly requested to update the LoEP in case this is required. Syngenta can support the RMS if needed upon request. RMS: LoEP will be provided.	Addressed

		document from the published EFSA conclusion. EFSA can make a word version of this document available on request to the pesticide peer review mailbox.		
2(15)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/01 (M3; NOA447204)	FI: Only slight body weight loss was observed in pregnant females at 100 and 300 mg/kg/day and no statistally significant difference was observed compared to controls. In addition, no clinical signs related to NOA447204 exposure were detected. Based on the available data, FI considers that setting the maternal NOAEL at 30 mg/kg/day, as suggested by the RMS, is not justified. As no clear toxicity was detected up to 300 mg/kg/day, FI would suggest a NOAEL for maternal toxicity at 300 mg/kg bw/day. In addition, when looking at the preliminary dose ranging studies, where NOA4472043 was dosed up to 300 mg/kg/day in non-pregnant (KIIA 5.8/02) and pregnant (KIIA 5.8/03) rabbits, only about ≤4% body weight loss was observed at the highest dose. No test-item related clinical signs were observed at any dose level in either of the studies. Based on the available results, it appears that the doses selected for the main test have not been high enough to reach a sufficient level of maternal toxicity.	Applicant (SYN): Thank you for the comments. Syngenta disagree that the doses used for the rabbit developmental toxicity study were not high enough to reach a sufficient level of maternal toxicity. M3 has been dosed up to a concentration of 300 mg/kg/day, this is equivalent to 3x the top dose which was dosed with pinoxaden and adequately investigates if the developmental toxicity classification of parent is relevant for metabolite M3 also. **Bodyweight and food consumption effects on main study (KIIA 5.8/01):** At doses of 300 mg/kg/day, absolute bodyweight loss was observed at the beginning of the study which persisted through to Day 9 of gestation and, bodyweight gain lagging beyond day 9 for the remainder of gestation compared to other dose groups. Animals in dose group 5 (300 mg/kg/day) had a mean absolute bodyweight loss of 115 grams (-3.3%) over 8 days of dosing (day 6 – 13). In contrast, the control group, who had a net gain in mean body weight of 72.5 grams (~2.5%). Absolute bodyweight loss at 300 mg/kg/day was accompanied by decreased food intake -23 %. Food consumption is a strong indicator of toxicity in rabbits. An absolute bodyweight loss in combination with reduced food consumption of with no	See 2(3).

sign of recovery is considered adverse.

Toxicokinetic study in pregnant rabbits (KIIA 5.8/03):
In the toxicokinetic study in pregnant rabbits, Animals in group 7 (300 mg/kg/day) had a mean absolute bodyweight loss for the first 9 days of treatment (days 6-14). From Day 15 onwards, animals in group 7 gained weight but lagged behind the control group and at the end of treatment (Day 28). Between day 6 and 28, control animals had a group mean body weight gain of 0.3275 kg, compared to the 300 mg/kg/day dose which had a group mean bodyweight gain of 0.175 kg. This equates to a bodyweight gain of 53% of the control value for the same period.

Dose range finder study in non-pregnant rabbits (KIIA 5.8/02):
Animals were dosed for 7 days. During this dose period, the control group mean bodyweight on Day 1 (2.9375 kg) and Day 7 (3.035 Kg) equates to a net bodyweight gain of (0.0975 kg), approximately +3.3%. In Contrast to this the 300 mg/kg/day group mean bodyweight on Day 1 (3.4875 kg) and Day 7 (3.4025 kg) equates to a net loss of absolute body weight of 0.085 kg, approximately -2.4%. During the time period Day 1-8, the control group mean food consumption was approximately 159 grams per day; in contrast, the 300 mg/kg/day dose group had a group mean food consumption of approximitaly 99 grams per day (~38% lower food

			consumption than controls). Reduced absolute bodyweight and reduced food consumption, especially in rabbits, is considered adverse. RMS: please refer to answer provided by applicant.	
2(16)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/01 (M3; NOA447204)	FI: We agree with RMS in setting the NOAEL for developmental toxicity of NOA447204 at 30 mg/kg bw/day. This conclusion is based on a statistically significantly increased litter incidence of one cartilage variant at 300 mg/kg/day compared to control. A similar finding was seen at 100 mg/kg bw/day, although not statistically significant. In conclusion, both foetal and litter incidences at 100 and 300 mg/kg bw/day are above the historical control range supporting a NOAEL value of 30 mg/kg bw/day. The values are also above the concurrent control values, especially concerning litter findings.	Applicant (SYN): Thank you for the comments. The number of foetuses with 'Rib – one or more: costal cartilage interrupted' was detailed in the report as follows: No. Foetuses effected (HCD 3.2-7.9): 0 mg/kg/day: 13 (9.4%) 10 mg/kg/day: 18 (9.2%) 30 mg/kg/day: 6 (3.1%) 100 mg/kg/day: 15 (9.5%) 300 mg/kg/day: 24 (14.1%) No. of Litters (HCD 27.3 – 42.9): 0 mg/kg/day: 9 (42.9%) 10 mg/kg/day: 9 (42.9%) 30 mg/kg/day: 6 (28.6%) 100 mg/kg/day: 12 (60.0%) 300 mg/kg/day: 13 (61.9%)* Syngenta has requested additional HCD to cover the time period after the study was conducted (Up to July 2020) to be able to analyses a 5-year HCD period (2.5 years either side of study date). Extract from additional HCD is highlighted below: **Updated HCD is as follow**: No. Foetuses effected (HCD 3.2-13.8) No. of Litters (HCD 27.3 – 71.4) The number of foetuses with incidence of 'Rib – one or more: costal cartilage interrupted' observed at 300 mg/kg/day is not statistically	See 2(3).

			significant but still marginally outside of updated HCD range: 14.1 vs 3.2-13.8 (HCD). The number of litters with incidence of 'Rib – one or more: costal cartilage interrupted' observed at 100 mg/kg/day and 300 mg/kg/day was 12 (60.0) and 13 (61.9)* respectively, with 300 mg/kg/day being statistically significant compared to control group. Due to the incidence at both 100 and 300 mg/kg/day being within updated HCD range (27.3 - 71.4), the finding is considered to be spontaneous and not a treatment related adverse effect. Updated HCD are stated in an amended report of KIIA 5.8/01 (Study No. [redacted]) and will be submitted in course of AIR6. Amended report can be provided upon request. RMS: thank you.	
2(17)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/01 (M3; NOA447204)	FI: As FI is of the opinion that it is questionable if doses high enough have been tested in the main study to observe toxic effects, the possible need for classification of M3 for developmental toxicity also remains unclear. This problem concerns equally other metabolites whose developmental toxicity was considered to be covered by the toxicity of metabolite M3.	Applicant (SYN): Thank you for the comment. Please see reply to comment 2(15) for detailed assessment of toxicity effects. RMS: please refer to answer provided by applicant.	See 2(3).
2(18)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/02 (M3; NOA447204)	FI: In the preliminary dose-ranging study in non-pregnant rabbits where the NOA447204 was dosed up to 300 mg/kg/day, only about ≤4% body weight loss was observed at the highest dose. No test-item related	Applicant (SYN): Thank you for the comment. Please see reply to comment 2(15) for detailed assessment of toxicity effects in preliminary dose-ranging study.	See 2(3).

		clinical signs were detected. Based on the available results, it appears that the doses selected for the main test have not been high enough to reach a sufficient level of maternal toxicity.	RMS: please refer to answer provided by applicant.	
2(19)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/03 (M3; NOA447204)	FI: In the preliminary dose-ranging study in pregnant rabbits where the NOA447204 was dosed up to 300 mg/kg/day, initial reductions in body weight were seen between days 6 and 13 (at 300 mg/kg/day) of gestation which resulted only in slightly reduced body weight gain over the dosing period. No test-item related clinical signs were detected. Based on the available results, it appears that the doses selected for the main test have not been high enough to reach a sufficient level of maternal toxicity.	Applicant (SYN): Thank you for the comment. Please see reply to comment 2(15) for detailed assessment of toxicity effects. RMS: please refer to answer provided by applicant.	See 2(3).
2(20)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites; General comment on *in vivo* MN tests	FI: It is extremely challenging to reach a sufficient bone marrow exposure in an *in vivo* micronucleus test for substances whose plasma concentration declines rapidly showing rapid excretion. For those substances an *in vitro* MN test would be a better choice for getting reliable results especially for aneugenicity. *In vitro* MN test is also recommended by the EFSA strategy for testing metabolites. Besides, connecting direct measurement of test substance concentration in bone marrow to an *in vivo* MN test would give a more accurate interpretation of bone marrow exposure.	Applicant (SYN): Thank you for the comments. Syngenta can confirm that proof of exposure studies conducted in 2019 have been conducted in accordance with the EFSA guidance (*Clarification of some aspects related to genotoxicity assessment* - 10.2903/j.efsa.2017.5113) and OECD 414 guidance (2016) to supplement *in vivo* micronucleus studies conducted prior to the OECD 474 guideline update in 2016. See excerpts from the guidance noted below: **Clarification of some aspects related to genotoxicity assessment - 10.2903/j.efsa.2017.5113:** ***"3.2. The adequacy to demonstrate target tissue exposure in in vivo studies,***	Addressed. In line with OECD TG 414 (2016) proof of exposure studies (plasma analysis) have been conducted. See also 2(21, 23, 24, 29).

			particularly in the mammalian erythrocyte Micronucleus test *"As mentioned in Section1.2, the SC assumes that the in vivo mammalian erythrocyte micronucleus (MN) test (OECD TG 474) has been selected as the appropriate test to follow-up a positive in vitro outcome. The SC notes that in this context appropriate means in vivo testing for the same endpoint as observed in vitro. If a positive result is observed in the in vivo mammalian erythrocyte MN test, demonstration of target tissue exposure is not needed. However, evidence of bone marrow exposure is needed to conclude that a substance is not genotoxic based on a negative mammalian erythrocyte MN test outcome.* ***3.2.1.7. Test substance detected systemically in a specific blood/plasma analysis*** *According to the revised version of the mammalian erythrocyte MN TG (OECD TG 474) adopted in July 2016 'A blood sample should be taken at appropriate time(s) in order to permit investigation of the blood/plasma level of the test substances for the purposes of demonstrating that exposure of the bone marrow occurred, where warranted and where other exposure data do not exist'. Detection of the test substance in a specific blood/plasma analysis above the quantification limit is sufficient evidence of systemic bioavailability of the test substance and, therefore, could be considered as a line of evidence of bone marrow exposure.*

			Regarding bone marrow exposure, the OECD Test Guideline (TG) 474 (July 2016), states: • *A blood sample should be taken at appropriate time(s) in order to permit investigation of the plasma level of the test substances for the purposes of demonstrating that exposure of the bone marrow occurred, where warranted and where other exposure data do not exist'* • *'[...]. Evidence of exposure of the bone marrow to a test substance may include a depression of the immature erythrocyte ratio or measurement of the plasma or blood level of the substance. In case of intravenous administration, evidence of exposure is not needed. Alternatively, ADME data, obtained in an independent study using the same route and same species, can be used to demonstrate bone marrow exposure. [...]'* • *If there is evidence from the mammalian erythrocyte MN test that the test substance induces toxic effects in the bone marrow, it can be concluded that the substance has reached the bone marrow. Moreover, as the bone marrow is a well-perfused tissue, systemic bioavailability of a test substance can be considered*

as a line of evidence of bone marrow exposure. Evidence on systemic bioavailability can also be obtained from toxicity studies when test-substance-related systemic toxicity is observed."

OECD 474 (2016) Mammalian Erythrocyte Micronucleus Test

"Evidence of exposure of the bone marrow to a test substance may include a depression of the immature to mature erythrocyte ratio or measurement of the plasma or blood levels of the test substance. In case of intravenous administration, evidence of exposure is not needed. Alternatively, ADME data, obtained in an independent study using the same route and same species can be used to demonstrate bone marrow exposure. Negative results indicate that, under the test conditions, the test chemical does not produce micronuclei in the immature erythrocytes of the test species."

Conclusion: Proof of exposure plasma bioanalysis has been conducted in line with relevant guidance documents and OECD test guidelines. This has demonstrated systemic bioavailability of the test substance and exposure of the bone marrow.

It is worth noting that recently it has been shown that in the majority of cases where the concentration of an administered test substance has been determined in the plasma, including in the area of pesticides, test

substance concentrations determined in the bone marrow are similar or in many cases higher, *"confirming that the measurement of plasma levels is suitable for evaluation of bone marrow exposure"* (Kirkland *et al.,* 2019). Additionally, it has been shown there is no correlation between the lowest effective concentration in an in vitro study and the lowest effective dose in an appropriate in vivo follow-up assay. (Kirkland *et al.,* 2022). Furthermore, the recent expert working group of the IWGT agreed it is unacceptable to reject a negative in vivo bone marrow MN test conducted to the maximum tolerated dose, maximum feasible dose or limit dose when the plasma concentration is below the in vitro concentration (IWGT 2022).

IWGT 2022. Feedback from 8th IWGT, Hans-Jorg Martus, David Kirkland, Andreas Zeller for the IWGT Steering Committee.

Kirkland, D., Uno, Y., Luijten, M., Beevers, C., van Benthem, J., Burlinson, B., Dertinger, S., Douglas, G.R., Hamada, S., Horibata, H., Lovell, D.P., Manjanatha, M., Martus, H-J., Mei, N., Morita, T., Ohyama, W., Williams, A., (2019) In vivo genotoxicity testing strategies: Report from the 7th International workshop on genotoxicity testing (IWGT 2022). Mutat. Res. Gen. Tox. En. 847 403035.

Kirkland, D., Whitwell, J., Smith, R., Hashimoto, K., Ji, Z., Kenny, J., Koyama, N., Lovell, D.P., Martus, H-

			J., Meurer, K., Roberts, D., Takeiri, A., Uno, Y., van der Leede, B-J., White, P., Zeller, A., 2022. A comparison of the lowest effective concentration in culture media for detection of chromosomal damage in vitro and in blood or plasma for detection of micronuclei in vivo. Mutat. Res. Gen. Tox. 879-880, 503503 RMS: please refer to answer provided by applicant.	
2(21)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/04 (M3; NOA447204)	FI: Mean concentration of NOA447204 in plasma after 4 hours was only one fourth of the mean concentration observed 1 hour after a single oral administration. No NOA447204 was observed 24 h after administration. Although no other measurement points are available, it is clear that concentration of NOA447204 declines rapidly in plasma.	Applicant (SYN): Thank you for the comments. See response in section 2(20) for detailed answer. Syngenta followed EFSA guidance (*Clarification of some aspects related to genotoxicity assessment* - 10.2903/j.efsa.2017.5113) and OECD 414 guidance (2016) to supplement *in vivo* micronucleus studies conducted prior to the OECD 474 guideline update in 2016. Proof of exposure in the plasma is sufficient to satisfy the data requirements. As intimated above in reply to comment 2(20) and the references cited, bone marrow concentrations may be in many cases be higher than those observed in plasma. Furthermore, as described above, there is no correlation between in vitro LOEC and in vivo LOED. RMS: please refer to answer provided by applicant. _____ FI: Aneugenic properties mediated through effects on mitotic spindle can be manifested only if the substance is present in the cell at the time of	See 2(20).

			spindle formation i.e. during metaphase. Since metaphase is only a short part (typically 1 h in human) of the cell cycle length (typically 24 h in human), there has been a possibility for only a small fraction of bone marrow cells to be exposed by NOA447204 in the mouse micronucleus test since the substance declines rapidly from plasma. Since concentration of a substance in bone marrow is practically always lower than concentration in plasma, this causes an additional uncertainty factor. Hence, it can be concluded that there has not been a possibility for a sufficient bone marrow exposure in a mouse *in vivo* micronucleus test.	
2(22)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/08 (M11; SYN504574)	FI: Since no results of the measurements were included in the assessment by the RMS, it is not possible for a reader to draw any conclusion. Could the RMS include the results of plasma measurements in the text of the Addendum.	Applicant (SYN): Thank you for the comment. Systemic exposure to SYN504574 in mice, following single oral administration of 2000 mg/kg, has been demonstrated in the proof of exposure study (KIIA 5.8/08). Plasma concentration data confirm, that all animals were continuously exposed to SYN504574 over the 24 hour period. This study was also dosed to limit dose (2000 mg/kg/day), which is the highest dose recommend by the test guidelines. Furthermore, please see the recommendations of the IWGT expert group and the acceptability on in vivo micronucleus studies described above in reply to comment 2(20). RMS: Table 1 from original study report with measured plasma concentrations was added into the commenting box from RMS below the study summary of study KIIA 5.8/08.	Addressed. Tables were included in the RAR addendum.

2(23)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/10 (M52; SYN546105)	FI: Results of three animals differ from each other considerably; especially results at 24 h differ for two orders of magnitude. Having such a big variability in results, FI cannot consider them reliable.	Applicant (SYN): Thank you for the comments. Although there is variability in exposure between animals, plasma concentrations demonstrate that all animals were continuously exposed to SYN546105 over the 24-hour dosing period. Animals were dosed to limit dose in this study (2000 mg/kg), which is the highest dose recommended by the test guidelines. Syngenta followed EFSA guidance (*Clarification of some aspects related to genotoxicity assessment* - 10.2903/j.efsa.2017.5113) and OECD 414 guidance (2016) to supplement *in vivo* micronucleus studies conducted prior to the OECD 474 guideline update in 2016. Proof of exposure in the plasma is sufficient to satisfy the data requirements. For a detailed answer, the reply to comment 2(20) is also applicable to this question. RMS: please refer to comment provided by applicant.	See 2(20).
2(24)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/12 (M54; SYN546106)	FI: The results show that there was only a negligible proportion of the test substance SYN546106 present in plasma 24 hours after administration showing that there has not been a possibility for a sufficient bone marrow exposure in a mouse *in vivo* micronucleus test.	Applicant (SYN): Thank you for the comments. Plasma concentrations demonstrate that all animals were continuously exposed to SYN546105 over the 24-hour dosing period. Animals were dosed to limit dose in this study (2000 mg/kg), which is the highest dose recommended by the test guidelines. The requirements of EFSA guidance (*Clarification of some aspects related to genotoxicity assessment* - 10.2903/j.efsa.2017.5113) and OECD	See 2(20).

			414 guidance (2016) to supplement *in vivo* micronucleus studies conducted prior to the OECD 474 guideline update in 2016 has been satisfied by demonstrating exposure to plasma. Proof of exposure in the plasma is sufficient to satisfy the data requirements and demonstrate exposure to bone marrow. For a detailed answer, the reply to comment 2(20) is also applicable to this question. RMS: please refer to comment provided by applicant.	
2(25)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/14 (M55; SYN546107)	FI: Since no results of the measurements were included in the assessment by the RMS, it is not possible for a reader to draw any conclusion. Could the RMS include the results of plasma measurements in the text of the Addendum.	Applicant (SYN): Thank you for the comments. Below are the data for the measured samples for animals dosed with 2000 mg/kg as stated in the final report (KIIA 5.8/14): **Nominal time (h): 0.5** Male Animal 1: 17900 ng/mL Male Animal 2: 22400 ng/mL Male Animal 3: 23300 ng/mL **Nominal time (h): 1** Male Animal 1: 13100 ng/mL Male Animal 2: 11100 ng/mL Male Animal 3: 17900 ng/mL **Nominal time (h): 4** Male Animal 1: 3310 ng/mL Male Animal 2: 12400 ng/mL Male Animal 3: 24100 ng/mL **Nominal time (h): 24** Male Animal 1: 322 ng/mL Male Animal 2: 320 ng/mL Male Animal 3: 456 ng/mL	Addressed. RMS to provide additional details of the plasma analysis on M55 in the RAR addendum.

			In case the RMS considers the information necessary, the RMS is kindly requested to update the study summary accordingly. RMS: Applicant provided data which was added as Table IIA 5.8-20.	
2(26)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/16 (M55; SYN546107)	FI: We agree with RMS, that the result of the *in vivo* rat alkaline comet assay in the duodenum is equivocal after SYN546107 oral administration of male Crl:CD(SD) rats due to the confounding presence of hedgehog cells.	Applicant (SYN): Thank you for the comments. Syngenta agree that the *in vivo* rat alkaline comet assay in the duodenum is equivocal after SYN546107 oral administration of male Crl:CD(SD) rats due to the confounding presence of hedgehog cells. Syngenta has discussed the findings with new RMS for upcoming AIR6 submission (FI) and agreed with the new RMS that the most appropriate way forward is to conduct a transgentic rodent assay (OECD 488) in the rat with SYN546107 to understand the equivocal results in the duodenum. This study has been commissioned and will be submitted in course of AIR6. RMS: thank you.	See 2(6).
2(27)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/17 (M55; SYN546107)	FI: We agree with RMS that benchmark dose modelling is not a suitable approach for addressing the equivocal outcome of the comet assay in target tissue (duodenum) as the DNA damage observed by the comet assay is not considered to have a threshold.	Applicant (SYN): Thank you for the comments. Syngenta disagree with the RMS that benchmark dose modelling cannot be used for genotoxicity risk assessment. The use of benchmark dose modelling to generate a Margin of Exposure (MOE) risk assessment of genotoxic compounds has been promoted by a joint EFSA/WHO international conference with support of ILSI Europe (EFSA, 2006). EFSA has also reiterated its support for use of MOE for safety assessments of impurities which are genotoxic in substances	See 2(6).

added to food/feed (EFSA, 2012) and in the guidance document 'update: use of the benchmark dose approach in risk assessment' (EFSA, 2017). The International Workshop on Genotoxicity Testing (IWGT) 2013 quantitative workgroup (QWG) "critically examined methods for determining Reference Point metrics that could be used to estimate low-dose risk of genetic damage, from which extrapolation to acceptable exposure levels could be made by using appropriate mode of action information and uncertainty factors. Based on analysis of the strengths and weaknesses of each method, the QWG (MacGregor et al. 2015a; MacGregor et al. 2015b) as well as the ILSI-HESI Genotoxicity Testing Technical Committee, or GTTC (Johnson et al. 2014), concluded that the order of preference of Reference Point metrics is "the statistical lower bound on the BMD > the NOGEL > a statistical lower bound on the threshold dose (BPD)". It is therefore considered appropriate to analyse the *in vivo* genetic toxicity data using the BMD approach. Recently the use of the BMD has been re-affirmed by the expert working group of the IWGT. (IWGT 2022)

References:

EFSA (2006) EFSA/WHO International Conference with support of ILSI Europe on Risk Assessment of Compounds that are both Genotoxic and Carcinogenic. https://doi.org/10.2903/sp.efsa.2006.EN-92

EFSA (2012) Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578.

EFSA (2017) Update: use of the benchmark dose approach in risk assessment. DOI: https://doi.org/10.2903/j.efsa.2017.4658

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MacGregor JT, Frötschl R, White PA, Crump KS, Eastmond DA, Fukushima S, Guérard M, Hayashi M, Soeteman-Hernandez LG, Johnson GE, Kasamatsu T, Levy D, Morita T, Müller L, Schoeny R, Schuler MJ, Thybaud V. 2015a. IWGT Report on Quantitative Approaches to Genotoxicity Risk Assessment II. Use of Point-of-Departure (PoD) metrics in defining acceptable exposure limits and assessing human risk. Mutation Research - Genetic Toxicology 783:66-78.

MacGregor JT, Frötschl R, White PA, Crump KS, Eastmond DA, Fukushima S, Guérard M, Hayashi M, Soeteman-Hernandez LG, Kasamatsu T, Levy D, Morita T, Müller L, Schoeny R, Schuler MJ, Thybaud V, Johnson GE. 2015b. IWGT Report on Quantitative Approaches to Genotoxicity Risk

			Assessment I. Methods and metrics for defining exposure-response relationships and points of departure (PoDs). Mutation Research - Genetic Toxicology 783:55-65. Johnson GE, Soeteman-Hernandez LG, Gollapudi BB, Bodger OG, Dearfield KL, Heflich RH, Hixon JG, Lovell DP, MacGregor JT, Pottenger LH, Thompson CM, Abraham L, Thybaud V, Tanir JY, Zeiger E, van Benthem J, White PA. 2014. Derivation of point of departure (PoD) estimates in genetic toxicology studies and their potential applications in risk assessment. Environ Mol Mutagen 55(8):609-623. RMS: thank you.	
2(28)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, Position paper (M55; SYN546107)	FI: We agree with RMS that the biological relevance of the observed gene mutations still remains open and that the genotoxicity assessment of SYN546107 is still not finalised.	Applicant (SYN): Thank you for the comment. Please see reply to comment 2(26) for detailed response RMS: thank you.	See 2(6).
2(29)	Addendum 3 to Volume 3, Section B6, IIA 5.8 Toxicity studies on metabolites, KIIA 5.8/20 (M56; SYN546108)	FI: Based on the measurements and data given, it is not possible to conclude that bone marrow exposure has been sufficient since the results show that there was only a negligible proportion of the test substance SYN546108 present in plasma 24 hours after administration.	Applicant (SYN): Thank you for the comments. See response and citations in section 2(20) for detailed answer. The requirements of EFSA guidance (*Clarification of some aspects related to genotoxicity assessment* - 10.2903/j.efsa.2017.5113) and OECD 414 guidance (2016) to supplement *in vivo* micronucleus studies conducted prior to the OECD 474 guideline update in 2016 has been satisfied by demonstrating exposure to plasma. Proof of exposure in the plasma is sufficient to satisfy the data	See 2(20).

			requirements and demonstrate exposure to bone marrow. RMS: please refer to comment provided by applicant.	
2(30)	Volume 3, Annex B6. [redacted], 2017. NOA447204 - Oral (Gavage) Prenatal Developmental Toxicity Study in the Rabbit.	FR: Tabulated results of body weight gains at different intervals would have been appreciated in order to conclude on maternal toxicity. From data on body weights, it seems that initial body weight loss was also evident in dams of the 30 mg/kg bw/d group, and not only at 100 and 300 mg/kg bw/d. Indeed, at 30 mg/kg bw/d, body weight loss occurred between GD7-8 and the resulting body weight gain for the period GD6-9 was 0 in this group (body weight changes during GD6-9: 0.025, 0.034, 0.0, -0.004, -0.023 kg at 0, 10, 30, 100, 300 mg/kg bw/d respectively). Therefore, the maternal NOAEL seems to be 10 mg/kg bw/d.	Applicant (SYN): Thank you for the comments. Tabulated results can be made available to RMS upon request. RMS: Provided tables were included (new Table 5.8-2.2, and graph 5.8-1 and graph 5.8-2).	Addressed Table 5.8-2.2, and graph 5.8-1 and graph 5.8-2) were included in RAR addendum.
2(31)	Volume 3, Annex B6. [redacted], 2017. NOA447204 - Oral (Gavage) Prenatal Developmental Toxicity Study in the Rabbit.	FR: Please discuss the relevance of available historical control data. Minimum information according to EFSA Administrative Guidance 2019 and Regulation (EU) No 283/2013 should be available to assess their relevance. Information on (at least) species, strain, laboratory, breeder, dates of the studies (5-year centred on the date of the study), diet characteristics, route of administration should be available. The HCD should contain information on the range of values, the mean, the median, the standard deviation and the number of experiments, as well as the single values for those studies.	Applicant (SYN): Thank you for the comments. A report amendment has been requested which contains additional Historical control date (5 year centred on the date of the study). Please see reply to comment 2(16) for additional HCD of interest. The full report as well updated summaries with HCD will be made available for AIR6 and can be submitted upon request. RMS: refer to answer provided by applicant. HCD were updated and included in the respective tables.	Addressed. Historical control data were updated and included in the RAR addendum.
2(32)	Volume 3, Annex B6. [redacted], 2017. NOA447204 - Oral	FR: FR agrees to consider the variant rib cartilage finding (costal cartilage	Applicant (SYN): Thank you for the comments. A report amendment has been requested which contains	See 2(3).

	(Gavage) Prenatal Developmental Toxicity Study in the Rabbit.	interrupted) as treatment-related and adverse at 100 and 300 mg/kg bw/d. Furthermore, dumbbell ossification of one or more centra of thoracic vertebrae should also be considered treatment-related. Indeed, this finding occurred at the highest dose level only (i.e. not in the control nor in other treated groups), showed statistically significance, and litter and fetal incidences were well above historical control data.	additional Historical control date (5 year centred on the date of the study). Please see reply to comment 2(16) for additional HCD of interest. The full report as well updated summaries with HCD will be made available for AIR6 and can be submitted upon request. RMS: thank you.	
2(33)	Volume 3, Annex B6. [redacted] (2018) M55: SYN546107 – Crl:CD(SD) Rat In Vivo Comet Test.	FR: According to OECD TG 489, a test substance is considered to be clearly positive if 1/ at least one dose exhibits a statistically significant increase compared to the concurrent control group, 2/ a trend test shows positive response, 3/ the results are outside HCD. It seems that these 3 criteria were fulfilled for M55 in the duodenum. It should therefore be concluded that the test is positive, i.e. M55 is able to induce DNA strand breakage in the duodenum under the conditions of this study. The fact that increased number of Hedgehog cells was increased may bring a certain level of uncertainty to this result, but no arguments in favour of cytotoxicity are available and a clear genotoxic response is not excluded. Indeed, as detailed in OECD TG 489, hedgehogs could be the consequence of cytotoxicity (not demonstrated in this study) but also of more extreme effect of genotoxicity.	Applicant (SYN): Thank you for the comments. Syngenta strongly disagree that the OECD TG489 is positive. Due to the presence of hedgehog cells, the results are considered to be equivocal, indeed the uncertainty in the duodenum results is cited in the comments (FR). It is further noted that PBPK modelling demonstrated that the concentration at the site of contact tissue (duodenum) was equivalent to 9-36g/L or 23.91327-95.6531 mM. This is equivalent to 2.4-9.6 times the maximum concentration required for an in vitro mammalian cell genotoxicity test in the OECD test guideline (10 mM). This limit was defined originally as a limit low enough to avoid artefactual increases in chromosomal damage and/or mutations due to excessive osmolality. Although cytotoxicity cannot be conclusively demonstrated, the findings are still considered to be uninterpretable without higher tier assessment. Please see reply to comment 2(26) for detailed response. RMS: As it is still not clear what hedgehog cells are, RMS considers	See 2(6).

			the data as not assessable and therefore equivocal, as no clear result can be drawn for this endpoint.	
2(34)	Volume 3, Annex B6. Johnson G. (2019) SYN546107 COMET Assay Data Analysis, Using the Benchmark Dose Approach to Define a Reference Point.	FR: Agrees with RMS conclusion. The benchmark dose modelling approach cannot address the outcome of the COMET Assay in duodenum.	Applicant (SYN): Thank you for the comments. Please see reply to comment 2(27) for detailed response. RMS: thank you.	See 2(6).
2(35)	Volume 3, Annex B6. KIIA 5.8/24 [redacted], (2011), SYN546108 - Micronucleus assay in bone marrow cells of the mouse.	FR: In the table 3, the results of *in vivo* micronucleus test with "SYN546107" is described, but the test item used in the study is "SYN546108", could you please rectify?	Applicant (SYN): RMS is kindly requested to correct the typo. RMS: thank you. Amended.	Addressed Typo amended.
2(36)	Addendum_Volume 1_ relevance of metabolites Grouping approach	FR: The grouping approach proposed by the applicant is solely based on adaptation of the pragmatic approach available in SANCO/221/2000 Guidance document and potential biotransformation pathway of metabolites in soil. No toxicological arguments are provided to support the suggested extrapolation. It is noteworthy that some metabolites are not structurally closed to each other's (e.g. additional cycles, rearrangements). At least a robust and substantiated read-across analysis (including QSAR analysis, coefficients for structural similarities…) should be provided to support the proposed grouping from a toxicological point of view.	Applicant (SYN): The need to assess the relevance of metabolites is not dictated by structural similarity or *in vivo* metabolism, it is purely based on the hazard classification of the parent molecule alone. Taking this into consideration, M3 is the environmental parent molecule to M11, M54, M55 and M56 and therefore the hazard profile of M3 can be used to determine the relevance of metabolites which form from M3 (M11, M54, M55 and M56). In agreement with EFSA, the relevance of metabolites formed from another metabolite would be covered by the toxicity profile of the precursor and, providing a lack of developmental toxicity is demonstrated for M3 metabolite, this should reasonably be applicable to metabolites proven to be degradation products of M3 in the environment in line with the guidance document on the assessment of groundwater metabolites (stage 3 of	See 2(4).

			step 3 of the assessment of the relevance of metabolites). To summarise, we couldn't (and still cannot) synthesise these metabolites in kilogram quantities required, hence we proposed testing with M3 and grouping approach which was accepted by EFSA in 2016. In addition, we conducted a pan-European groundwater monitoring study to establish realistic levels of these metabolites in the groundwater. The developmental toxicity study with M3 was negative and the monitoring study demonstrated that the metabolites are not found at levels above 0.1µg/L in the groundwater. Further to this the metabolites have been demonstrated not to have ACCase inhibition properties – see reply to comment 2(9) below for further details. For a more detailed answer on the grouping approach, reference is made to reply to comment 2(7) RMS: please refer to comment under 2(7).	
2(37)	Vol. 3, 5.8: KIIA 5.8/01 ([redacted], 2017)	NL: With regard to the developmental toxicity study of metabolite M03, we have the following comments: - It would be helpful to include relative changes (in %) in Table IIA 5.8-2. It seems that neither body weights, nor body weight gains are exceeding ±10% compared to the control for any dose group. Taking this into account, in addition to the fact that no statistically	Applicant (SYN): Thank you for the comments. Syngenta would like to refer to reply to comment 2(15) for detailed response on the bodyweight effects. RMS: Thank you. Additional information by applicant were included into the respective tables.	Addressed. Additional information was included into the respective tables of the RAR addendum.

		significant differences were reported, it is questioned whether the NOAEL for maternal toxicity should indeed be set at 30 mg/kg bw/day. - Are more details on the HCD available (e.g. period in which HCD were generated, number of studies included in the HCD, etc.? Notwithstanding of the above, NL agrees that M03 does not need to be classified for reproductive toxicity.		
2(38)	Vol. 1, 1.5: Relevance assessment of M52	NL: According to the toxicity assessment (step 3, stage 3), no conclusions can be made for reproductive toxicity (and the metabolite would be considered as relevant). However, it seems that the metabolite is not considered to be relevant by the RMS since concentrations in groundwater remain below 0.1 µg/L. Could the RMS please provide a final conclusion on the (non-) relevance of M52 for the sake of clarity?	Applicant (SYN): Thank you for the comments. Syngenta refers to reply to reply to comment 2(13) for detailed response. RMS: Data provided from Section 8 are based on monitoring results. Since no clear endpoints have been provided by FATE section (only ranges), no final conclusions have been drawn for the metabolites. However, RMS agrees that for M52 values are below 0.1µg/l and the metabolite does not need to be further evaluated.	See 2(5).
2(39	Vol. 1, 1.8: Relevance assessment of M55; Vol. 3, 5.8: KIIA 5.8/16 ([redacted], 2018) and KIIA 5.8/17 (Johnson, 2019)	NL: NL supports the conclusion of the RMS that benchmark dose modelling cannot be accepted. Furthermore, given the equivocal results obtained in the comet assay (target tissue: duodenum), it is agreed that the genotoxic assessment of M55 is not finalised, but that this can be further discussed with other Member States and EFSA.	Applicant (SYN): Thank you for the comments. Please see reply to comment 2(27) for detailed response. RMS: thank you.	See 2(6).
2(40)	5.8/17	PL: EFSA guidance on use of the BMD approach in RA (2009) is superseded by a newer version 2017.	Applicant (SYN): Thank you for the comments and contributing to the BMD discussion. Please note that	See 2(6).

		In PL opinion the genotoxic activity of metabolite M55 cannot be excluded.	Syngenta is in the process of conducting higher tier genotoxicity assessment to conclude the genotoxicity of M55. Please see reply to comment 2(27) for detailed response. RMS: thank you.	

Section 3 – Residue data

Estimation of the potential exposure through diet and other sources				
No.	**Column 1** **Reference to addendum to assessment report**	**Column 2** **Comments from Member States / applicant / EFSA**	**Column 3** **Evaluation by rapporteur Member State**	**Column 4** **EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data**
3(1)	Addendum to Volume 1 – Relevance of metabolites in groundwater	EFSA: EFSA notes that RMS provided a comprehensive assessment of the different metabolites M2, M3, M11, M52, M54, M55 and M56 in groundwater according to the EU GD SANCO/221/2000-rev.10 and reported in the Addendum to Volume 1. Pending upon a firm conclusion on the "relevance" or "non relevance" of these metabolites according to the hazard assessment as outlined in Step 3 of the GD, a consumer exposure assessment through drinking water might need to be performed for the potentially "non-relevant" groundwater metabolites. When carrying out this assessment, RMS should also consider the potential exposure for consumers through sources other than drinking water, i.e. whether the metabolites under	Applicant (SYN): The applicant would like to highlight that none of the groundwater metabolites M2, M3, M11, M52, M54, M55 or M56, are part of the residue definition for plant and animal commodities. Therefore, the step 4 exposure assessment should be based on the monitoring data of the groundwater metabolites submitted. In accordance with the EU GD SANCO/221/2000-rev. 10, step 4 exposure assessment assesses the exposure level of each groundwater metabolite against the threshold of 0.75ug/L individually: *"such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L."*	Not addressed. Action may be needed pending the conclusions of the proposed peer review (see 4(2)). An assessment of the potential exposure for consumers through sources other than drinking water, i.e. whether the metabolites under assessment are also found in plant and animal commodities was not provided. For the assessment of the relevance of metabolites in groundwater according to EU GD SANCO/221/2000-rev.10 that is employing a TTC approach, it is irrelevant if a metabolite was finally included in the residue definition for plant and animal commodities. As the applicant and RMS might be aware, not every metabolite occurring in plant and animal commodities is included in the residue definition, yet, the impact

		assessment are also recovered in plant and animal commodities. Referring to the comments made in the Mam Tox section (see section 2) regarding the read-across approach, as proposed by RMS, from M3 is applicable to M11, M54, M55 and M56, the respective concentration in groundwater of M3, M11, M54, M55 and M56 should be added up at each FOCUS scenario, or monitored location, in order to perform the consumer exposure assessment. Should all the routes of exposure have been considered, the total exposure of the consumers to this group of metabolites may exceed the relevant threshold of concern of 0.02 µg/kg body weight per day (please refer to the GD SANCO/221/2000-rev.10). In that case, additional toxicity data on this group of metabolites will have to be provided. The Addendum to Volume 1 should be amended accordingly. See also sections 2 and 4.	Based on the groundwater monitoring data evaluated by AGES, and based on the 90th percentile (spatial/temporal) maximum annual concentration (rate-normalized) (M3: 0.027 ug/L; M11: 0.016 ug/L; M52: 0.020 ug/L; M54: 0.010 ug/L; M55: 0.015 ug/L; M56: 0.025 ug/L), exposure levels of each metabolite do not exceed the threshold of 0.75ug/L. The threshold of 0.75ug/L is also not exceeded if the individual exposure levels were combined for M3, M11, M54, M55, and M56. (sum=0.093 ug/L). As the threshold of concern is not exceeded at the step 4 exposure assessment, step 5 refined risk assessment is not triggered, and therefore additional toxicology data are not required. RMS: please refer to answer provided by applicant.	of all identified metabolites or even unidentified residues occurring in food on the consumer risk assessment is still assessed as part of the exercise of setting the residue definition for plant and animal commodities. This approach is based on a different concept than the use of a TTC approach, i.e. with the TTC approach it needs to be established if exposure to a chemical or group of chemicals, where appropriate, will be below a pre-defined threshold. EU GD SANCO/221/2000-rev.10 requires exposure of metabolites from other sources to be considered. Therefore, potential exposure to the metabolites M3, M11, M54, M55, and M56 from food commodities should have been assessed as a first step. It is noted that based on the data available, e.g. metabolite M3 occurs in wheat, several rotational crops, ruminant kidney and milk and exposure estimates to prepare a TTC approach should be provided if a consumer risk assessment in line with EU GD SANCO/221/2000-rev.10 will be triggered by the concentrations of the metabolites in groundwater and the toxicological assessment. As for the appropriate metabolite concentrations it is referred to the peer review proposed in 4(2)
3(2)	Missing documentation	EFSA: RMS is kindly requested to provide an updated list of endpoints that incorporates a section regarding the consumer exposure assessment through drinking water. Such a document is needed that should as the starting point for its preparation, use the document from the published EFSA conclusion. EFSA can make a	Applicant (SYN): In case it is considered required, the RMS shall update the LoEP accordingly. Please refer to the following groundwater monitoring data used in step 4 consumer exposure assessment:	An updated LOEP for the section Residues was not provided. An update is pending the conclusions of the proposed peer review (see 4(2)).

		word version of this document available on request to the pesticide peer review mailbox.	90th percentile annual maximum concentrations (spatial/temporal; rate-normalized): M3: 0.027ug/L; M11: 0.016 ug/L; M52: 0.020 ug/L; M54: 0.010 ug/L; M55: 0.015 ug/L; M56: 0.025 ug/L RMS: LoEP will be provided.	

Section 4 – Environmental fate and behaviour

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**	**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)	Missing documentation	EFSA: RMS has not provided an updated list of endpoints that incorporates the new endpoints coming from their assessment of what was submitted against confirmatory data. Such a document is needed that should as the starting point for its preparation, use the document from the published EFSA conclusion. EFSA can make a word version of this document available on request to the pesticide peer review mailbox.	Applicant (SYN): The applicant kindly requests the RMS to update the LoEP accordingly. RMS AT: The LoEP, kindly provided by EFSA, has been updated accordingly.	RMS provided an updated list of endpoints that incorporated the new endpoints coming from their assessment of what was submitted against confirmatory data and their assessment / conclusion on what should be the endpoints resulting from the last updates made by the previous RMS (UK). However, some action is still needed in this respect, to align the endpoints with pertinent guidance documents on how they should be finalised.

Route and rate of degradation 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**	**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)	Vol. 3 B.8 A.S., page 84	EFSA agrees the RMS assessment and conclusion regarding the degradation modelling endpoint presented in Table RMS 25 for all tiers and in the case of FOCUS Tier-1 only, an additional 'higher-tier' assessment for M2 and M3 based on the field DegT50 values of 2.23 and 49.4 days for M2 and M3, respectively.	Applicant (SYN): In the applicant's view it is justifiable to deviate from current regulatory practice to present a consistent set of endpoints for regulatory modelling at both Tier-1 and Tier-4, acknowledging that futher guidance on best-practice for input parameter selection in such cases may be useful. RMS AT: It appears that there are different views on the most appropriate modelling endpoints to be used at different tiers (see other comments below). We suggest to discuss this issue with MS's experts.	Peer review proposed. Experts to discuss and agree the most appropriate modelling endpoints to be used at different tiers for the groundwater exposure assessment. See reporting table comments 4(2), 4(6) and 4(8).
4(3)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.2.1.2. Rate of degradation of metabolite M55 Robinson, N. (2012a)	FR: For 18 acres soil, DFOP was selected. However, considering that the DFOP g value is rather low, that the DT_{90}/DT_{50} ratio is close to 3.32, SFO might still be considered acceptable for modelling.	Applicant (SYN): The applicant agrees with this view. Considering the expected revision of the FOCUS Kinetics guidance, and the anticipated paradigm shift towards more freedom to accept SFO fits, also an SFO fit for the 18 Acres soil may be considered. The X^2 error of 5.8% for the SFO fit is considerably below the threshold of 15%, and the visual fits for decline and residuals can be considered acceptable. Also, the SWARC approach that is sought to be implemented in the updated kinetic guidance indicates that the SFO fit would be acceptable, and hence a DT50 for the 18 Acres soil of 86.3 days may be considered.	Addressed.

			RMS AT: Without further criteria (e.g., the new SWARC criterion in CRD's update on the FOCUS kinetic GD) the answer to the key question "is SFO good enough?" will always remain a matter of taste. From our point of view, SFO is not "good enough" in this particular case as SFO will underestimate residues later on.	
4(4)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.2.2.1 Field studies metabolite M3	FR: it is noticeable that in the 3 field trials, the recoveries in the deposition trays and in samples at DAT 0 are far below the targeted application rate of 45 g/ha. At DAT 0, mean concentration recovered in soil are equivalent to 23.8g/ha, 15.3 g/ha and 20 g/ha respectively for Spanish, German, and French trials. For the German trial moreover, there is huge variation of residue level within the 40 days of the trial. Although initial level less than targeted application rate and variations could be expected under field experiment conditions, it is questionable whether the data from this experiment are sufficiently robust to derive a modelling endpoint.	Applicant (SYN): It is agreed that the recoveries in the deposition trays and in samples at DAT 0 for the 3 field trials are below the targeted application rate of 45 g/ha. However, if initial values are too low, kinetic fits will result in conservative degradation rates, and hence conservative inputs for modelling. For the German trial, DT50 values and X^2 errors for all kinetic models are in the same range (while X^2 error is also in a similar range as for the selected fit in the FR trial). This clearly shows that the observed scatter in the German trials does not have a considerable adverse effect on the reliability of the kinetic fits. Excluding the degradation value derived for the German trial would result in a lower geomean DT50 for modelling (while also running below the number of required studies to derive a geomean modelling endpoint from field data for M3 in acidic soils). Since a conservative estimate for a DT50 can be concluded on for the German trial in comparison to the other trials, and the X^2 does not give evidence of an inadequate fit, despite the stronger data scatter, we do not see a reason to exclude the data from the German trial.	Addressed.

			On an independent note, further field trials on M2 and M3 are conducted for the AIR6 submission. The data from these trials suggest degradation rates for M3 under field conditions in a similar range as for the presented studies in the Confirmatory Data dossier. AT RMS: We agree that deposition tray recovery is low. However, the subsequent decline of the residues (even if lower as intended) should be largely independent from the initial amount in the soil. We also agree that the scatter in the residue data is rather high, but not necessarily higher than often observed in field studies. In the case of the German field trial, the SFO fit obtained is considered conservative, e.g., when compared to the more consistent residue decline period from 30.4 DAT (norm) onwards. On overall, we do not think that deficits raised by FR invalidate the field trials for deriving robust modelling endpoints for M3.	
4(5)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.2.2.1 Pietsch, K. (2016) Time-step normalisation	FR: It is not clear what kind of daily soil moisture and soil temperature were used for time-step normalisation. It is written for instance in the "data treatment" of Pietsch, K. (2016) that "Daily day length corrections were made on the basis of the daily measured average soil moisture and temperature values", while in the next paragraph, it is indicated "…depending on the soil moisture and temperature, as calculated by PERSIST" Please clarify whether the daily soil moisture and temperature available	Applicant (SYN): It is the applicant's understanding that the calculation of reducing or increasing daylengths was done with PERSIST, and in accordance with FOCUS (2006), based on measured temperature and moisture data as input to these calculations. RMS AT: It is also our understanding that day-length corrections have been appropriately made on basis of daily measurements (temperature and moisture) in soil (10 cm soil depth): "*Actual daily soil moisture and temperature data measured in 10 cm*	Addressed.

		on site were used or not, and what was calculated with PERSIST.	*depth in the treated plot were <u>used for the normalisation process</u>. Both were measured with data loggers and probes installed at 10 cm inside the treated plot. Soil temperature was measured with two 10 kΩ thermistor sensors while soil moisture was measured with two volumetric water content sensors. The data loggers recorded daily values based on twenty minute interval measured values, hence reported daily averages are based on up to 72 single values."* Measured data and normalization results are given for each day in the appendix of the report. PERSIST was obviously used to support these calculations (which could of course also be done with a simple EXCEL sheet).	
4(6)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.2.4. RMS AT's summary of rate of degradation of pinoxaden and its metabolites in soil (laboratory and field Studies)	FR: Potential pH dependence for metabolite M55: FR agrees that a reliable statistical evaluation of the pH dependent degradation cannot be obtained with 3 soils, but however does not support the selection of mean value for M55 for consistency reason among tier 1 and tier 4. It is noticeable that the lowest tested pH value for M55 degradation is 6.14, and thus degradation may be even slower in more acidic conditions. FR is of the opinion that DT50 from 18 acres soil should be selected for modelling. As indicated in previous comment, FR would rather support the selection of SFO kinetic for this soil, and therefore use of DT50 value of 86.3 days for modelling.	Applicant (SYN): The FOCUS GW guidance (FOCUS, 2021) states that 'where there are a number of experimental values (e.g. degradation rate, sorption constants etc.) then the mean or median (as estimated by a geometric mean) values should generally be used rather than the extreme value. This is because the vulnerability of the scenarios has been shared between the soil and weather data, and so should not rest also with the substance properties (FOCUS, 2000)'. Following this principle, we see the use of the geomean value as supported by guidance, particularly as it cannot be ruled out that the degradation behaviour of the 18 Acres soil is an outlier for different reasons than, e.g. pH.	See proposal for peer review / experts' meeting discussion at comment 4(2).

			RMS AT: There may be different aspect to be considered here: From a pure Tier-1 modelling (and regulatory) point of view it may be perfectly understandable that a conservative DT50 is used for M55 (as a terminal metabolite) as there is indeed some indication that degradation of M55 may be pH dependent. From a Tier-3b/Tier-4 modelling point of view (i.e., spatially distributed modelling for vulnerability assessment and contextualisation of monitoring sites), using the worst case DT50 all over the EU adds bias to the calculations as clearly not all locations in the EU will show this worst-case DT50. So, for consistency reasons, we consider the geomean value at all Tiers a reasonable compromise. We also want to stress that on basis of 3 soils only no statistically robust pH dependency assessment is possible. We suggest to discuss the most appropriate modelling endpoints at different tiers with MS's experts.	
4(7)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.2.4. RMS AT's summary of rate of degradation of pinoxaden and its metabolites in soil (laboratory and field Studies)	FR: Potential pH dependence for metabolite M11: pH dependence may not be as clear as for M55, and may be biased by the FOMC pseudo-DT50 at lower pH value. FR support in this case the use of the mean DT50.	Applicant (SYN): The applicant agrees with this view, that the use of a geomean from the fits of the three soils as modelling DT50 M11 is considered appropriate. RMS AT: Noted.	Addressed.
4(8)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.2.4. RMS AT's summary of rate of degradation of pinoxaden and its	FR: RMS AT wishes to avoid overly conservative modelling using default formation fractions of 1.0 and proposes a manually adjusted ffm between M2 and M3 based on laboratory data. This is indeed in	Applicant (SYN): As long as no reliable field data on formation fractions are available, it is reasonable to assume a formation fraction from the lab as best estimate for a field formation fraction. It	See proposal for peer review / expert meeting discussion at comment 4(2).

metabolites in soil (laboratory and field Studies)	principle an acceptable method for determining an ffm, but the resulting ffm of 0.42 cannot be used together with the field degradation data for M2 and M3 (as proposed for modelling of M2 and M3). RMS check of the appropriateness of its approach (Table RMS-23) is performed on laboratory residues and laboratory DT50 for M3, and not field DegT50. The appropriateness of the approach using the ffm of 0.42 when only field DegT50 are used for M2 and M3 is not demonstrated. FR also underlines that following EFSA 2014, only field data has to be used once it has been checked that they are statistically shorter than laboratory data, and the tiered approach (tier 1 lab data /tier 2 field data) no longer is to be considered. FR acknowledges that in this case no ffm can be derived for M3. Regarding the fact that the use of field DegT50 for M2 and M3 leads to overly conservative residues for subsequent metabolites: this might be true, however it is current regulatory practice to use shorter field DegT50 for precursor (see also comment under PECgw section). Moreover, this was not raised by applicant (applicant tier 2 considers only ffm of 1 between M2 and M3, and Field DegT50), and should not be further explored by RMS for GW modelling.	should be noted that EFSA (2014) refers to DegT50 values, but not explicitly to formation fractions, and hence no steer can be derived how field DT50s can or cannot be used in combination with lab formation fractions. It is furthermore noted in guidance (e.g., FOCUS 2000 GW guidance) that vulnerability of the scenarios has been shared between the soil and weather data, and so should not rest also with the substance properties (FOCUS, 2000)'. With this the use of a lab formation fraction as best estimate for a field formation fraction can be justified. Regarding the proposed use of Tier1a and Tier 1b as consistent laboratory datasets for use at both FOCUS Tier-1 as well as Tier-4 (GW modelling vulnerability assessment), it is noted that the claimed current regulatory practice to use field data for precursor metabolites contradicts the aim of RMS AT to establish a consistent input parameter set that can be used at Tier-1 as well as at FOCUS Tier-4. Therefore, in our view it is justifiable to deviate from current regulatory practice here, acknowledging that further guidance on input parameter selection in such cases may be useful. AT RMS: It appears to be common practice that field DegT50 and lab formation fractions are combined in modelling. This seems sensible, as there is *per se* no reason why formation fractions in lab and field should be that different. In this respect it seems irrelevant, whether formation fractions are obtained from

			regular parent-metabolite fits or from forward modelling to adequately cover residues observed (as proposed by the RMS AT; notice that formation fractions for all lysimeter metabolites have be obtained by forward modelling as well). In our opinion, the issue of "inconsistent" datasets for modelling is not necessarily related to combining field DegT50 values with lab formation fractions (if field DegT50 is used for all substances in the modelling exercise). Indeed, combining substances in a modelling exercise with either field or lab DegT50 gives troubles. In general, we do not support such a DegT50 mix approach, although it appears to be common practice as well. As already highlighted in the DAR, this situation may lead to unrealistic metabolite occurrences in the modelling exercise. We also want to stress, that formation fractions for all lysimeter metabolites have been obtained on basis of forward modelling as well (adjusted to give approx. 5 % occurrence). Strictly following FR's objections it would be necessary to also use a default formation fraction of 1.0 for all these metabolites. In view of the RMS-AT, the impact of mixing formation fractions and degradation rates from lab and field (in all combinations) in the exposure modelling was never thoroughly checked. We prefer having some

			more elaboration and guidance in this respect. We suggest discussing the most appropriate modelling endpoints at all Tiers with MS's experts.	
4(9)	B.8.1.2	Chirality of groundwater metabolites M52, M54, M55 and M56 SYN: The stereoisomeric guidance was noted after the submission of the Confirmatory Data dossier in April 2019. In principle, different enantiomeric forms of a molecule may degrade in soil at significantly different rates. In this case, this will manifest as biphasic kinetics. The FOCUS kinetics guidance is very conservative and for biphasic decline curves, the endpoint would automatically consider the DT50 of any single slowly degrading enantiomeric component. Thus, the mass of chemical species leaching to groundwater is considered sufficiently conservative.	RMS AT: The applicant is asked to appropriately address the chirality of the groundwater metabolites in near future (e.g., AIR 6) in line with pertinent guidance.	Addressed.
4(10)	KIIA 7.2.3/04 Robinson, 2012a Rate of degradation of metabolite M55	Kinetic fit of 18 Acres soil SYN: With view to the revision of the FOCUS Kinetics guidance, and the anticipated paradigm shift towards more freedom to accept SFO fits, also an SFO fit for the 18 Acres soil may be considered. The X^2 error of 5.8% for the SFO fit is considerably below the threshold of 15%, and the visual fits for decline and residuals can be considered acceptable. Also, the SMAUG approach that is sought to be implemented in the updated kinetic guidance indicates that the SFO fit would be acceptable, and hence a	Applicant (SYN): The phrase 'SMAUG approach' should read as 'SWARC approach' RMS AT: Please refer to comment 4(3). It's not SMAUG but SWARC.	Addressed.

<table>
<tr><td></td><td></td><td>DT50 for the 18 Acres soil of 86.3 days may be considered.</td><td></td><td></td></tr>
<tr><td>4(11)</td><td>KIIA 7.2.3/05
Caviezel, 2013
Rate of degradation of metabolite M55</td><td>Kinetic fit of 18 Acres soil
SYN: The calculation for SFO of the 18 Acres soil should result in a DT50 value of 105 days, instead of 110 days. Please check.
Residues as follows:<table><tr><th colspan="3">18 Acres</th></tr><tr><th>Time (d)</th><th>Rep</th><th>SYN546108</th></tr><tr><td>0</td><td>A</td><td>103</td></tr><tr><td>0</td><td>B</td><td>102.8</td></tr><tr><td>7</td><td>A</td><td>92.5</td></tr><tr><td>7</td><td>B</td><td>89.5</td></tr><tr><td>14</td><td>A</td><td>82.4</td></tr><tr><td>14</td><td>B</td><td>78.1</td></tr><tr><td>30</td><td>A</td><td>76.1</td></tr><tr><td>30</td><td>B</td><td>77.3</td></tr><tr><td>58</td><td>A</td><td>59.8</td></tr><tr><td>58</td><td>B</td><td>55.1</td></tr><tr><td>90</td><td>A</td><td>53.1</td></tr><tr><td>90</td><td>B</td><td>63.5</td></tr><tr><td>120</td><td>A</td><td>34.9</td></tr><tr><td>120</td><td>B</td><td>55.5</td></tr></table></td><td>RMS AT: Please note that in the residue data, provided in the applicant’s comment for M56 (!) for 18 Acres soil, the 58-DAT samples should read “77-DAT” samples. The RMS AT’s SFO DegT50 of 110 days is correct (also confirmed by the study authors).</td><td>Addressed.</td></tr>
<tr><td>4(12)</td><td>KIIA 7.2.3/05
Caviezel, 2013
Rate of degradation of metabolite M55</td><td>Kinetic fit of Marsillargues soil
SYN: With view to the revision of the FOCUS Kinetics guidance, and the anticipated paradigm shift towards more freedom to accept SFO fits, also an SFO fit for the Marsillargues soil may be considered. The X^2 error of 8.3% for the SFO fit is considerably below the threshold of 15%, and the visual fits for decline and residuals can be considered acceptable. Also, the SMAUG approach that is sought to be implemented in the updated</td><td>RMS AT: You comment obviously relates to M56 and not to M55.

The new guidance is still not in place and the current guidance allows some user freedom when to consider a “SFO fit good enough”. From our point of view, SFO is not good enough as residues at later time are underestimated.

It’s not SMAUG but SWARC.</td><td>Addressed.</td></tr>
</table>

<table>
<tr><td></td><td></td><td>kinetic guidance indicates that the SFO fit would be acceptable, and hence a DT50 for the Marsillargues soil of 86.3 days may be considered.</td><td></td><td></td></tr>
<tr><td>4(13)</td><td>KIIA 7.3.1/04
Pietsch, 2016
Field Soil Dissipation Kinetics for Modelling Endpoints</td><td><u>RMS AT:</u> The RMS AT notes that FOCUS kinetic guidance (FOCUS, 2014) is indeed inconclusive with respect of handling of LOQ and LOD. This is particularly true if there are < LOQ and < LOD residues in the data set. For field data (with several soil layers), there is no guidance at all. In this respect, one may consider deeper soil layers similar to what is done in the case of 'metabolites'.

<u>SYN:</u> Considering deeper soil layers similar to what is done for metabolites is 'off-guidance' and not in line with the data handling <u>recommendations</u> in FOCUS (2014<u>)</u> guidance and the CTGB (Boesten et al, 2015) recommendation for handling of spatial aspects (depth) of field study data. The applicant has re-calculated kinetics for the field dissipation studies strictly in line with these recommendations, resulting in modelling DT50 values of 49.6 days (Spain; FOMC DT90/3.32), 89.3 days (Germany; SFO) and 28.9 days (France; SFO).</td><td>RMS AT: Recalculated DegT50 (d) values by the applicant are almost the same as proposed by the RMS AT (see below). It is acknowledged that in the proposed new kinetic guidance, handling of LOQ and LOD values in fields is more prominently addressed.

<table><tr><td></td><td>Applicant</td><td>RMS-AT</td></tr><tr><td>Spain</td><td>49.6</td><td>47.9</td></tr><tr><td>Germany</td><td>89.3</td><td>88.0</td></tr><tr><td>France</td><td>28.9</td><td>28.6</td></tr><tr><td>Geomean</td><td>50.4</td><td>49.4</td></tr></table></td><td>Addressed.</td></tr>
</table>

4(14)	B.8.1.2.4 RMS AT's summary of rate of degradation of pinoxaden and its metabolites in soil (laboratory and field studies)	RMS AT: *In order to account for a potential soil pH dependent degradation of M55, the applicant used the worst case DegT50 of 106 days […]. Whilst this worst-case selection is considered acceptable […] the large variability in DegT50 values […] adds uncertainty in the overall assessment of the monitoring sites' leaching vulnerability and contextualisation at FOCUS Tier-4 […]. The RMS AT considers the geometric mean DegT50 of 17.5 days at both tiers […] more appropriate. Keeping the small data set in mind (n = 3 for all metabolites), the RMS AT considers a statistical evaluation with respect to a potential soil pH dependent degradation unreliable at all.* SYN: In the light of a consistent data set for use in both Step-1 and Step-4 (contextualization), it is agreed to use the geomean value of 17.5 days as degradation endpoint for metabolite M55. In the SW Repair guidance it is acknowledged that establishing statistically robust relationships between substance and soil properties is difficult, if the number of soils is at the minimum of the data requirements. The Kendall's Tau statistical test shows no significant (p-value: 0.05) pH dependence for the DT50 of M55.	RMS-AT: Noted. Please also refer to comment 4(6).	See proposal for peer review / expert meeting discussion at comment 4(2).
4(15)	B.8.1.2.4 RMS AT's summary of rate of degradation of pinoxaden and its metabolites in soil (laboratory and field studies)	More reliable formation fractions for M2 (from parent) and M3 (from M2), deduced from the EFSA conclusion (2013) for M2 and for M3 in neutral/alkaline soils. For the formation fraction of M3 in acidic soils	RMS AT: Noted.	Addressed.

		a manual adjustment of the formation fraction is proposed by the RMS AT. SYN: The approach to derive formation fractions for M2 and M3 is agreed. However, it should be noted that for the AIR6, all laboratory and field degradation studies will have re-calculated kinetics according to the latest guidance, including the derivation of formation fractions, which will then be used in the new submission.		
4(16)	B.8.1.2.4 RMS AT's summary of rate of degradation of pinoxaden and its metabolites in soil (laboratory and field studies)	RMS AT: *The RMS AT notes that the maximum occurrence of unknown metabolite fractions in acidic soils is actually 5.7 % AR (see Welfer-Borgeln soil, Fent & Hein, 2003) and 2.4 % AR in neutral/alkaline soils (Plaza soil, Clark, 2003a). For consistency reasons, the RMS AT proposes to adjust formation fractions for M11, M52, M54, M55 and M56 separately for acidic and neutral/alkaline soils, thus targeting a maximum occurrence of 5.7 and 2.4 % in acidic and neutral/alkaline soils, respectively, in the exposure model.* SYN: In a follow-up study, the peak of 5.7% in the Welver-Borgeln soil has been identified to be none of the lysimeter metabolites, but the metabolite SYN515622. This is being accounted for in the AIR6 submission, but respective data can already be provided upon request. Hence, the use of 5.7% AR to derive formation fractions of M11, M52, M54, M55 and M56 under acidic conditions seems overly conservative, and it is considered more appropriate to use the maximum value of 4.5 %	RMS AT: Once there is agreement on manually adjusted formation fractions in the case of pinoxaden metabolites, it is proposed to reconsider this approach in order to meet the new proposed max. occurrence of individual unknowns in acidic soils (now 5.7 %, 4.5 % proposed by applicant in the comment). This is something which can be checked and provided for AIR6. The RMS AT is wondering which "follow-up" study is meant by the applicant.	Addressed.

		AR from the Pappelacker soil (Fent & Hein, 2003) to calculate formation fractions in acidic soils.		
4(17)	B.8.1.2.4 RMS AT's summary of rate of degradation of pinoxaden and its metabolites in soil (laboratory and field studies)	RMS AT: *The RMS AT proposes to use a consistent substance property data set, based on lab degradation data only, for all tiers. At FOCUS Tier-1 only, an additional 'higher-tier' assessment for M2 and M3 based on field degradation data is supported as well.* SYN: The reasoning of the RMS for using a consistent input parameter dataset for use in Tier-1 as well as Tier-4 modelling is a sensible approach, supported by the applicant. However, it is not clear to the applicant why the 'higher tier' assessment for M2 and M3 at Tier-1 may not as well be considered appropriate and applicable for calculations supporting Tier-4 contextualization, as concentrations for M2 and M3 obtained by the 'higher tier' modelling approach are more in line with concentration magnitudes observed in the Tier-4 monitoring.	RMS AT: In view of the RMS AT, supporting assessments for M2 and M3 at Tier-3b/Tier-4 may of course be also based on the "higher-tier" modelling dataset (i.e., field degradation data) for these two metabolites. However, when it comes to supporting assessments for the lysimeter metabolites at Tier-3b/Tier-4, it is proposed to use the lower tier data set (lab data) for all substances for consistency reasons. This would make it necessary to run Tier-3b twice (once for M2 and M3 and once for the lysimeter metabolites).	Addressed.
4(18)	B.8.1.2.4 RMS AT's summary of rate of degradation of pinoxaden and its metabolites in soil (laboratory and field studies)	RMS AT: *Notice that there is no field degradation endpoint available for M3 in neutral/alkaline soils. However, in view of the pH dependency observed in the lab, the field DegT50 of 49.4 days in acidic soils is considered to adequately cover the exposure assessment in neutral/alkaline soils as well.* SYN: This is a reasonable approach and supported by the applicant.	RMS AT: Noted.	Addressed.

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**	**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(19)	Vol. 3 B.8 A.S., pages 125-126.	EFSA agrees the RMS assessment and conclusion regarding the adsorption modelling endpoint presented in Tables RMS 31 to 35.	Applicant (SYN): The applicant also agrees with the pragmatic approach by RMS AT to derive adsorption endpoints. For the submission of the AIR6, new adsorption studies are being prepared for the lysimeter metabolites, and Kfoc endpoints from these new studies are generally in the same order of magnitude as the ones derived by RMS AT. RMS AT: Noted.	Addressed.
4(20)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.3.1.2 New studies for metabolites	FR: the new adsorption studies were performed with unlabelled test items: within each study summary the LOQ was reported, however no further reference to the analytical method used and the validation of its accuracy is given. Please add information on this.	Applicant (SYN): A description of the analytical methods used within these studies and their validation is given in the Addendum 2 to Volume 3 – B.5. RMS AT: Please refer to Addendum 2 to Volume 3 – B.5.	Addressed.
4(21)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.3.1.2 Völkel, W. (2012b) - Adsorption of metabolite M52	FR: there is a mistake in RMS conclusion on this study (last bullet point of commenting box). It is the Marsillargues soil for which RMS proposes a correction, and not the Gartenacker soil (Gartenacker soil and 18-acres soil are considered sufficiently robust). Still, with such a poor mass balance in the Marsillargues sol (41.9%), FR would consider it is outside an acceptable range where correction can be considered. FR proposes rather to exclude this soil, and keep	Applicant (SYN): The applicant agrees that the conclusion statement is incorrect and that it should be Marsillargues soil which is considered for correction rather than Gartenacker soil which is sufficiently robust. The low mass balance for Marsillargues soil is likely to have been caused by insufficient extraction with M52 (SYN546105) binding more strongly to Marsillargues soil over the 48-hour incubation period. This is demonstrated by a proportionately higher Kd desorption value compared	See proposal for peer review / expert meeting discussion at comment 4(22).

		the lowest Kfoc value for GW modelling (54.1 mL/g).	to the kd adsorption value than observed in the other soils, indicating irreversible binding. An acceptable mass balances was achieved in both 18 Acres and Gartenacker soil and preliminary testing indicated M52 was stable for up to 48 hours in 0.01 M CaCl2. Furthermore, in the preliminary testing on Marsillargues soil only a minor increase in the adsorption was observed between 24 and 48 hours in the time to adsorption test and a constant concentration was observed in the time to desorption test. These all suggest the test item was stable over the course of the experiment with extraction being insufficient. Therefore, rather than excluding the soil a conservative value should be calculated for modelling taking into account the uncertainty caused by the low mass balance, as done by the RMS Austria. Further adsorption data for metabolite M52 (SYN546105) has been generated and will be submitted with AIR6. RMS AT: The typo has been corrected. As correction of the Kfoc values, proposed by the RMS AT, is clearly "off-guidance", we suggest discussing this approach with MS's experts. This may include criteria (e.g., minimum test item mass balance) when such an approach is considered sufficiently robust or not.	
4(22)	Addendum_Volume_3CA_B-8_2022-05-10	FR: Approach for correcting Kfoc: This is a novel approach that indeed should be further discussed. In	Applicant (SYN): The applicant accepts the correction proposed by AT as a conservative estimation of	Peer review proposed. Experts to discuss and agree the most appropriate adsorption

	B.8.1.6. RMS AT's summary section on adsorption and mobility	principle it could be a good approach in some cases, providing that it can be clearly identified what may have caused a high KfE/Kf ratio (very weak adsorption domain, or low mass balance). Proposing a systematic correction may be arbitrary. In some cases, it may be investigated what causes a poor mass balance (NER, degradation…) and the impact on the final endpoint may be somewhat relativized. However, this become challenging with unlabelled test item. RMS AT indicates that the KfE/Kf criterion may be relaxed given that the test item mass balance was measured after desorption step. This is perfectly understandable. However, in case a correction is conducted, the correction may also become overly conservative since the ratio is expected to be lower after adsorption phase than the one accounted for the correction procedure. In any case, correction procedure cannot be applied in situation where mass balance is clearly outside acceptable range (considering 70% for unlabelled test item), and soils in this situation are to be rejected (for example Marsillargues soil for M52).	the adsorption in Marsillargues soil. The low mass balance in Marsillargues soil was likely caused by insufficient extraction (see comment reply to 4(21)). The measured mass balance is considered conservative as it was measured after desorption (48 hours) and could therefore be expected to be significantly higher after adsorption (24 hours). Using the proposed correction recognises that the soil was not extracted sufficiently and provides a conservative Kfoc of 62.5 mL/g for risk assessment. This is within the range of measured Kfoc values for 18 Acres and Gartenacker soils and therefore provides a true reflection of measured adsorption. Further adsorption data for metabolite M52 (SYN546105) has been generated and will be submitted with AIR6. RMS AT: We suggest to discuss this "off-guidance" correction approach of Kfoc with MS's experts.	endpoints to be used for the soil metabolites including a detailed consideration for the Marsillargues soil and metabolite M52.
4(23)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.1.6. RMS AT's summary section on adsorption and mobility Metabolite M11 endpoint	FR: RMS AT proposes to use the arithmetic mean for adsorption endpoint for M11 as the data set includes 0. However, an alternative solution for geomean calculation when data sets include 0 has now been agreed on at EU level, and is reported in the aged sorption guidance. This solution should be referred to. However in that case, it	Applicant (SYN): This is acknowledged. We agree that the approach outlined in the aged sorption guidance should be used for datasets including 0 and acknowledge that in the case at hand with M11, this does not change the endpoint for modelling.	Addressed.

		results in same mean endpoint of 2.4 mL/g.	RMS AT: The RMS AT agrees with the approach suggested by France. However, it is noted that the approach by Habib (2012) (weighted average geomean) gives a geometric mean of 2.2 mL/g. The DAR was updated accordingly (however, no new exposure assessments have been performed).	
4(24)	KIIA 7.4.2/01 Robinson, 2012b Adsorption/Desorption Properties of Metabolite SYN504574 (M11) in Three Soils	RMS AT: *The RMS AT considers none of the sorption properties of M11 sufficiently robust for regulatory use. The RMS AT suggests correcting the adsorption results on basis of the K_{fE}/K_f ratio as outlined in the RMS AT's summary section on adsorption and mobility* SYN: The conclusion by the RMS is agreed upon, and a new adsorption study for M11 is being conducted for the AIR6. In the meantime, the correction approach on basis of the K_{fE}/K_f ratios is considered a pragmatic approach to derive conservative estimates of sorption endpoints for use in regulatory modelling, noting that the approach is 'off-guidance'.	RMS AT: Noted.	Addressed.
4(25)	KIIA 7.4.2/02 Völkel, 2012b Adsorption/Desorption Properties of Metabolite SYN546105 (M52) in Three Soils	RMS AT: *In conclusion, the RMS AT considers sorption properties of M52 obtained in the Gartenacker and 18-Acres soil sufficiently robust for regulatory use. In the case of the Gartenacker soil, the RMS AT suggests correcting the adsorption results on basis of the K_{fE}/K_f ratio as outlined in the RMS AT's summary section on adsorption and mobility* SYN: It is assumed that the RMS is referring to the Marsillargues soil in the second sentence, not Gartenacker. SYN agrees that the	RMS AT: Noted. The type has been corrected.	Addressed.

		Kfoc values of the Gartenacker and 18 Acres soils are suitable for regulatory use, and agrees that the sorption endpoint from the Marsillargues soil is unreliable. A new adsorption study for M52 is being conducted for the AIR6. In the meantime, the correction approach on basis of the K_{fE}/K_f ratios for the Marsillargues soil is considered a pragmatic approach to derive conservative estimates of sorption endpoints for use in regulatory modelling.		
4(26)	KIIA 7.4.2/03 Völkel, 2012c Adsorption/Desorption properties of Metabolite SYN546106 (M54) in Three Soils	RMS AT: *In conclusion, the RMS AT considers sorption properties of M54 obtained in the Gartenacker and Marsillargues soil sufficiently robust for regulatory use. In the case of the 18 Acres soil, the RMS AT suggests correcting the adsorption results on basis of the K_{fE}/K_f ratio as outlined in the RMS AT's summary section on adsorption and mobility* SYN: All three soils have 2 or 3 out of 5 concentrations failing the Kd x soil/solution ratio. Data is available to fully recalculate Gartenacker using the direct method however the lowest concentration needs to be disregarded due to the excessively high recovery (~250%). There is not enough data to fully recalculate the other soils by the direct method. A new adsorption study for M54 is being conducted for the AIR6. In the meantime, the proposed Kfoc values by the RMS are considered suitable to derive conservative estimates of sorption endpoints for use in regulatory modelling.	RMS AT: Noted.	Addressed.

4(27)	KIIA 7.4.2/04 Robinson, 2012c Adsorption/Desorption Properties of Metabolite SYN546107 (M55) in Three Soils	RMS AT: *The RMS AT considers none of the sorption properties of M55 sufficiently robust for regulatory use. The RMS AT suggests correcting the adsorption results on basis of the K_{fE}/K_f ratio as outlined in the RMS AT's summary section on adsorption and mobility.* SYN: The conclusion by the RMS is agreed upon, and a new adsorption study for M55 is being conducted for the AIR6. In the meantime, the correction approach on basis of the K_{fE}/K_f ratios is considered a pragmatic approach to derive conservative estimates of sorption endpoints for use in regulatory modelling, noting that the approach is 'off-guidance'.	RMS AT: Noted.	Addressed.
4(28)	KIIA 7.4.2/05 Caviezel, 2014 Adsorption/Desorption Properties of Metabolite SYN546108 (M56) in Three Soils	RMS AT: *The RMS AT considers sorption properties of M56 obtained in the Gartenacker soil sufficiently robust for regulatory use. In order to obtain more reliable sorption properties for M56 in the case of the 18 Acres soil, the RMS AT suggests correcting the adsorption results on basis of the K_{fE}/K_f ratio as outlined in the RMS AT's summary section on adsorption and mobility (B.8.1.6). Due to inconclusive results obtained in the Marsillargues soil, the RMS AT suggests to reject these data.* SYN: It is noted that all soils fail Kd x soil to solution ratio at nearly every concentration and have adsorption of <20%. The indirect method was inappropriate and should not have been used. A full direct method calculation could be conducted for the Gartenacker soil. There is not enough	RMS AT: Noted.	Addressed.

		data to fully recalculate the other soils by the direct method. A new adsorption study for M56 is being conducted for the AIR6. In the meantime, the proposed Kfoc values by the RMS are considered suitable to derive conservative estimates of sorption endpoints for use in regulatory modelling.		
4(29)	B.8.1.6 RMS AT's summary of adsorption and mobility in soil of pinoxaden and its metabolites	RMS AT: *In view of the RMS AT, the small dataset of only 3 soils does not allow applying any reliable pH assessment for adsorption in soil.* SYN: In the SW Repair guidance it is acknowledged that establishing statistically robust relationships between substance and soil properties is difficult, if the number of soils is at the minimum of the data requirements. Therefore, the applicant agrees with the RMS.	RMS AT: Noted.	Addressed.

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**	**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(30)	Vol. 3 B.8 C.P., pages 36-40. PEC groundwater	EFSA agrees the RMS assessment and conclusion regarding the substance modelling endpoints presented in Table RMS 1 and 2 and related results in tables 3-10.	Applicant (SYN): This is acknowledged. However, we would like to note that in agreement with EFSA (2014), a groundwater modelling 'Tier 2' approach, using field DT50s for M2 and M3, but also considering calculation of PECgw for the downstream metabolites M11, M52, M54, M55 and M56 may be applicable. While this would lead to somewhat higher PECgw for the metabolites downstream of M3 (also	Addressed.

			caused by conservative estimates of the formation fractions), it would demonstrate that M52 is clearly below the threshold of 0.1 µg/L in modelling. RMS AT: We agree with the applicant that mixing field and lab degradation data in the exposure assessment at Tier-1 is common practice. In this sense, we are of course willing to provide additional Tier-1 PEC gw for M11, M52, M54, M55 and M56 using field DegT50 for M2 and M3 if considered appropriate by the MS's experts. However, we do not necessarily support such a mixed DegT50 approach for reasons outlined several times. For some metabolites, this approach will lead to higher and for some other ones to lower PEC gw values. So how proceed then? Case-by-case decision for each metabolite? We don't think that there is a consistent way to handle this issue. On overall, we would like to stress that mixing lab and field DegT50 in a complex degradation pathway may lead to unexpected formation of metabolites in the exposure assessment (as is the case of pinoxaden). In our opinion, possible consequences of such an 'apples & pears' approach have never been thoroughly checked. We would highly welcome a more dedicated guidance here.	
4(31)	Addendum 1 to Volume 3 – B.8 (PPP) Section B.8.2.4.1 (groundwater)	FI: A TSCF of 0.784 has been calculated based on the logKow value of 1.8 and the Briggs equation. On that basis, a PUF value of 0.5 was used in the FOCUS groundwater	Applicant (SYN): The current FOCUS GW guidance (FOCUS, 2021) states that a default PUF of 0 should be used, however allows for a refinement with the Brigg's equation.	Addressed. Using the guidance in place the TSCF value for M3 of 0.784 can be used in modelling (https://esdac.jrc.ec.europa.eu/public

		modelling for M3. We note that the Briggs equations has many uncertainties because the uptake is affected by many other factors than logKow. Therefore, the PUF value of 0.5 might overestimate plant uptake. In general, we recommend using the current default PUF = 0 for Tier I, and introducing any other values as refinements (Tier 2).	It is not stated that in cases where refinement is possible, calculations with a PUF of 0 have to be carried out and presented, but it is our understanding of the guidance that a robust PUF value derived with the Brigg's equation shall be accepted. For metabolite M3, a reliable log Pow was determined to be 1.8 in the study by Das (2001) conducted according to OECD 107 guidelines and as reported in the EFSA conclusion (EFSA, 2013). Using the log Pow value of 1.8 in the Briggs equation gives a calculated TSCF value of 0.784. This is the maximum value possible and so strongly indicates that plant uptake of M3 occurs. It is noted that FOCUS (2021) does not explicitly specify a maximum value of 0.5 for the PUF. Therefore, even the maximum value of 0.784 can be considered in groundwater modelling, as proposed by RMS AT, and in accordance with the guidance. The use of a TSCF value of this magnitude applying the Brigg's equation is supported further by experiments published in - Schriever & Lamshoeft (2020) 'Lipophilicity matters - a new look at experimental TSCF data from litera-ture'. Science of the Total Environment 713, 2020 RMS AT: We are aware that there a highly diverse views and even rejections of the limited PUF guidance. However, following pertinent guidance it appears not necessary to also provide calculations with a PUF of 0, at least not at the	_path/projects_data/focus/gw/NewDocs/focusGWReportOct2014.pdf).

			level of EU approval. Nevertheless, we can provide such calculations if considered necessary.	
4(32)	Addendum_Volume 1_ relevance of metabolites.	FR: it is noticeable that in the summary tables of relevance assessment for each metabolite, RMS only refers to PECgw derived from monitoring data. Pending reliability assessment of the monitoring results, it should be avoided to refer to these as being the final PEC considered for regulatory assessment. PECgw from FOCUS modelling should be included in the tables, and complete relevance assessment should be performed at fist approach on these PECgw.	Applicant (SYN): A reliability assessment has been carried out by RMS AT, which we are certain has also fed into the overall conclusion by RMS AT that the use of PECgw from monitoring is fit-for-purpose to be considered in Volume 1, and as basis for the non-relevance assessment. We share this view, as a number of critical points have been addressed, e.g. the rate normalization approach proposed by RMS AT to account for lower application rates than intended, or e.g. the results based on a hydraulic connectivity assessment presented by Syngenta in comments 4(55) and 4(97). Applying these refinements, the overall picture remains that exceedance of metabolites of pinoxaden above 0.1 µg/L are sporadic, while strengthening the confidence in the monitoring results then ultimately to be useable and appropriate for the non-relevance assessment. RMS AT: We understand concerns raised by FR. Pending the discussion on the reliability of the monitoring results and the final endpoints to be assessed we are of course willing to also provide a summary on lower Tier PEC gw values (including lysimeter results as well), if considered necessary. In the meanwhile we have added Tier-1 results based on the FOCUS gw scenarios in Vol. 1 of the updated DAR. Whether there is a need to provide a full relevance assessment at each Tier level may be	Addressed. Vol 1 summary tables now include Tier 1 groundwater modelling exposure concentrations that it is noted may be subject to change considering the expert consultations proposed.

			discussed as well. Notice that the preliminary Tier-1 assessment needs agreement as well.	
4(33)	Addendum_Volume_3CP_B-8_2022-05-10 PECgw modelling of metabolites M2 and M3	FR: Ffm of 0.91 and 0.42 are ffm based on laboratory degradation data for M2 and M3, while they are used with DT50 from field studies in the PECgw modelling of M2 and M3. FR understands the aim of RMS AT not to produce overly conservative modelling using default ffm of 1, however ffm manually adjusted with laboratory degradation data for M2 and M3 cannot be used with field DegT50 in modelling. FR would keep applicants proposal of field data with ffm of 1, or ffm should be manually adjusted with field residue data.	Applicant (SYN): Please refer to reply to comment 4(8). RMS AT: As already noted, following France's proposal would make it necessary to also set the formation fractions of M11, M52, M54, M55 and M56 from their precursor to 1.0. This will lead to an overly conservative Tier-1 assessment for all metabolites, which in view of the RMS AT is not justified. Please also refer to comment 4(8). MS's experts should discuss the most reliable modelling endpoints at all Tiers.	See proposal for peer review / expert meeting discussion at comment 4(2) and comment 4(8).
4(34)	Addendum_Volume_3CP_B-8_2022-05-10 PECgw modelling of metabolites M11, M52, M54, M55 and M56	FR: The use of Laboratory DT_{50} for M2 and M3 in the modelling of subsequent metabolite should be further discussed, since it is not in line with EFSA. DegT50 guidance (2014). RMS indicates that it "the replacement of the laboratory DegT50 of M2 and M3 with field degradation data leads to highly exaggerated modelled occurrences of all subsequent metabolites", and that the theoretical max occurrence of metabolite M56 is brought to 12.4% if based on field data instead of 5.7%. This holds certainly true for M56, which is a rather persistent metabolite; however it might be the case for any compound, any time a shorter field $DegT_{50}$ is used for its precursor in calculations, which is current practice for active substance, regardless of the consequences on	Applicant (SYN): Current regulatory practice to use field data for precursor metabolites contradicts the aim of RMS AT to establish a consistent input parameter set that can be used both at Tier-1 as well as at FOCUS Tier-4. This appears useful to reliably determine vulnerability of sites, but also for e.g. context-setting or Tier 3b assessments supporting the monitoring at Tier-4. Therefore, in our view it is justifiable to deviate from current regulatory practice here, acknowledging that futher guidance on input parameter selection in such cases may be useful. RMS AT: Please refer to comment 4(8) and 4(30). We propose to discuss most appropriate modelling input	See proposal for peer review / expert meeting discussion at comment 4(2) and comment 4(8).

		their primary metabolite occurrence. It was for instance the case for M3 in EFSA (2013) while shorter field $DegT_{50}$ of 2.56 days was selected for M2 instead of laboratory mean DT50 of 17.3 days, Moreover what is true for M56 will not necessarily be true for all other metabolites, depending on their persistence behaviour. Looking at the initially proposed calculations by applicant, it can be seen that under acidic conditions, field $DegT_{50}$ for M3 (Tier 2) provides indeed higher max PECgw for subsequent metabolites M55 and M56 (in comparison with tier 1a). However, for metabolites M11 and M54, it gives a slightly lower max PECgw (and lower PECgw for 6 scenarios/9 for winter cereals for both metabolites).	parameters at Tier-1 and Tier-3b/Tier-4 with MS's experts.	
4(35)	Addendum_Volume_3CP_B-8_2022-05-10 PEcgw	FR: typo; in RMS commenting box from p. 36, it seems that all references to Vol. 3CA regarding $DegT_{50}$ and ffm selection should be B.8.1.2.4 and not B.8.1.4.	Applicant (SYN): Noted. RMS is kindly requested to correct the typo. RMS AT: Indeed. The typo has been corrected in the updated DAR.	Addressed.
4(36)	B.8.2.4.1 Calculation of concentrations in groundwater	RMS AT: *The plant uptake factor for M3 is set to 0.784 as calculated with the Brigg's equation. To the knowledge of the RMS AT, there is no maximum permissible plant uptake factor of 0.5 according to pertinent guidance (EC, 2014).* SYN: This is considered appropriate, considering the text of the latest version of the groundwater guidance document (FOCUS, 2021): *"When a reliable measured octanol:water partitioning coefficient for neutral pH is available, the equation […] produced by Briggs et al. (1982) should be used to calculate the TSCF*	RMS AT: Noted.	Addressed.

		[…].PRZM and PELMO require a plant uptake factor. The TSCF should be used for this value."		

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	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(37)	Volume1 - Relevance of metabolites – "Relevance assessment of the pinoxaden metabolite …"	DE: All tables with summaries of the relevance assessment for the metabolites the RMS state the annual average concentration of the 90th spatial/temporal percentile. DE disagrees with the usage of temporal average 90th percentile. In regards of using a temporal average (arithmetic mean?) there is no knowledge of the leaching water volume and therefore no information on the fluxes. Consequently, averaging concentrations over time in our opinion is not scientifically sound and needs further expert discussions.	Applicant (SYN): We agree that guidance is needed to interpret the results of monitoring studies. In the absence of guidance, Syngenta used an average to represent concentrations within a year. We acknowledge that other options to derive endpoints from GW monitoring studies are available, as outlined in comments 4(55), 4(114) and 4(137), which, however, also show that pinoxaden metabolites do not exceed the regulatory trigger of 0.1 µg/L. RMS AT: DE is kindly asked to also focus on the RMS AT's assessment given in the dedicated assessment tables for each metabolite and in the commenting boxes. Here, different assessments endpoints including also the overall maximum concentration are given. We are aware that there are different views on whether to use averaged (e.g., annual mean) concentrations or not. We fully agree that there is discussion/agreement needed on the most appropriate type of assessment endpoint at the level of EU and MSs,	Addressed.

			considering the type of this monitoring, which is a highly targeted edge-of-field-monitoring.	
4(38)	Volume1 - Relevance of metabolites – "grey Boxes …"	DE: The RMS AT notes in most grey boxes:" … that a 90th percentile sample concentration, as proposed by the applicant, is not necessarily an agreed trigger endpoint for a relevance assessment at the level of groundwater monitoring in the EU, FOCUS Zones or Member States." We want to emphasize that a 90th percentile should only be calculated for the shallow groundwater sites. The usage of 90th percentile from sites with different application rates and patterns when they don't represent good agricultural practice is not appropriate.	Applicant (SYN): All sites were in areas with shallow groundwater and applications were made according to good agricultural practice. Pinoxaden is used on an as-needed basis for the control of black grass which does not induce pest pressure annually. This study therefore reflects realistic applications for black grass control in cereal growing regions of Europe, consequently applications are not made every year and not always at the full label rate. The RMS (AT) has made a simple, pragmatic proposal for scaling applications to the maximum rate (see Comment 4(111)) and analysis of this approach demonstrates the safety of pinoxaden applications. Yearly applications were made at the full registered label rate within the German National Federal wells, and the results of this study were the same as that in the pan-European monitoring study. No trigger was exceeded. The monitoring data are consistent in showing that applications of pinoxaden do not result in unacceptable groundwater concentrations. RMS AT: Please refer to comment 4(37).	Addressed.
4(39)	B.8.5.1.2.2. Selection of candidate areas for monitoring	DE: As the RMS for S-metolachlor we assessed a similar complex monitoring program. The notifier used a new set of percentiles (50/50/50) compared to the approach used for S-metolachlor (50/50/60). We are curious why the notifier changed the percentile or more generally	Applicant (SYN): The S-metolachlor and pinoxaden studies used the same methodology to estimate leaching vulnerability because we consider this the best approach: it is consistent with other Tiers of the groundwater assessment (FOCUS Tier-1 through Tier-3b), is transparent and	Addressed.

		speaking, how where the percentiles chosen/justified.	reproducible. Other methods could have been followed (see Comment 4(124)), but it is difficult to see how these would fit within the extisting groundwater assessment framework for Europe. It is not surprising therefore that the two studies used the same methodology to estimate leaching vulnerability. Differences between the two programs arise from having different aims: The target of the S-metolachlor program was Annex I renewal and the calculation of a 90th percentile leaching concentration for European groundwater and thereby the demonstration of safe uses at a European level. This approach required a strict statistical methodology. A high drop-out rate can be expected when potential monitoring sites have been identified as growers often may not wish to participate in studies. The statistical nature of the S-metolachlor programme meant that an exceptional non-adoption rate was expected, which meant a larger pool of candidate sites (n>120) was required to reach the desired final total. The vulnerability criterion was therefore relaxed to sites in the upper 60th percentile of vulnerability (so called 50/50/60) i.e., sites having 40th percentile vulnerability and above were considered for random selection. Once the statistical frame was set (i.e., before sites were identified) it could not be changed without compromising the outcome of the study.	

			The aim of the pinoxaden project was establishing safe uses at a Member State level. There was no requirement for random selection of vulnerable sites and so a smaller pool of candidate sites could be considered (n>60). The 50th percentile gave sufficient sites and fit with the percentile selection of the other criteria i.e., 50/50/50. The two studies are therefore similar in the way they use models to estimate vulnerability but use different selection criteria to address their different aims. RMS AT: Please refer to the applicant's response.	
4(40)	B.8.5.1.2.9 Pinoxaden use history at the monitoring sites	DE: See Comment 8.	Applicant (SYN): Syngenta assumes this refers to comment 4(44), and a reply is presented there. RMS AT: No need for a reply here.	Addressed.
4(41)	B.8.5.1.2.10 Hydraulic Connectivity	DE: In column 2 (sampling well number) of the table "Table RMS-39. Summary on the hydraulic conductivity … "the foot notes **, * and # indicate findings or no findings of pinoxaden or its metabolites. Does a missing footnote any row of column 2 indicate a metabolite finding without rate-normalization? Considering the connectivity issues, we acknowledge the amount of work done by the applicant and the RMS. For this type of study, (edge of field, very shallow groundwater, …) changing flow directions a probably are very common. Therefore, we think a higher frequency (quarterly or synchronised with the sampling	Applicant (SYN): Syngenta's understanding of the footnotes of Table RMS-39 is: (**) Indicates a site/well with detections of pinoxaden metabolites > 0.1 µg/L without a rate-normalization; (*) Indicates a site/well with detections of pinoxaden metabolites > 0.1 µg/L if residues are rate-normalized; (#) indicates a site/well with no detections of a pinoxaden metabolite (all < LOD) In order to address groundwater directions, regular manual dip data (i.e. 4-8 values per year, quarterly or bimonthly collected, always synchronized with the sampling schedule) are available for all the sites since 2017-2018 and are used to re-assess connectivity over the	Addressed.

		schedule) considering determining the flow direction should be mandatory to ensure a predominately flow direction towards the measuring well.	year in the AIR6 dossier. In addition, pressure transducers have been installed at most of the monitoring sites in 2018-2019 to allow in the future an even more comprehensive assessment of the hydrodynamics of the shallow aquifer through time. Furthermore, the applicant has presented a refined preliminary assessment on hydraulic connectivity in Comment 4(97), as well as results taking into account the final assessment on conductivity to be submitted at AIR6 (see reply to comment 4(55)), calculating statistics and endpoints only for sites that can be considered hydraulically connected. At last, further guidance on this aspect is encouraged going forward to reduce uncertainties and foster harmonization of different monitoring programs in Europe. RMS AT: A monitoring site without footnote (so no **, * or #) is indeed considered having detects of at least one of the pinoxaden metabolites > LOD but < 0.1 µg/L. We agree with DE that a more frequent sampling (monthly?), more frequent measurement of the groundwater flow direction and a higher number of sampling wells all around the field will finally decrease if not eliminate most concerns regarding hydraulic connectivity. The most appropriate set-up of monitoring sites for such a kind of

			edge-of-field monitoring should be addressed in a guidance document.	
4(42)	B.8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	DE: We agree with the overall statement and concerns of the RMS AT. We followed a similar approach during the S-metolachlor RAR with requesting soil concentration maps instead of mass flux maps to compare both approaches.	Applicant (SYN): We consider that mass flux is the appropriate metric to estimate vulnerability because it is independent on leachate volume, unlike concentration. It is well known that high modelled concentrations result from small, modelled leachate volumes and that this situation would not result in high groundwater concentrations in the field. We consider that mass flux is therefore the appropriate metric to compare vulnerability. RMS AT: As noted in the DAR we have no strong objections against using an annual mass flux as a metric for site vulnerability. However, we would prefer a higher percentile annual mass flux (instead of the median) in order to account for climate variability, similar to what is done at Tier-1. Please also refer to comments 4(60) and 4(101).	Addressed.
4(43)	B.8.5.1.2.12 Contextualisation	DE: We share the opinion that this approach seems to be over simplistic. Without any guidance and only 70 sites this approach seems practicable. Nevertheless, we think contextualisation (if used at all) should not "just" include verification of sites by cross checking the temperature and rainfall (appropriate sites). We think if contextualisation is needed it always should be a synopsis of all data (temperature, rainfall, soil, mass flux modelling, vulnerability mapping, vulnerability density	Applicant (SYN): The contextualization to FOCUS zones was used to determine whether a monitoring location was appropriate for a Member State. Many Member States also use this approach. In principle it would be possible to use the extent of cereals in a Member State and the MARS data to determine the ranges of environmental parameters, but we believe that this would not make a substantial difference. Nevertheless, these data could be presented upon RMS request.	Addressed.

		function etc.) to proof if a site is suitable for risk assessment on a Member State level. Additionally, we think a Member State should have the chance/allowance to assess if a site is suited to represent the desired vulnerability (without any guidance) for evaluating the risk inside their Member State. Generally speaking we think that at least 20 sites per FOCUS Zone are necessary.	RMS AT: As outlined in the DAR we have no reservations against the assignment of monitoring sites to certain FOCUS climate zones as long as the climate properties of the FOCUS zones are clearly defines (agreed climate database). In the case of contextualisation of sites located outside of a FOCUS zone or a MS, a synopsis of all local data mentioned in DE's comment is in principle given applying a spatially distributed FOCUS-Tier-1 leaching model. The point is that an agreed contextualisation approach (e.g., a spatially distributed leaching model or an index based approach) is needed first. We have no reservations against MSs defining their own criteria for evaluating monitoring sites being relevant for them. However, there are probably several (smaller) MSs, which do not have the resources to do so. These MSs may insist on a transparent and EU agreed approach they can refer to. We have no strong views on the exact minimum number of sites necessary for an assessment area (e.g., a FOCUS zone). This may also depend on the area of a FOCUS climate zone. Clearly, more is better. This is something which should be addressed in a dedicated guidance document.	
4(44)	B.8.5.1.2.13 - Accounting for actual application rates and	DE: We do not support the approach of scaling GW concentrations measured in the monitoring studies	Applicant (SYN): We acknowledges the concerns from DE that this approach may be simplistic and not	Peer review proposed. Experts to discuss the RMS assessment approach for scaling GW

application frequencies other than intended	because we considered it not being scientifically sound. The highest Tier 4 monitoring studies try to show a safe use under most realistic conditions (Climate, Soil, Use, etc.). By introducing a scaling factor for applications and measured concentrations we reduce the complexity and therefore theoretically step back in terms of being the most realistic case with regard to report and assess the natural behaviour of the substances. Using normalisation factors (up- and downscaling) probably leads to concentrations which might not be realistic under the heterogenic site-specific environmental conditions. While using a normalisation factor for upscaling as well as for downscaling the real world information gets altered in a very just way. Using a factor which "artificially" changes the actual substance behaviour (in terms of movement of the contamination plume etc.) and the peak concentration in groundwater under the prevailing pedo-climatic conditions and the intended use. For example, altering applications quantities and/or the measured concentrations might result in over-/ underestimating the contamination in the aquifer because the dispersion influence is ignored.	account for the complexity of site-specific variability in a way that could be considered scientifically robust. On that note, we want to point out that also the RMS AT acknowledged in its evaluation that the rate-normalization approach presented is pragmatic and simplifying, not backed up by any guidance and may not be scientifically sound. At the same time, in order to address the situation that lower application rates at a number of sites may lead to measured residues not representative of the targeted application rate of 60g/ha, the rate-normalization approach proposed by RMS AT is considered to alleviate this concern. It can be shown that even considering this more conservative approach does not significantly alter the picture that exceedances of metabolites above 0.1 µg/L are sporadic, and hence is a way of increasing confidence in the use of the monitoring results for regulatory decision-making. We would also like to note that in the German National Federal wells monitoring program farmers were incentivized to proactively apply pinoxaden on their cereals fields by providing products free of charge to them, thus also creating an incentive to prioritize cropping of cereals over other crops. With that, it is reasonable to assume that the monitoring program in Germany covers an "unrealistically" high area with full-rate applications (58.5 g/ha) during the study period.	concentrations measured in the monitoring studies, considering the need to conclude in the context of the representative uses assessed which diverge from the farmer practice in the situations monitored.

			AT RMS: We propose discussing the pragmatic and simple approach of scaling monitoring results with MS's experts.	
4(45)	B.8.5.1.2.14 - Minimum number of (relevant) monitoring sites required	DE: We think at least 20 relevant monitoring sites per FOCUS Zone as stated in FOCUS report (EC, 2014) are necessary.	Applicant (SYN): The program consists of 33 sites within the Hamburg Zone and 21 sites in Thiva zone, which should be enough to demonstrate safe use according to this criterion. The original spread of sites was more even across FOCUS Zones, however, the change in the MARS weather data from a 50km to a 25km grid in 2014 i.e., after site selection, meant that many sites changed their FOCUS Zone attribution, which was beyond the control of the Applicant. A more flexible approach would be to assume that 20 years of FOCUS data would be required to demonstrate a FOCUS pass for a Zone as in the FOCUS Equivalent Concentration (FEC) approach (see comment 4(114) and 4(123)) AT RMS: The number of relevant sites necessary for each FOCUS zone or other assessment area (e.g., a MS) should be addressed in a dedicated guidance document.	Addressed.
4(46)	B.8.5.1.2.16 - Monitoring assessment endpoints	DE: See Comment 1.	Applicant (SYN): We assume this refers to comment 4(37), and a reply is presented there RMS AT: No reply needed here.	Addressed.
4(47)	B.8.5.1.2.21 - RMS AT's concluding remarks on the evaluation of the targeted pinoxaden	DE: The very detailed work done by AT helps understanding the complexity of this TIER 4 edge of field monitoring study. We strongly agree with AT that there is a need for regulatory guidance on how to	Applicant (SYN): The applicant highly appreciates the effort by RMS AT to evaluate this complex and extensive groundwater monitoring program in this detailed and structured way.	Addressed.

	edge-of-field monitoring study	conduct, evaluate and assess such a type of study.	The applicant agrees that more specific guidance is needed and, in the absence of such guidance, have followed principles for the conduct of groundwater monitoring studies such as they are available e.g. in Gimsing et al (2019) and Aden et al (2002) and it is considered that the monitoring study submitted generally conforms to those principles. Syngenta agrees that more targeted guidance on how to conduct and interpret groundwater monitoring studies would help in future, but until guidance is available the FOCUS (2014) principles on PECgw determination may – together with the aforementioned publications – need to be considered as a steer for 'best practice'. The applicant strongly supports that the development of more targeted guidance is an important step to ease the design and evaluation of GW monitoring studies, which benefits both applicants as well as evaluators. RMS AT: This feedback is highly appreciated.	
4(48)	Vol. 3 B.8 A.S., pages 185-255. Pan EU targeted edge of field groundwater monitoring assessment.	EFSA thanks the RMS for the very clear evaluation of the monitoring site selection, monitoring site contextualisation, connectivity considerations and associated targeted monitoring results. EFSA appreciates the RMS pragmatic and simple data processing approach to scale the monitoring results with a monitoring site specific rate normalisation factor in order to bring them in line with the intended use rate of 60g /ha (pages 208-210). EFSA also appreciates the clear	Applicant (SYN): The applicant has made an extensive effort to demonstrate the safety of pinoxaden and its metabolites in groundwater by combining a large, dedicated monitoring programme across Europe and national monitoring programmes in individual Member States. The dedicated monitoring programme used state-of-the-art modelling, consistent with higher Tier modelling approaches used to estimate groundwater concentrations in	Peer review proposed. Experts to discuss the RMS assessment approach and what might be considered as appropriate practice regarding temporal sampling and temporal practice for expressing concentrations when using them to compare to parametric limits in the context of edge of field sampling wells, samples from the saturated zone.

		description in section B.8.5.1.2.16 (pages 212-213) regarding selecting monitoring assessment endpoints. In the case of the targeted monitoring exercise for S-metolachlor and its metabolites, because sampling was only quarterly (as here except for German sites), because sampling from the saturated zone can already include some dilution dependent on the use intensity in the upstream catchment and the changing direction of groundwater flow, till now annual maximum concentrations have been the basis for a comparison against the drinking water limit and for completing relevance assessments and not annual average concentrations for each monitoring site (DE final amendments to the RAR for S-metolachlor). It seems that continuing to follow this approach also for the metabolites of pinoxaden can be concluded as appropriate, considering these issues are also present in the pinoxaden dataset.	Europe, to identify vulnerable locations in seventy groundwater locations and has measured concentrations in these locations for over 5 years. The practicalities involved in this exercise need to be considered when evaluating such programmes i.e., it is not always possible to select groundwater monitoring locations which satisfy all vulnerability criteria. Nevertheless, the applicant has made every effort to address concerns over the study: Reply to comment 4(55) addresses the hydraulic connectivity at the sites and presents results for 62 out of the 70 sites that can be considered hydraulically connected; the study (in common with the S-metolachlor study) has an edge-of-field setup (Gimsing et al. 2019), which is consistent with best practices for a monitoring study of shallow groundwater in vulnerable agriculture regions. In addition, the selection of the sampling wells followed EFSA quality criteria for monitoring studies (SANCO/13144/2010, EC, 2014) and is consistent with UBA guidance for groundwater monitoring wells (UBA, 2020). Comment 4(114) addresses potential concentrations arising from the storage stability of M55, and uses annual maximum concentrations to demonstrate a proposed FOCUS pass (FEC – FOCUS Equivalent concentration) to show acceptable uses for pinoxden at the FOCUS zone level. This approach is also consistent with the proposal by EFSA to use annual maximum concentrations rather than annual averages and

			addresses a perceived lack of vulnerability of the sites. Reply to comment 4(55) shows that either considering the small number of exceedances, or the concentrations at the sites, it is unlikely that pinoxaden or its metabolites will exceed trigger values in groundwater. This result is confirmed by national monitoring in which more locations received year-on-year applications at the full label rate with more frequent measurements. The applicant therefore considers that the safety of pinoxaden and its metabolites in groundwater has been extensively demonstrated. RMS AT: We would like to thank EFSA for their positive feedback. We acknowledge that apparently (annual) maximum instead of (annual) average concentrations have been the basis for regulatory decisions of other substances. Finally, it comes down to the question, to which extend (if at all) any kind of spatial/temporal percentile of annual maximum concentrations is acceptable at EU, FOCUS or MS level, keeping in mind that a maximum concentrations itself already includes some conservatisms. This is something we would like to discuss with MS's experts.	
4(49)	Vol. 1.	EFSA notes that it seems that M3, M11, M54, M55 and 56 being proposed to have their non relevance assessed following a grouping approach (see toxicology comment 2). Should they be grouped, then for the Step 4 relevance assessment it is	Applicant (SYN): The applicant would like to highlight that none of the groundwater metabolites, M2, M3, M11, M52, M54, M55 or M56, are part of the residue definition for plant and animal commodities. Therefore, the step 4 exposure assessment should	See 2(4)

		not any longer necessarily appropriate to compare each metabolite separately to a concentration of 0.75 µg/L. (Anyway for each metabolite separately any food residues would need to also be considered such an assessment was not presented). See residues section comment 1 for more details. Therefore it might be that modelling results for each FOCUS scenario and monitoring results for each monitoring site from the pan European groundwater monitoring study need to be summed for the metabolites in this group, before comparing to the threshold of concern of 0.02 µg/kg body weight per day at relevance assessment Step 4 (please refer to the GD SANCO/221/2000-rev.10). So it seems at the moment not so clear that Step 5 of the non relevance assessment would not be triggered for M3, M11, M54, M55 and 56. Note that it also seems not so clear that M55 will not be indicated relevant at Step 3 of the guidance (genotoxicity indications, see toxicology comment 6).	be based on the monitoring data of the groundwater metabolites submitted. In accordance with the EU GD SANCO/221/2000-rev. 10, step 4 exposure assessment assesses the exposure level of each groundwater metabolite against the threshold of 0.75ug/L individually: *"such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L."* Based on the groundwater monitoring data evaluated by AGES, and based on the 90th percentile (spatial/temporal) maximum annual concentration (rate-normalized) (M3: 0.027 ug/L; M11: 0.016 ug/L; M52: 0.020 ug/L; M54: 0.010 ug/L; M55: 0.015 ug/L; M56: 0.025 ug/L), exposure levels of each metabolite do not exceed the threshold of 0.75ug/L. The threshold of 0.75ug/L is also not exceeded if the individual exposure levels were combined for M3, M11, M54, M55, and M56. (sum=0.093 ug/L). As the threshold of concern is not exceeded at the step 4 exposure assessment, step 5 refined risk assessment is not triggered, and therefore additional toxicology data are not required. AT RMS: This has to be addressed/discussed in the section on human toxicology.	
4(50)	Addendum 1 to Volume 3 – B.8 (PPP) Section B.8.5.1 (groundwater)	FI: We acknowledge the extensive work done by the applicant with respect to groundwater monitoring data across five EU countries (France,	Applicant (SYN): The applicant has made every attempt to design the monitoring study in a sound way to obtain reliable results for regulatory	Addressed.

		Germany, Italy, Lithuania, and the UK). We thank RMS AT for their excellent summary, evaluation and partial re-evaluation of the data. AT RMS raises pertinent questions on uncertainties of the monitoring data, such as limited hydraulic connectivity between treated fields and sampling wells, and application rates and frequencies less than intended. These uncertainties need to be taken into consideration when using the monitoring data as a basis for decision making. Although the monitoring is referred to as a PAN-European monitoring programme, it needs to be emphasized that no monitoring data are available for the Northern Zone. Thus, conclusions based on the monitoring are not directly applicable to Nordic conditions. We agree with AT RMS that there is an urgent need to develop more targeted regulatory guidance on how to evaluate monitoring studies, and consider the issues listed under B.8.5.1.2.21 as a good starting point.	decision-making. The concerns by RMS AT are being addressed: - Hydraulic connectivity: Variable groundwater flow directions at a number of sites were not expected *a priori*, but whenever such changes were identified as a considerable factor in the course of the monitoring study, additional sampling wells were established at sites. Transducers have been installed at all wells in 2020, and based on those data, the applicant is able to respond more quickly in establishing additional sampling wells in future. Furthermore, the applicant has presented a refined preliminary assessment on hydraulic connectivity in comment 4(97), as well as results taking into account the final assessment on conductivity to be submitted at AIR6 (see reply to comment 4(55)), calculating statistics and endpoints only for sites that can be considered hydraulically connected. - The rate-normalization approach is a pragmatic means by RMS Austria to generate conservative estimates for concentrations based on the targeted application rate of 60 g/ha, and is supported by the applicant It is pointed out that there are three vulnerable sites located in Lithuania, which may be representative for conditions in the Northern Zone. At last, we strongly agree that the development of more targeted guidance is an important step to ease the design and evaluation of GW

			monitoring studies, which benefits both applicants as well as evaluators. RMS AT: This feedback is highly appreciated.	
4(51)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.5.1 Pan-european groundwater monitoring programme	FR: we would like to thank RMT AT for the very clear and structured assessment of this extensive monitoring program. We acknowledge the huge work done, and the synthesis tables provided by RMS are very appreciated to get an overall picture of the information available per sites. FR globally agrees with AT concluding remarks and the need for further work and discussion on reliability assessment of the monitoring sites with regard to hydraulic connectivity, leaching vulnerability, contextualisation, use rate and frequencies, and the definition of assessment endpoint for groundwater monitoring study. Please find below additional comments/thoughts from FR reading this assessment, for further discussions.	Applicant (SYN): The practicalities of establishing a programme of this size should be considered. The applicant followed an open and transparent process, using agreed groundwater models and parameterisation to identify 70 monitoring locations across Europe. It is an extremely difficult task to have enough monitoring sites in all FOCUS Zones and at the same time having a compilation of the requested worst-case vulnerability properties at each site, while ensuring hydraulic connectivity and regular applications at the target rate. The applicant considers that the practicalities of such a complex task should also be discussed and taken into account when targeted guidance for regulatory groundwater monitoring is developed. Meanwhile, the applicant makes every attempt to adequately address the limitations of the GW monitoring program, as reflected in further comments. RMS AT: This feedback is highly appreciated.	Addressed.
4(52)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.5.1 Pan-european groundwater monitoring programme	FR: The results of the leaching vulnerability assessment indeed indicate that the 1) the targeted vulnerability for sites selection is not fulfilled for 40% of sites, and 2) the 80th percentile (theoretically	Applicant (SYN): The practicality of installing 70 groundwater monitoring locations across Europe means that it is not possible to ensure that all selected locations meet precise vulnerability criteria. Sites were	See expert consultation proposed at comment 4(48).

		expressed with the FOCUS scenarios) is not fulfilled for a large majority of sites. This clearly cannot be considered representing a realistic worst-case for groundwater monitoring, and this needs to be accounted for in the analysis of the results.	selected based upon the vulnerability of 10km grid squares to leaching of M2 and M3. This size was chosen because it allowed for a reasonable pool of candidate farmers from which to select edge-of-field monitoring locations. It is known that only a small percentage of growers are willing to participate in such an exercise which means that a large pool of candidates is needed. Even if Syngenta had conducted the selection at a finer resolution, differences between field soil and soil types appearing in a GIS data layer mean that a specific vulnerability cannot be guaranteed. The 50th centile groundwater leaching may not have been reached if it is assumed that all groundwater is at 1m depth. However, not all European groundwater is so shallow. Syngenta went to every effort to identify vulnerable sites with shallow groundwater and monitor them edge-of-field. Syngenta believes that this exercise has resulted in a set of monitoring locations that reflect worst-case exposure in the reality of vulnerable European groundwater beneath cereal growing regions. This can be seen in comment 4(124), where 80% of the selected sites would be classified as having very high or high intrinsic groundwater vulnerability according to the DRASTIC map produced by JRC. In addition, Syngenta makes a proposal to address any shortfall of modelled site vulnerability in comment 4(123). RMS AT: We agree with the applicant that even with all these tremendous

			efforts made, selected sites may finally not be that vulnerable or suitable (from an applicant point of view) as intended. For regulatory purposes, it is important to adequately assess the site's vulnerability and to adequately set the site's overall vulnerability (and the monitoring results) into context, e.g., for MS without monitoring sites. In some situation this may lead to the decision to entirely discard individual sites and their monitoring results, e.g., if it is not considered sufficiently vulnerable. However, some criteria on the reliability assessment of monitoring sites for contextualisation are needed first. Other approaches outside of the "FOCUS modelling world", e.g., index methods as the DRASTIC approach or similar (see comments below) may give additional information on the site's vulnerability.	
4(53)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.5.1.2.9 Pinoxaden use history at the monitoring sites	FR: It is our understanding that, considering the monitoring is an edge-of-field monitoring, pinoxaden application rate and frequencies were only surveyed from the field next to monitoring well. However some edge-of-field monitoring sites cannot be assimilated to field leaching experiment, and the catchment area of the monitoring well may be far larger than the field of interest targeted for well installation. Is there any estimation of the catchment area for each site? Is there any indication of other potential uses of pinoxaden within the catchment area of the monitoring sites? Information should be available on the catchment size and the proportion represented by the targeted field.	Applicant (SYN): We do not have information on the catchment area, only the size of the relevant, upgradient field. The program has a strict edge-of-field setup, so we only collect product use history for the field considered upgradient (i.e. treated). The 70 monitoring sites were selected in agriculture regions with intensive cereals cropping. Thus, background concentrations from the catchment cannot be excluded by default. However, the edge-of-field setup is consistent with best practices for the conduct of field leaching studies as explained in Gimsing et al (2019). Connectivity with the specific field can be assumed by default in this kind of	See expert consultation proposed at comment 4(48).

		This seems essential to estimate the flux contribution of the targeted field within the whole contribution area, and/or the contribution of any other sources of pinoxaden in the monitoring wells. For instance, for site PXDIT-1203, the field site is 0.9 ha, while the groundwater is about 4.7 m bgl; it should be known whether the field have only limited contribution to the whole "flux" caught by the monitoring well.	setup due to the proximity of the sampling well to the field and the small distance between the filter area (i.e well screen) and the water table. In addition, to reduce unexpected issues with representativeness, the selection of the sampling wells followed EFSA quality criteria for monitoring studies (SANCO/13144/2010, EC, 2014) and is consistent with UBA guidance for groundwater monitoring wells (UBA, 2020). In particular, the length of the filter is <=4m (generally 2m) and the distance between the top of the filter and the water table is <=3 m (generally 1-2 m). Finally, leaching in the unsaturated zone is mainly a vertical process, while the transport in the saturated zone (aquifer) is mainly horizontal or sub-horizontal. Under this premise, site PXDIT-1203 has 0.9 ha treated, located fully upgradient to the sampling well (Well-1), which is on the edge of the field, downgradient. The average depth-to-watertable is 4 - 4.8 mbgs (depending on the season), the sampling well is 5.5 m deep and the screen is 2 m long, which appears as a robust setup to monitor residues in that field. RMS AT: As indicated by the applicant there is neither information on the exact catchment area of each well nor is the groundwater flow direction that well known. Thus, temporal dilution with "untreated" upstream groundwater or upstream input from other treated fields cannot be ruled out. This is probably also a reason

			why many authorities, for conservativeness reasons, tend to rely on maximum concentrations instead of, e.g., average concentrations. As already indicated in the DAR, issues with hydraulic connectivity (changing groundwater flow direction, dilution with upstream groundwater, etc.) can be probably reduced with a more sophisticated setup of sampling wells (i.e., permanently sampled wells in all directions around the field of interest, various sampling depths, more frequent sampling, etc.). Of course, this will add additional effort and extra costs to the monitoring campaign.	
4(54)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.5.1.2.9 Pinoxaden use history at the monitoring sites	FR: Regarding the collected application dose, RMS notes that in some cases, pinoxaden was not applied on the whole field surface. This is indicated in table RMS-38. However, it is not clear whether this was accounted for in the rate-normalisation factor calculation. This does not seem so. Regarding the application frequency, FR agrees that splitting the monitoring set into subgroups of annual, biennial or triennial applications will reduce the number of site per groups. However, it is essential that risk managers are aware that the application frequency covered by monitoring results are not in line with the intended annual application. In addition, in relation with FR previous comments on the catchment	Applicant (SYN): In 81% of cases in the pan-EU monitoring study, more than 90% of the field area has been treated. There were in total only 7 out of 244 occasions, where half of the field or less has been treated. It should be noted that it has not been recorded whether the applications were carried out at the close or at the far end of the field from the well. Generally, the application practice as recorded is considered representative of realistic agronomic conditions in cereals growing regions. The EU-wide monitoring study of Syngenta reflects typical farming practice for control of black grass in the EU at worst case sites. The result of this monitoring clearly demonstrates that there are practically no exceedances of legal limits in agricultural practice for PXD in the EU, and hence safe uses exist.	See expert consultation proposed at comment 4(48).

		area definition, the question of frequency of sampling is also linked with other potential contribution from adjoining fields were pinoxaden might be used (crop rotation). Was this point accounted for?	Moreover, in the German National Federal wells monitoring program farmers were incentivized to proactively apply pinoxaden on all their cereal fields in the sub-catchment by providing products free of charge to them, thus also creating an incentive to prioritize cropping of cereals over other crops. This national federal well monitoring study, conducting also monthly samplings, showed no exceedances of any trigger with an unrealistically high rate of annual applications across the whole sub-catchment. It may therefore be concluded that even under such an "unrealistic" high use pressure safe uses for PXD must exist in FOCUS Hamburg and Kremsmuenster zones with yearly applications. RMS AT: No information on applications on other fields in close vicinity to the treated field is available. Potentially treated fields in the upstream area, other than the targeted field, have not been accounted for. We agree with FR that actual application frequencies (which are typically less than intended in the GAP) have to be taken into account somehow. This is something which should be discussed with MS's experts.	
4(55)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.5.1.2.10 Hydraulic connectivity assessment	FR: The Applicant's investigation on the hydraulic connectivity and flow direction, and further elucidation, is very extensive and the most sophisticated ever seen in monitoring programs. It indeed confirms what	Applicant (SYN): Correct, empty cells in the Table RMS-39 are considered downgradient by RMS, based on the interpretation of data from Langridge & Schofield, 2020; Andrews et al., 2020; Schofield et al., 2019, 2020	Addressed.

		was already foreseen in previous programs, that the hydraulic connectivity is not obvious, even in case of targeted well installation in shallow groundwater. RMS table 39 is very useful. However we need a clarification: in the first columns with information from application groundwater contour plot assessment, there is "grey cells", "X" and "na" which are defined in the table footer. However, could RMS confirm that an empty cell mean that the well was visited and considered located down-gradient? Thanks for clarification.	and the EXCEL file "Pinoxaden EU AIR Confirmatory data – Sampling wells informa.xlsx" Assessing flow direction over time is indeed not an obvious exercise. The hydrodynamic of shallow aquifers, especially in agricultural regions, is complex and usually variable over time and space. For this reason, it was put so much effort into providing comprehensive investigations and updated analysis of the data. The RMS (AT) have performed an extensive review of the hydraulic conductivity at the monitoring sites. We conducted a preliminary assessment for the first commenting round on sites that can be considered hydraulically connected in Comment 4(97), which by now has been further refined, and is going to be presented in the AIR6 submission. This new assessment on hydraulic connectivity comes to similar conclusions as the assessment by RMS AT, and the report can be provided to the RMS upon request. Our assessment shows that there are 62 sites where connectivity can be demonstrated. Hence, eight sites have been removed from the evaluation (DE-44B, IT-1217, IT-1231, IT-1254, IT-1259, LT-891, UK-496, UK-580). Of these 62 sites, there are eight sites (DE-44A, DE-1551, DE-249, DE-259, FR-1101, FR-1112, FR-687, IT-1260) that we consider benefiiting from further elucidation by means of tracer tests

to improve the overall understanding on the groundwater dynamics.

Taking into account these 62 sites that can be considered sufficiently connected only, the following results for pinoxaden metabolites were calculated for the years 2015 to 2021 (rate-normalized only):

	M2	M3	M11	M52
Total number of samples	2651	2651	2651	2651
Number of rate-normalized residues ≤ LOD	1527	1323	1483	1543
% of rate-normalized residues ≤ LOD	81.27	70.41	78.92	82.12
Number of rate-normalized residues > LOD	352	555	396	336
% rate-normalized of residues > LOD	18.73	29.54	21.08	17.88
Number of rate-normalized residues > LOQ	25	170	50	27
% of rate-normalized residues > LOQ	1.33	9.05	2.66	1.44
Number of rate-normal. residues > 0.1 µg/L	4	46	4	3
% of rate-normalized residues > 0.1 µg/L	0.21	2.45	0.21	0.16
Highest rate-normalized residues (µg/L)	0.592	0.649	0.154	0.258

	M54	M55	M55 D9.2*	M56
Total number of samples	2651	2651	2651	2651
Number of rate-normalized	1549	1499	1499	1270

residues ≤ LOD				
% of rate-normalized residues ≤ LOD	82.44	79.78	79.78	67.59
Number of rate-normalized residues > LOD	330	380	380	608
% rate-normalized of residues > LOD	17.56	20.22	20.22	32.36
Number of rate-normalized residues > LOQ	16	20	44	167
% of rate-normalized residues > LOQ	0.85	1.06	2.34	8.89
Number of rate-normal. residues > 0.1 µg/L	1	0	3	10
% of rate-normalized residues > 0.1 µg/L	0.05	0	0.16	0.53
Highest rate-normalized residues (µg/L)	0.153	0.078	0.169	0.161

* M55 concentrations corrected for chilled storage stability of 9.2 days

The annual maximum concentrations of pinoxaden metabolites were calculated as follows (rate-normalized):

Database		Percen-tile	M2	M3	M11	M52
Annual *maximum* concentration (µg/L)	Maximum year (spatial percentile)	100th	**0.592**	**0.649**	**0.154**	**0.258**
		95th	0.033	**0.137**	**0.101**	0.094
		90th	0.026	0.061	0.070	0.067
	Individual years (spatial/ temporal percentile)	100th	**0.592**	**0.649**	**0.154**	**0.258**
		95th	0.022	0.058	0.033	0.033
		90th	0.015	0.033	0.022	0.015
All samples (entire period)		90th	0.015	0.033	0.022	0.015

Database	Percen-tile	M54	M55	M56

				Un-corr.	*DT50* = 9.2 d	
Annual *maximum* concentration (µg/L)	Maximum year (spatial percentile)	100th	**0.153**	0.078	**0.169**	**0.161**
		95th	0.037	0.054	0.069	**0.125**
		90th	0.032	0.032	0.052	0.077
	Individual years (spatial/ temporal percentile)	100th	**0.153**	0.078	**0.169**	**0.161**
		95th	0.021	0.023	0.025	0.062
		90th	0.013	0.016	0.016	0.031
All samples (entire period)		90th	0.013	0.016	0.016	0.031

These results clearly demonstrate that at the 90th percentile annual maximum concentration, no exceedances above the trigger value of 0.1 µg/L for metabolites of pinoxaden are observed, even considering only those sites, where a connection between wells and fields can be concluded.

RMS AT: We confirm that an empty cell indicates that the sampling well was considered located in the down-hydraulic gradient at the time of sampling. We have added a footnote at table RMS-39 of the DAR in this respect.

In table RMS-39 of the updated DAR we have also highlighted the 8 sites where the applicant claims that for these sites hydraulic connectivity cannot be sufficiently demonstrated (see applicant reply to FR's comment). The additional 8 sites where the applicant claims that they would benefit from further hydraulic connectivity elucidation have been highlighted for illustrative purposes as well. If requested by the MS's experts, we are also willing to

			evaluate the new hydraulic conductivity assessment on beforehand of the AIR6 procedure. From further (albeit unevaluated) results provided by the applicant (as a reply to FR's comment) for the sampling period from 2015 – 2021 (i.e., two further years of sampling!) it appears that the overall picture of the monitoring campaign has slightly worsened when compared to the sampling period from 2015 – 2019 presented in the DAR. For reasons of completeness and transparency, we have added these preliminary result provided by the applicant in the revised DAR, indicated as *preliminary/unevaluated* (see table RMS-58b and RMS-84b). If considered necessary by the MS's expert, we are of course willing to evaluate these new data on the extended monitoring period on beforehand of the AIR6 procedure.	
4(56)	Addendum_Volume_3CA_B-8_2022-05-10 B.8.5.1.2.20. RMS AT's overall conclusion	FR: RMS conclusion is that despite the limitations, all pinoxaden metabolite are highly unlikely to exceed the regulatory trigger of 0.1 µg/L. FR agrees that they are very few exceedance observed within the monitoring programme, however, this conclusion should be relativized pending further discussion and reliability assessment regarding the hydraulic connectivity and the leaching vulnerability of each site, and other limitations.	Applicant (SYN): The applicant has made every attempt to design the monitoring study in a sound way to obtain reliable results for regulatory decision-making. The concerns by RMS AT are being addressed: - Hydraulic connectivity: Variable groundwater flow directions at a number of sites were not expected *a priori*, but whenever such changes were identified as a considerable factor in the course of the monitoring study, additional sampling wells were established at sites. Transducers have been installed at all wells in 2020, and based on	See expert consultation proposed at comment 4(48).

			those data, the applicant is able to respond more quickly in establishing additional sampling wells in future. Furthermore, the applicant has presented a refined preliminary assessment in comment 4(97), as well as results taking into account the final assessment on conductivity to be submitted at AIR6 (see reply to comment 4(55)), calculating statistics and endpoints only for sites that can be considered hydraulically connected - The rate-normalization approach is a pragmatic means by RMS Austria to generate conservative estimates for concentrations based on the targeted application rate of 60 g/ha, and is supported by the applicant In conclusion, the GW monitoring program is considered robust enough to conclude on safe uses for pinoxaden in the EU. RMS AT: We agree with FR. Please notice that according to the extended sampling period from 2015 – 2021 the overall picture of the groundwater sampling campaign has slightly worsened (apparently particularly with respect to M2). Please also refer to comment 4(55). Regarding hydraulic connectivity issues we recommend re-considering the site's standard monitoring set-up and instrumentation.	
4(57)	Volume 3, CA section B.8.5.1.2 RMS evaluation	NL: NL would like to compliment the RMS on the way it has summarized the applicant's assessment of the monitoring data and the elaborate RMS evaluation of this assessment. This was very helpful in the	Applicant (SYN): This is acknowledged. RMS AT: This feedback is highly appreciated.	Addressed.

		commenting process. Especially the use of separate section headings in the RMS evaluation made navigation through the document very easy.		
4(58)	Volume 3, CA section B.8.5.1.2.3 Selection of final drilling sites for monitoring	NL: The minimum requirement of 2 out of 4 years with an application of pinoxaden, is based upon estimated arrival times and peak occurrences of metabolites in shallow groundwater (Patterson, 2016; Bird, 2018). RMS already had some remarks regarding the uncertainty in these estimation. NL is of the opinion that the accuracy or uncertainty of these estimations cannot be determined based on the information in this study. No calibration or validation was performed for these simulations. In addition, only two scenario's were used. Therefore, NL considers these estimation not to comply with the quality criterion specified in section in section 9.5 of the FOCUS report regarding "robust estimates of solute travel times". Additional information: For this monitoring study for pinoxaden, the estimation of the travel time might be considered less relevant, because in the majority of the sites metabolites of pinoxaden have been detected. The only plausible source is agricultural use. So if the GAP and historical application rates, have not changed over the years, than determination of the "temporal connectivity" between recorded applications on upgradient fields and the detections measured in sampling wells downgradient, maybe less important. However, in the RMS considers that the monitoring results	Applicant (SYN): Estimates of potential travel times are needed before sites are selected to define the length of a study and to identify fields where the history of applications enables groundwater concentrations to be possible at study initiation. In the absence of any field data the approach outlined in (Patterson, 2016; Bird 2018) is a reasonable approach to estimate potential travel times. RMS AT: As indicated in the DAR, we agree with NL that the travel time estimate based on an extended 1-m leaching model is not necessarily robust in a scientific sense. However, it is probably better than having no estimate at all, and at least an indication for the time to pass the uppermost 5 m of the unsaturated zone. Nevertheless, guidance is needed on how to conduct and interpret such a modelling exercise.	Addressed.

		should not be just indicative of the label use rate of 60 g a.s./ha, but should really reflect this application rate; therefore RMS proposed a rate-normalization approach to correct for lower application rates. In that case also the issue of "temporal connectivity" becomes important.		
4(59)	Volume 3, CA section B.8.5.1.2.3 Selection of final drilling sites for monitoring	NL: In the second-last sentence "groundwaster" should read "groundwater".	Applicant (SYN): Noted. RMS is kindly requested to correct the typo. RMS AT: Typo corrected in the revised dRAR.	Addressed.
4(60)	Volume 3, CA section B.8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	NL: RMS states that it does not necessarily support the use of a *median* annual mass flux, as it would ignore extreme weather conditions. NL notes that a median value does not ignore more extreme conditions. The position of a median value is also dependent on the extreme values. In addition, NL notes that Appendix 11 of the FOCUS report on higher tier GW assessments (EC, 2014) shows that for the 90% vulnerability concept, the spatial variability of the pesticide fluxes is more important than the *temporal* variability of pesticide fluxes. That is also why in GeoPEARL simulations for the Netherlands a median annual average concentration (50th percentile) is combined with a spatial 90th percentile, in order to approach the 90th percentile vulnerability within the area of use.	Applicant (SYN): We consider that the median annual mass flux is an appropriate metric to estimate the potential vulnerability of a monitoring site. The median reflects typical behaviour i.e., where greater mass flux occurs because of typical weather at a site, rather than because of extreme weather. High percentile events cannot be relied upon during a study and could not be enforced over such an extensive study. We consider that the use of the median is justified given the practicalities of conducting large-scale monitoring studies. RMS AT: The most appropriate vulnerability metric may be discussed with MS's experts.	See expert consultation proposed at comment 4(48).
4(61)	Volume 3, CA section B.8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	NL: proposes an alternative approach of estimating the vulnerability of monitoring sites by comparing FOCUS-Tier-1-type PEC_{GW} values for a monitoring site with the PEC_{GW} of the associated FOCUS Tier-1 scenario. RMS states that "a	Applicant (SYN): It is agreed that consistency should be maintained across different Tiers of assessment. The Tier-1 FOCUS concentration is less relevant than the Tier-3b concentration to estimate the	See expert consultation proposed at comment 4(48).

		monitoring sites with a FOCUS-Tier-1-type PECGW value higher than the PECGW of the associated FOCUS Tier-1 scenario may also be considered protective in a broader sense (at least with respect to this FOCUS Zone).". This last point mentioned in brackets is crucial. The FOCUS Tier 1 scenarios, do not take into account the crop area in a FOCUS zone. This means that if the FOCUS-Tier-1-type PECgw of the site is lower than the PECgw value of the FOCUS scenario, than potentially in term of the potential area of use (i.e. crop area) within the FOCUS Zone, a site might still rank in the upper percentiles of the CDF of the area of use; but also the other way around. In a tiered approach, the higher tiers should become more realistic at higher tiers. Therefore, NL is of the opinion that the vulnerability assessment of the monitoring sites at Tier 4, should be more realistic (i.e. more in line with the Tier 3b vulnerability ranking than in line with the Tier 1 vulnerability).	vulnerability of a monitoring site for a FOCUS Zone. Comment 4(123) outlines a method by which the Tier-3b concentration can be used to demonstrate an equivalent FOCUS pass for a FOCUS zone. RMS AT: We are aware that FOCUS standard scenarios do not take into account the area of intended crop (otherwise crop-specific scenarios would be needed for each FOCUS zone). However, at Tier-1, for regulatory decision taking, nobody worries about that. So, from a regulatory point of view, locations which are more vulnerable than FOCUS standard scenario should be adequate to supersede results obtained at FOCUS gw scenarios (particularly if there is a sufficient number of them). We suggest discussing the issue of contextualisation with MS's experts.	
4(62)	Volume 3, CA section B.8.5.1.2.12 Contextualisation of monitoring sites	NL: Last line on p. 205, "Regulators Zones" should read "Regulatory Zones".	Applicant (SYN): Noted. RMS is kindly requested to update the typo. RMS AT: Typo corrected in the revised DAR.	Addressed.
4(63)	Volume 3, CA section B.8.5.1.2.12 Contextualisation of monitoring sites	NL: The applicant makes a distinction between "appropriate" and "protective sites". NL notes that the "appropriate" sites, only take into account only a selection based on spatial variability in the climatic conditions. In addition, some of these appropriate sites are considered "protective" sites, if the leaching vulnerability is above the 90th percentile. NL notes that this criterion	Applicant (SYN): Leaching conditions can be affected by seasonal patterns of rainfall and temperature. It is likely that each of the metabolites of pinoxaden M2, M3, M52, M53, M54, M55, M56 may each have a different sensitivity. We therefore took the pragmatic approach to contextualise monitoring locations using the FOCUS zone concept and conditions within	See expert consultation proposed at comment 4(48).

		only takes into account spatial variability in the soil conditions. However, the relevance of the results from samples from monitoring sites also is determined by the actual temporal variability of weather conditions at a given site. A site might be considered vulnerable based on Tier 3b leaching simulations encompassing 20-years of weather variation. If the actual weather in the period after application is not "conservative" enough compared to the 20-years of weather simulated in Tier 3b, than a the results from a relevant site might still be considered not relevant. Additional information: In the opinion of NL seasonal rainfall or even timing of rainfall events after application have a significant impact on the actual leaching to groundwater. In the opinion of NL, the selection proposed by the applicant only results in *potential* relevant sites as it only concerns a selection based on spatial variability. In the end the actual rainfall during and before the monitoring period will determine if this captures sufficiently the temporal variation in climatic conditions.	Member States as a pragmatic proposal. RMS AT: We suggest discussing the issue of contextualisation with MS's experts.	
4(64)	Volume 3, CA section B.8.5.1.2.15 percentile calculation approach	NL: NL notes that in Appendix 13 of the FOCUS Report (Sanco/13144/2010) three methods for calculating percentiles is presented, and the method by Hazen appears to be recommended for calculation of the 80th percentile. NL agrees with RMS that Guidance is needed on this point, which clarifies the minimum number of data points	Applicant (SYN): For the presented results, the EXCEL function percentile.inc() was used as a pragmatic choice for the analysis. The applicant acknowledges that the method used for percentile calculation impacts the outcome, especially for small populations of samples. For this reason, Hazen percentile method is proposed going forward. This is in line	Addressed.

		required for calculation of a certain percentile and whether or not the 0th and 100th percentile should be considered to lie outside the dataset.	with recommendations in FOCUS (2014). At the same time, the applicant agrees that guidance should clarify this point on how to calculate percentiles from results of GW monitoring studies. RMS AT: Noted.	
4(65)	Volume 3, CA section B.8.5.1.2.16 Monitoring assessment endpoints	NL: In the fourth paragraph, in the sentence "A groundwater monitoring may still be conservative..", probably the word "study" is missing.	Applicant (SYN): Noted. RMS is kindly requested to update the typo. RMS AT: Typo corrected in the revised DAR.	Addressed.
4(66)	Volume 3, CA section B.8.5.1.2.16 Monitoring assessment endpoints	NL: NL agrees with the handling of measurements <LOD and >LOD but <LOQ as proposed by the RMS. NL agrees with using actual sampling dates for calculation of bimonthly/quarterly/annual average values. NL agrees with omitting results from incomplete time series. NL agrees with using the maximum value of samples obtained from multiple sampling wells at a given site on a given sampling date.	Applicant (SYN): We propose that going forward the following may be used: ½ LOD for < LOD measurements, and the maximum of either, the mean of LOD and LOQ, or the actual measured value, if > LOD, but < LOQ. We agree with the use of actual sampling dates instead of the intended sampling quarter. RMS AT notes that a closer inspection of those sites, where residues (particularly M3 and M56) are more frequently found at higher concentrations (e.g., PXDDE-145, PXDDE-259, PXDDE-1515, PXDDE-1561 or PXDLT-823), does not allow identifying a certain quarter or season where concentrations are consistently highest or lowest. In addition, due to the time of flight of 1-2 years and considering that many sites had PXD applications in 2013 and 2014, some detections could happen in 2015. With view to the inclusion of incomplete years, the practicalities of sample collection should be	Addressed.

			considered. It may not always be possible to sample at a well due to e.g. temporal inaccessibility of wells, or when wells are dry. In the absence of guidance, we followed a reasonable and pragmatic approach to keep all samples taken. Furthermore, guidance should determine what constitutes an 'incomplete year' that may need to be omitted. Based on these considerations, we disagree to omit incomplete years by default. We agree to use the maximum value of measurements taken in a given sampling time in different wells of a same field site. RMS AT: Agreement of NL for raw data handling is highly appreciated. With respect to the applicant's reply we would like to stress that we consider a year incomplete only, if there was *consistently* limited sampling at all sites. E.g., in 2015 or in 2020. We do not consider a year incomplete if there are, e.g., 1 or 2 out of 4 monthly samplings missing within a longer time period due to problems at sampling or inaccessibility.	
4(67)	Volume 3, CA section B.8.5.1.2.18. Reliability assessment	NL: Based on the results in Table RMS-56, RMS states that "one may conclude that individual sets of monitoring sites located in a certain FOCUS Zone are on overall not sufficiently vulnerable to allow a meaningful calculation of, e.g., a 90th, 95th, 97, or 99th spatial/percentile". NL does not fully agree that this comparison can lead to such a conclusion. The FOCUS Tier 3b-type PECgw value is simulated based on site specific data. In	Applicant (SYN): Comment 4(123) outlines a method by which the Tier-3b modelling can be incorporated into the calculation of the FOCUS concentration represented by a collection of sites within a FOCUS Zone. RMS AT: We suggest to discuss vulnerability criteria for monitoring sites or sets of (relevant) monitoring with MS's experts. Ideally, dedicated	See expert consultation proposed at comment 4(48).

		principle, in order to actually determine if a meaningful percentile for the whole area of interest can be calculated, the whole distribution of PECgw values simulated based on **site specific data** for each unique combination in the area of interest should be available. In this case, site specific information is not available for each unique combination, and spatial data sets/maps were used to calculate Tier 3b PECgw values for the area of interest. The fact that the Tier 3b-type PECgw is lower based on a limited number of sites, does not necessarily mean that these sites are not vulnerable enough. (see further explanations) Further explanations: In the opinion of NL, a more meaningful exercise would be to determine based on the Tier 3b modelling results from the applicant, the minimum number of unique combinations to be simulated in order to approximate to a certain accuracy the spatial/temporal percentile calculated based on the results of all unique combinations. For example for GeoPEARL NL, it has been established that simulation of 250 plots/unique combinations, is sufficient to estimate the 90th spatial percentile for the area of interest that would result from simulations of all 6405 unique combinations.	guidance should become available addressing this issue.	
4(68)	Volume 3, CA section B.8.5.1.2.18. Reliability assessment	NL: NL agrees with RMS that no detailed harmonized criteria to assess the reliability of monitoring sites is available. However, in section 9.5 of the FOCUS report on higher tier GW assessments (EC, 2014), six quality	Applicant (SYN): We agree that Tier-3b modelling could form the basis of a definition of vulnerability at a FOCUS Zone level. See comment 4(123) for a proposal of how this could be done.	See expert consultation proposed at comment 4(48).

		criteria are mentioned. Four of these concern the sampling and analytical analysis. The other two relate to the history of use and hydrological connectivity. For both of these last criteria, RMS proposed more detailed elaboration for these criteria, illustrated for the pinoxaden monitoring sites. In addition, RMS also considers leaching vulnerability as an important reliability criterion. NL notes that in section 9.5 of the FOCUS report, vulnerability is not mentioned as a quality criterion; although in section 9.3. it is stated that the appropriateness of a site should take into account soil vulnerability. NL agrees that when a exposure assessment endpoint expressed in terms of spatial and temporal percentiles needs to be derived, that vulnerability of the sites and the minimum number of sites needs to be a taken into account.	RMS AT: We suggest to discuss vulnerability criteria for monitoring sites or sets of (relevant) monitoring with MS's experts. Ideally, dedicated guidance should become available addressing this issue.	
4(69)	Volume 3, CA section B.8.5.1.2.18. Reliability assessment	NL: In the first sentence of this section, the word "prosed" should probably read "proposed". In the last sentence of the third paragraph, "true-word" should read "true-world".	Applicant (SYN): Noted. RMS is kindly requested to update the typo. RMS AT: Typos have been corrected in the revised DAR.	Addressed.
4(70)	Volume 3, CA section B.8.5.1.2.18. Reliability assessment	NL: Below Table RMS-56, "for the entire are in this FOCUS Zone" should read "for the entire **area** in this FOCUS Zone"	Applicant (SYN): Noted. RMS is kindly requested to update the typo. RMS AT: Typo has been corrected in the revised DAR.	Addressed.
4(71)	Volume 3, CA section B.8.5.1.2.21. RMS concluding remarks	NL: NL agrees with the urgent need to develop more detailed regulatory guidance on how to evaluate monitoring studies. NL would recommend to also include the issue of "temporal connectivity" between the documented applications and the	Applicant (SYN): More guidance is needed on evaluation of monitoring studies. In the absence of such guidance Syngenta have put forward pragmatic proposals for how these data could be interpreted at a FOCUS Zone level. In comment 4(83),	Addressed.

		results from the samples of the monitoring sites. In section 9.5 of the FOCUS report (EC, 2014) it is stated that "Data are from areas where the active substance has been used for a long period of time, the use pattern employed at least in general terms is known and documented and evidence is provided how it is still being used during the sampling period". Although it is not specified what a "long period of time" is, in practice these data are usually only available for a couple of years. In this case, it becomes also very important to be able to "estimate robust solute travel times". Therefore, NL would advocate to also include the method and criteria to determine such robust estimates of travel time, in the list of issues to be covered in more detailed Guidance.	Syngenta stated that estimates of travel time are needed at the beginning of a study before sites are identified to estimate potential times and select sites. RMS AT: Noted.	
4(72)	Volume 3, CA section B.8.5.1.3. Design of the pan-European monitoring study	NL: in the study by Patterson (2016), travel times are estimated by PEARL simulations for two scenario's. RMS already has some remarks regarding the uncertainty in the estimation. NL is of the opinion that the accuracy or uncertainty of these estimations cannot be determined based on the information in these studies. No calibration or validation was performed for these simulations. In addition, only two scenario's were used. Therefore, NL considers these estimation not to comply with the quality criterion specified in section in section 9.5 of the FOCUS report regarding "robust estimates of solute travel times".	Applicant (SYN): Reference is made to comments 4(83) and 4(112). RMS AT: Please refer to comment 4(58).	Addressed.
4(73)	General	PL agrees with RMS approach considering the necessity of developing a guidance for	Applicant (SYN): The applicant strongly agrees that the development of more targeted guidance is an important step to ease the design and	Addressed.

		groundwater monitoring study conducting and evaluation.	evaluation of GW monitoring studies, which benefits both applicants as well as evaluators. RMS AT: Noted	
4(74)	General	PL: A great work on monitoring groundwater study evaluation was presented by RMS. The analysis on many aspects influencing the phenomenon of groundwater flow in different soils, different hydrogeological and climate conditions was commented in details. The wells installation in field sites were detailed described. The concentration of pinoxaden and its metabolites were presented and statistically analysed, if relevant.	Applicant (SYN): This is acknowledged. RMS AT: PL's feedback on our evaluation work is highly appreciated.	Addressed.
4(75)	KIIA 7.12/01 and KIIA 7.12/37	PL: Pan-EU pinoxaden monitoring study. The monitoring study is very well documented, information considering relevant data for monitoring area (field site), hydro- and geological and climate condition, installed wells were presented. An information on pinoxaden application rates (field uses); active substance and its metabolites concentration analysis (frequency, sampling, storage) was provided. A wide discussion considering measurement results were presented. The monitoring study results represents the 'real case' (less conservative than modelling results) and are considered acceptable.	Applicant (SYN): The applicant agrees that within the tiered assessment of FOCUS, monitoring studies are able to reflect 'real-world' exposure best. At the same time, the concerns of RMS AT on hydraulic connectivity, leaching vulnerability and application rates and frequencies are justified and are addressed by the applicant. That said, also the practicalities of establishing a programme of this size should be considered. It is an extremely difficult task to have enough monitoring sites in all FOCUS Zones and at the same time having a compilation of the requested worst-case vulnerability properties at each site, while ensuring hydraulic connectivity and regular applications at the target rate. The applicant considers that the practicalities of such a complex task should also be discussed and taken into account when targeted guidance	Addressed.

			for regulatory groundwater monitoring is developed. RMS AT: Noted.	
4(76)	KIIA 7.12/01 and KIIA 7.12/37	PL: The assessment of endpoints. However, the proposed by the Applicant use of 90th percentile is consistent with FOCUS approach, the opinion of RMS that 90th spatial/temporal percentile concentration of annual average groundwater concentrations may indeed be considered more appropriate.	Applicant (SYN): This is acknowledged. In order to increase conservatism further, also annual maximum concentrations may be considered an appropriate endpoint metric. Overall, the applicant appreciates the effort by RMS AT to provide different endpoint metrics. This extended view gives further confidence to the conclusion that exceedances of pinoxaden metabolites above 0.1 µg/L are highly unlikely, no matter from which endpoint metric perspective the data are being interpreted. RMS AT: We suggest to discuss the most appropriate type of endpoint for such a type of monitoring study with MS's expert.	See expert consultation proposed at comment 4(48).
4(77)	3CA B-8.5.1.2.1 Introduction	RMS AT: *In view of missing dedicated regulatory guidance on how to conduct, evaluate and to assess such a monitoring study, the RMS AT's evaluation and assessment may be predominantly seen as a basis for further discussion.* SYN: The effort made by the RMS AT to evaluate this extensive and detailed study and its accompanying evaluations is highly appreciated. SYN agree that guidance is needed and, in the absence of such guidance, have followed principles for the conduct of groundwater monitoring studies such as they are available e.g. in Gimsing et al (2019) and Aden et al (2002)	RMS AT: Noted.	Addressed.

		and it is considered that the monitoring study submitted conforms to those principles. SYN agrees that more targeted guidance on how to conduct and interpret groundwater monitoring studies would help in future, but until guidance is available the FOCUS (2014) principles on PECgw determination may need to be considered a steer for 'best practice'.		
4(78)	3CA B-8.5.1.2.1 Introduction	RMS AT: *The pan-EU monitoring study conducted for pinoxaden has a very similar setup compared to the pan-EU monitoring study conducted by the same applicant for s-metolachlor (RMS DE). However, no contextualisation on the level of Member States has been provided for s-metolachlor.* SYN: Contextualisation was not performed for the pan-EU S-metolachlor study because the aim was demonstration of safe use at a European level for Annexe I renewal, rather than appropriateness of monitoring sites at a Member State level. Therefore, although the approaches used by the two studies were similar in that they used the best available tools to identify groundwater monitoring sites and place those sites in a European and FOCUS Zone context, the studies had different aims and contextualisation at a Member State level was not the objective of the Annex I renewal of S-metolachlor.	RMS AT: Noted.	Addressed.
4(79)	3CA B-8.5.1.2.1 Introduction	RMS AT: *In the final assessment of the targeted edge-of-field monitoring, the United Kingdom is still considered part of the EU. This has not been changed by the RMS AT.*	RMS AT: Noted.	Addressed.

		SYN: The UK was part of the EU at the start of the study (first samples collected 2015) and was therefore an appropriate location for groundwater monitoring sites at study initiation. Agronomic conditions (expressed as FOCUS Zone) in the UK are relevant to the EU, particularly for cereals, and would be relevant to UK and GB registrations. SYN therefore agree to the retention of the UK sites.		
4(80)	3CA B-8.5.1.2.2 Selection of candidate areas for monitoring	RMS AT: *The RMS AT acknowledges the tremendous work made by the applicant to select suitable candidate areas for monitoring. There is of course no obligation to use such a highly sophisticated approach at this initial step. Other, less sophisticated approaches, e.g., index methods on basis of soil and weather data or metamodels as outlined in the FOCUS gw report II (EC, 2014), may have been similar successful.* SYN: The use of an index approach was evaluated at the beginning of the study, and it would have been much simpler to use this methodology. However, no metamodel can reproduce the results of complex process-based models used to estimate groundwater concentrations with perfect accuracy (see Tiktak et al., 2006). In anticipation of significant debate surrounding the choice and contextualisation of groundwater monitoring sites SYN wanted to eliminate differences between a metamodel and models used to estimate groundwater concentrations for registration purposes at a European and Member	RMS AT: As already indicated in the dRAR, selection and contextualisation of monitoring sites are independent from each other and may account for entirely different approaches (with different spatial resolutions, different leaching metrics, etc.). Notice that already installed wells may be applicable as well without any sophisticated substance specific selection procedure. From a regulatory point of view, only contextualisation of monitoring sites is relevant. Therefore, an agreed approach (as simple as possible) is needed to set monitoring sites into context. Whether contextualisation is based on a FOCUS-like leaching model (e.g., GeoPEARL) or, e.g., on much simpler (substance independent) index approaches (e.g., the DRASTIC approach or similar) needs agreement first. We suggest discussing the most appropriate approach for contextualisation of monitoring sites with MS's experts. Ideally, this issue should be addressed in a dedicated guidance.	Addressed.

		State level. SYN therefore decided to use the GeoPEARL model to select and contextualise groundwater monitoring sites because this model is the same as those currently used for national and European registrations for groundwater.		
4(81)	3CA B-8.5.1.2.2 Selection of candidate areas for monitoring	RMS AT: *It may be noted that the selection of candidate areas for monitoring was solely based on M2 and M3 mass fluxes, ignoring all other metabolites of pinoxaden (M11, M52, M54, M55 and M56) at this early stage of the monitoring study setup.* SYN: The modelling to support site selection was performed in 2013 using the so-called 2012 framework. Including the whole metabolite scheme was not possible then because the run time of the GeoPEARL 333 model would have been prohibitively long. SYN therefore made the pragmatic decision to model the mass fluxes of M2 and M3 and use these as surrogates for the other metabolites on the degradation pathway. The modelling framework was updated (2014 framework) in 2015 to include new MARS data. Access to more powerful computing resource meant that the whole metabolite pathway could now be modelled, and this was done. However, first sampling from the selected groundwater monitoring sites was in 2015. The new modelling therefore came too late to influence site selection process.	RMS AT: Noted.	Addressed.
4(82)	3CA B-8.5.1.2.2 Selection of candidate areas for monitoring	RMS AT: *Due to the fact, that the same spatially distributed leaching model has been used for site identification as well as for site*	RMS AT: Noted. Please also refer to comment 4(80).	Addressed.

		contextualisation, the applicant concluded that 'for consistency reasons' assumptions made for site identification and site contextualisation have to be the same […]. The RMS AT does not see a need for consistency here as both approaches are entirely independent from each other and may be relied on entirely different methods, thus assumptions and decisions made for site selection are not necessarily appropriate for site contextualisation. SYN: SYN made every effort to identify appropriate groundwater monitoring sites in a transparent and reproducible manner that also fit within the regulatory framework for groundwater exposure in the EU. In practice this meant that a modelling approach had to be taken. Groundwater modelling at a pan-European level to identify vulnerable locations allowed sites to be placed in context of a European distribution using a model that is also used to estimate groundwater exposure at Tier 1. SYN believe that the consistency between Tier 1 modelling, pan-European modelling (Tier 3b) and site contextualisation is a valuable way to understand the vulnerability of groundwater at chosen sites. SYN acknowledge that other methods are available (see Comment #48), however there is no agreed method to contextualise sites and any method will have advantages and disadvantages.		
4(83)	3CA B-8.5.1.2.3 Selection of final	RMS AT: *The RMS AT is aware that the modelling exercise conducted by Patterson (2016) […] is, at best, a*	RMS AT: Noted.	Addressed.

	drilling sites for monitoring	*rough estimation, as, e.g., neither the real groundwater level nor additional time needed for horizontal transport to the sample well […] is accounted for […]. Nevertheless, in case of the pinoxaden metabolites it seems reasonable to consider a period of roughly 3 to 4 years of travel time from the treated field to the sampling well.* SYN: It is agreed that the approach is approximate, concluding on travel times of 2-4 years on basis of chromatographic flow only. However, it needs to be borne in mind that no data were available prior to wells being identified. This method is a means by which some idea of potential travel times had been established before sites were identified. Detailed site modelling, also accounting for horizontal transport, is not possible before the identification of sites.	Please also refer to comments 4(58) and 4(72).	
4(84)	3CA B-8.5.1.2.4 Basic soil and climate character-istics of the monitoring sites	RMS AT: *[…] the monitoring site selection procedure was particularly successful with respect to covering areas with shallow groundwater as all sites have average groundwater levels < 10 m bgl. However, the overall soil and weather characteristics of the monitoring sites do not necessarily identify these locations being extremely vulnerable for leaching (e.g., compared to soil and weather properties of the FOCUS Tier-1 standard scenarios).* SYN: The applicant made every attempt to identify vulnerable sites, and the calculation of mass flux layers implicitly considers the	RMS AT: Noted. We would like to ask MS's experts to decide on the need evaluating weather data from nearby stations for confirmatory data purposes. Otherwise this information may be addressed at AIR6.	Addressed.

		vulnerability of sites in terms of soil properties as well as long-term climatic characteristics, specifically for the fate properties of pinoxaden metabolites. However, it can be assumed that compared to the long-term weather trends at the sites, some locations were exposed to more favourable, others to less favourable conditions during the monitoring period. Weather data for stations nearby all 70 sites during the monitoring period can be provided upon request.		
4(85)	3CA B-8.5.1.2.5 Initial well installation and instrumentation	RMS AT: *On overall, the site instrumentation is well documented and appears to follow common technical practice. However, in view of variable groundwater flows being more the rule than the exception, the RMS AT recommends reconsidering the appropriateness of the standard site instrumentation setup with usually only one sampling well in combination with two monitoring wells not used for residue sampling.* SYN: The applicant has made every attempt to design the monitoring study in a sound way for obtaining reliable results for regulatory decision-making. Variable groundwater flow directions at a number of sites were not expected *a priori*, but whenever such changes were identified as a considerable factor in the course of the monitoring study, additional sampling wells were established at sites. Transducers have been installed at all wells in 2020, and based on those data, the applicant is able to respond more	RMS AT: Noted. As indicated several times, dedicated guidance on the most appropriate set-up and equipment of monitoring sites in an edge-of-field monitoring campaign is required.	Addressed.

		quickly in establishing additional sampling wells in future.		
4(86)	3CA B-8.5.1.2.6 Well maintenance, additional sampling wells and well decommission	RMS AT: *Data from [transducers installed at 17 monitoring sites from 2017] have been assessed by Andrew et al. (2020). In view of the RMS AT, uncertainties in the groundwater flow direction assessment have a strong impact on the reliability of the monitoring results obtained at these sites, particularly, if there is indication (e.g., on basis of groundwater contour plots) that sampling well(s) are temporarily or even permanently unconnected to the treated field.* SYN: The applicant has conducted an additional evaluation considering only sites that can be considered hydraulically connected (downgradient or with residues above LOQ) between applications and sampling. Please refer to Comment #21 for details.	RMS AT: Noted. We would like to ask MS's experts to decide on the need evaluating further information on hydraulic connectivity for confirmatory data purposes. Otherwise this information may be addressed at AIR6.	Addressed.
4(87)	3CA B-8.5.1.2.7 Groundwater sampling, storage and analysis	RMS AT: *In general, the RMS AT considers a quarterly sampling of monitoring sites a minimum requirement for reliable monitoring results, albeit a more frequent sampling (e.g., on bimonthly basis) is clearly preferred. Notice that missing samples (for whatever reason) in a quarterly sampling schedule lead to distinct gaps in a series of samples, which is not necessarily the case if sampling is more frequent.* SYN: As shown in Bird (2018), the Expected Peak Window of pinoxaden metabolites ranges from 7 months to 13 months. Considering the limitations of the assessment, a	RMS AT: Noted. Dedicated guidance on the sampling frequency in an edge-of-field monitoring is required.	Addressed.

		quarterly sampling was concluded to be sufficient to capture residues close to the maximum concentrations. Bi-monthly to monthly sampling was carried out for sites in Germany, but it cannot be concluded that the higher sampling frequency led to distinctly different outcomes compared to (assumed) quarterly sampling. In total, 12 quarterly samplings at seven sites (1% of quarterly samplings) were missed from Q4-2015 to Q4-2019.		
4(88)	3CA B-8.5.1.2.8 Storage stability of pinoxaden metabolites in chilled and frozen groundwater	RMS AT: *[…] it is noted that in the dedicated sample fortification experiment at site PXDIT-1603 (with a chilled storage time of 4 days […]) degradation of M55 was even faster with an estimated chilled storage DT50 of 9.2 days only […]. The RMS AT therefore suggests correcting M55 residues with a chilled storage DT50 of 9.2 days.* SYN: It is noted that chilled storage stability of M55 is variable, ranging from DT50s of 25.8 days (Cross, 2019) to 9.2 days in the single travel fortification experiment. Hence, correcting concentrations using the most protective value of 9.2 days may overestimate concentrations of M55 for sampling occasions, where actual chilled storage stability was rather in the range of the dedicated storage stability studies (18.2-25.8 d). In the German national monitoring, samples were put on dry ice immediately (< 30 min.) after samples left the well. Hence, no correction factor is required here.	RMS AT: We agree with the applicant's proposal correcting M55 residues for storage decline. In the absence of dedicated guidance the most appropriate DT50 to do so is a matter of debate. We are aware that sampling storage stability is not an issue in the German national monitoring, where samples have been put on ice immediately.	Addressed.

4(89)	3CA B-8.5.1.2.9 Pinoxaden use history at the monitoring sites	RMS AT: *On request of the RMS AT, the applicant provided a detailed pinoxaden use history (Table RMS-38). In this table monitoring sites with detects of pinoxaden metabolites > 0.1 µg/L are indicated for illustrative purposes. The RMS AT notes that there are some (minor) inconsistencies in the [additional] data provided by the applicant [compared to Langridge & Schofield, 2020]* SYN: The difference in pesticide use history (PUH) between the Excel file submitted and the information in Langridge and Schofield (2020) is that in the report only the PUH information collected by Ramboll since the beginning of the monitoring program is included. In the Excel file also the Pinoxaden use history collected during the study design phase was included, that was performed by Arcadis, and is included in White and Hamer (2016). It is concluded that the excel file is the most referrable document as it contains all the PUH since the initiation of the groundwater monitoring efforts.	RMS AT: It is also our understanding that the dedicated EXCEL file gives the most complete pinoxaden use history.	Addressed.
4(90)	3CA B-8.5.1.2.9 Pinoxaden use history at the monitoring sites	RMS AT: *Notice that the application timing assumed in the sites' leaching vulnerability and contextualisation assessment (assuming winter cereals with an application on 1st of February all over the EU) somewhat deviates from the actual application timings in the monitoring study.* SYN: The application timing on 1st of February is considered realistic for conditions in the Southern EU, and	RMS AT: We do not necessarily agree with the applicant. The vulnerability distribution (based on mass flux) is of course affected by the local application date and using the same application date all over the EU leads to (spatial) bias in the vulnerability distribution. In this sense, we consider an application timing closer to reality (e.g., a FOCUS zone specific application date in line with FOCUS default crop development dates)	Addressed.

		conservative for other European regions, as lower temperatures and lower evapotranspiration earlier in the year promote leaching. It would be impractical to perform an EU-wide vulnerability analysis for each potential application date or for widely differing application dates in different regions of the EU.	minimizing such bias. However, we agree with the applicant that in the case of the pinoxaden monitoring the overall impact on the vulnerability assessment is probably minor. The RMS AT want's to stress, that at Tier-3b the concept of *conservativism* in the exposure assessment (as may be applicable at Tier-1) is not necessarily meaningful as it may lead to spatial bias in the assessment. To our understanding, Tier-3b should always be as close as possible to real-world local conditions (for soil, weather, crop, application and substance properties) to avoid bias. In this sense, handling of Tier-3b (supporting Tier-4) may be conceptually different from Tier-1.	
4(91)	3CA B-8.5.1.2.9 Pinoxaden use history at the monitoring sites	RMS AT: *It is also noted that pinoxaden was not always applied to the entire field (i.e., 31 % of applications), in some few cases (2 % of applications) less than half of the field was treated.* SYN: In 81% of cases in the pan-EU monitoring study, more than 90% of the field area has been treated. There were in total only 7 out of 244 occasions, where half of the field or less has been treated. It should be noted that it has not been recorded whether the applications were carried out at the close or at the far end of the field from the well. Generally, the application practice as recorded is considered representative of realistic agronomic conditions in cereals growing regions.	RMS AT: Thanks for further clarification. We do not consider the issue to completely invalidate the monitoring campaign. However, applicants are advised to adequately address such issues and to provide an impact assessment without request by the authorities.	Addressed.

4(92)	3CA B-8.5.1.2.9 Pinoxaden use history at the monitoring sites	RMS AT: *The applicant did in no way reflect the actual pinoxaden application rate and frequencies in the assessment of the monitoring results. Late in the evaluation process and on request of the RMS AT, the applicant submitted a position paper (Sweeney, 2020) concluding that results of the pinoxaden monitoring study are indicative of residues arising from applications of pinoxaden made at the maximum label rate of 60 g/ha. However, as highlighted in Sweeney (2020) this conclusion may only be considered valid for approx. one third of the entire 70 monitoring sites.* SYN: The position paper by Sweeney (2020) stated that sufficient sites in the pan-European monitoring study had applications at the maximum label rate, and that there was enough time for leachate resulting from those applications to have been detected, to understand the groundwater concentrations resulting from those applications. Pinoxaden is used on an as-needed basis for the control of black grass which does not induce pest pressure on an annual basis. This study therefore reflects typical farming practice for control of black grass in the EU.	RMS AT: The issue of application rates and frequencies less than intended and how to appropriately address them in the assessment of an edge-of-field monitoring study should be discussed with MS's expert. We are aware that the actual application rates and frequencies mirror local requirements for pest control. However, actual application rates and frequencies are rarely (if at all) in line with the intended GAP, which says 60 g/ha each year. If the GAP would say, e.g., 45 g/ha each third year, the overall situation would be entirely different.	See expert consultation proposed at comment 4(48).
4(93)	3CA B-8.5.1.2.10 Hydraulic connectivity assessment	RMS AT: *The RMS AT acknowledges the applicant's extensive elucidation activities on the hydraulic connectivity at each monitoring site […] It is noted that Andrews et al. (2020) did neither give criteria on how to define a net groundwater flow direction nor does the limited study report allow to more deeply evaluate*	RMS AT: As already highlighted, there is certainly room for improvement of the sampling strategy (number of sampling wells, well location, sampling frequency, etc.) in order to further reduce uncertainties regarding hydraulic connectivity.	Addressed.

		the outcome of this work. It also noted that Langridge & Schofield (2020) and Andrews et al. (2020) do not necessarily come to the same conclusion (see Table RMS-39). SYN: The applicant acknowledges the effort by the RMS to compile Table RMS-39. Based on this assessment, every site has at least one well that has at least temporarily been connected. Overall, 95% of wells had exposure to field residues. The applicant agrees that connectivity is a key aspect for the overall reliability of a monitoring study and is going to provide additional evaluations on hydraulic connectivity in the AIR6 submission. An evaluation taking only results of wells into account that can be considered connected with high certainty is found under Comment #21.		
4(94)	3CA B-8.5.1.2.10 Hydraulic connectivity assessment	RMS AT: *On basis of slug testing, Andrews et al. (2020) also assessed the hydraulic conductivity (K) values in the saturated zone of each monitoring sites as well as the associated groundwater flow velocity. […] The applicant did not further reflect the implications of these results on the reliability of the sampling results at each monitoring site, particularly with respect to sites having either extremely low or extremely high groundwater flow velocities.* SYN: The selection of monitoring sites did not consider hydraulic conductivity *a priori*. With this, it can be assumed that the conductivities reported show the variability of	RMS AT: Thanks for further clarification.	Addressed.

		hydraulic conductivity under realistic environmental conditions, as it would also be found in settings between treated fields and wells for (drinking) water extraction. The study shows that the majority of sites has velocity modes between 1-100 m/year, which should be sufficient in most cases to cover the distance between the field edge and the sampling well within a monitoring period of 4 years.		
4(95)	3CA B-8.5.1.2.10 Hydraulic connectivity assessment	RMS AT: *On overall, there is no evidence that highly isolated findings of M11 and M52 above 0.1 µg/L [at the sites PXDIT-1208, PXDIT-1263 and PXDFR-647, for which elucidations were carried out] are a result of processes or activities other than good agricultural practice. Consequently, results from these three monitoring sites are considered fully reliable.* SYN: This is acknowledged. However, the finding of M11 above 0.1 should relate to endpoint of 10 µg/L as being considered a non-relevant metabolite. Moreover, it is noted that the single detect of M52 at a concentration of 0.162 µg/L at site PXDIT-1208 was likely caused by an intense rainfall event shortly after application causing the groundwater table to rise, catching residues close to the surface into the saturated zone.	RMS AT: Noted. As long as the relevance assessment is not finalized, we consider 0.1 µg/L the appropriate threshold concentration.	Addressed.
4(96)	3CA B-8.5.1.2.10 Hydraulic connectivity assessment	RMS AT: *In view of the RMS AT, the bromide tracer experiments (limited to [PXDFR-1443, PXDIT-1215, PXDIT-1283, PXDUK-545 and PXDUK-580] only) are a further indication of the overall complexness and uncertainties in groundwater flow elucidations, giving evidence that nominated*	RMS AT: Noted.	Addressed.

		sampling wells at these 5 monitoring sites may partly be inadequately located, even if connectivity is indicated on basis of groundwater contour maps. SYN: The applicant agrees that connectivity is a key aspect for the overall reliability of a monitoring study and is going to provide additional evaluations on hydraulic connectivity based on transducer data at all 70 sampling locations in the AIR6 submission.		
4(97)	3CA B-8.5.1.2.10 Hydraulic connectivity assessment	RMS AT: *The extensive hydraulic connectivity assessment provided by the applicant did not trigger any further considerations regarding the reliability of the monitoring results obtained from sampling wells which appear to be permanently or temporarily unconnected to the treated field. Instead, in the applicant's assessment of the monitoring study each individual monitoring result from each individual sampling well, irrespective of its hydraulic connectivity status, is accounted for and has equal weight […]* SYN: Based on the Excel sheet provided to the RMS, indicating periods during which wells were connected to treated fields, a refined analysis of monitoring results is provided, with wells excluded that were clearly upgradient during the period of the sampling and wells excluded that had an unknown flow direction, but without any detection above LOQ:	RMS AT: The additional information announced by the applicant is acknowledged. We would like to ask MS's experts to decide on the need evaluating additional assessments of the monitoring data including only wells considered clearly down-gradient for confirmatory data purposes. Otherwise this information should be provided and evaluated at AIR6. We want to stress that "proven" connectivity at the time of sampling (e.g., by means of triangulation performed at sampling) does not necessarily mean that groundwater sampled at that time is actually representing the treated soil area. There are several months or even years of travel time from the soil surface to the well and changes in groundwater flow direction may occur all the time. So, even if the well is down-gradient at sampling, the groundwater samples at that time may have its origin outside of the treated area. Vice versa, a	Addressed.

Original refined data set:

	PXD	M2	M3	M11	M52	M54	M55		M56
							un-corrected	chilled storage DT50 = 9.2 d	
Number of residues ≤ LOQ	785	781	705	774	750	780	777	766	713
% Residues ≤ LOQ	100.00	99.49	89.81	98.72	95.66	99.49	99.11	97.70	90.83
Number of residues between LOQ and 0.1 µg/L	0	4	63	9	32	4	7	17	72
% residues between LOQ and 0.1 µg/L	0.00	0.51	8.03	1.15	4.08	0.51	0.89	2.17	9.17
Number of residues ≥ 0.1 µg/L	0	0	17	1	2	0	0	1	0
% residues ≥ 0.1 µg/L	0.00	0.00	2.17	0.13	0.26	0.00	0.00	0.13	0.00
Highest residues (µg/L)	0.008	0.064	0.361	0.108	0.162	0.051	0.068	0.107	0.095

There are 785 samples but one sample was reanalysed (1561 Oct 2015-well 1) for PXD, M2, M3 and M56, as both results were reported both have been considered, so for those analytes the total number of samples is 784

Rate-normalized refined dataset:

	PXD	M2	M3	M11	M52	M54	M55		M56
							un-corrected	chilled storage DT50 = 9.2 d	
Number of residues ≤ LOQ	784	777	686	763	750	773	770	770	691
% Residues ≤ LOQ	99.87	98.98	87.39	97.32	95.66	98.60	98.21	98.21	88.03
Number of residues between LOQ and 0.1 µg/L	1	6	76	19	30	10	14	14	89
% residues between LOQ and 0.1 µg/L	0.13	0.76	9.68	2.42	3.83	1.28	1.79	1.79	11.34
Number of residues ≥ 0.1 µg/L	0	2	23	2	4	1	0	0	5
% residues ≥ 0.1 µg/L	0.00	0.25	2.93	0.26	0.51	0.13	0.00	0.00	0.64
Highest residues (µg/L)	0.030	0.127	0.469	0.155	0.258	0.152	0.078	0.078	0.123

There are 785 samples but one sample was reanalised (1561 Oct 2015-well 1) for PXD, M2, M3 and M56, as both results were reported both have been considered in the STATS so for those analytes the total number of samples is 784.

Original refined data set:

FOCUS zone	Maximum annual average concentration per FOCUS zone (µg/L)						
	M2	M3	M11	M52	M54	M55	M56
Chateaudun	0.0075	0.0075	0.0117	0.0267	0.0075	0.0081	0.0075
Hamburg	0.0075	0.0121	0.0079	0.0083	0.0075	0.0090	0.0116
Kremsmunster	0.0075	0.0836	0.0098	0.0075	0.0075	0.0101	0.0449
Piacenza	0.0075	0.0075	0.0196	0.0254	0.0075	0.0075	0.0075
Porto	0.0075	0.0200	0.0221	0.0350	0.0075	0.0118	0.0075
Sevilla	0.0075	0.0075	0.0075	0.0075	0.0075	0.0075	0.0075
Thiva	0.0098	0.0129	0.0142	0.0292	0.0083	0.0075	0.0075

Rate-normalized refined dataset:

FOCUS zone	Maximum annual rate normalized average concentration per FOCUS zone (µg/L)						
	M2	M3	M11	M52	M54	M55	M56
Chateaudun	0.0088	0.0088	0.0160	0.0376	0.0088	0.0107	0.0088
Hamburg	0.0115	0.0156	0.0120	0.0120	0.0122	0.0132	0.0151
Kremsmunster	0.0101	0.1090	0.0140	0.0101	0.0101	0.0132	0.0584
Piacenza	0.0075	0.0075	0.0202	0.0306	0.0075	0.0075	0.0075
Porto	0.0079	0.0400	0.0425	0.0683	0.0101	0.0219	0.0079
Sevilla	0.0150	0.0150	0.0150	0.0150	0.0150	0.0150	0.0150
Thiva	0.0162	0.0225	0.0194	0.0293	0.0109	0.0099	0.0099

It should be considered that the metabolites M3, M11, M54 and M56 are considered non-relevant, and hence the trigger of 10 µg/L applies. The results show that even the dataset excluding situations with upgradient wells does not change the groundwater sample may perfectly represent the treated area even if the well is not down-gradient at sampling. Therefore, we do not support omitting individual samples or sampling periods in a series of samples taken at one well simply considering (assumed) connectivity at sampling. Instead, we would prefer omitting wells completely from further assessments if adequate connectivity cannot be proven, e.g., for a certain percentage of sampling dates.

		overall picture that exceedances above 0.1 µg/L are sporadic, and hence do not indicate an undue risk for the metabolites of pinoxaden in groundwater. A detailed Excel sheet containing the full evaluation can be provided upon request. Additional evaluations on hydraulic connectivity are provided in the AIR6 submission.		
4(98)	3CA B-8.5.1.2.10 Hydraulic connectivity assessment	RMS AT: *The RMS AT is of the opinion that the reliability of each monitoring site with respect to horizontal hydraulic connectivity could probably have been significantly improved by always sampling all wells around the field. […] The hydraulic connectivity could also have been improved by, e.g., locating sampling wells between two equally treated fields, or locating sampling well alongside the field boarder instead of the very edge of the field.* SYN: This is acknowledged and will be considered for an eventual continuation of the monitoring study. For the available dataset, an evaluation taking only monitoring results of wells into account that can be considered connected with high certainty is found under the previous comment (Comment #21). Transducers have been installed at all wells in 2020, and additional evaluations on hydraulic connectivity are provided in the AIR6 submission.	RMS AT: Noted.	Addressed.
4(99)	3CA B-8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	RMS AT: *The substance properties […] are not necessarily the final ones proposed by the RMS AT. In this respect, the applicant's leaching vulnerability assessment is considered a preliminary one and, in principle, should be updated*	RMS AT: We agree that an updated set of modelling input data may no substantially change the outcome of the vulnerability and contextualisation assessment in the case of the pinoxaden metabolites. However, we want to make aware that, depending,	Addressed.

		(repeated) once the substance properties have been agreed. SYN: SYN do not believe that proposed changes in endpoints will make a substantial difference to the modelled vulnerability of the groundwater monitoring sites, with the possible exception of M55 due to the shorter proposed DT50. SYN can produce an updated leaching vulnerability assessment with new EU agreed endpoints if this is thought necessary by the RMS.	on the changes in modelling properties, the impact may be significant in other circumstances. From this point of view, we consider a less sophisticated, substance-independent approach (which does not require re-calculation) for vulnerability and contextualisation purposes superior.	
4(100)	3CA B-8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	RMS AT: *The application date assumed in this [leaching vulnerability] modelling exercise, i.e., the 1st of February on winter cereals, is not necessarily in agreement with actual application dates in the targeted pinoxaden edge-of-field monitoring study (with the majority of applications made in March and April).* SYN: Refer to Comment #14	RMS AT: Please refer to comment 4(90).	Addressed.
4(101)	3CA B-8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	RMS AT: *The RMS AT has no objections on a substance mass flux as a leaching indicator vs., e.g., a substance concentration. […] However, the RMS AT does not necessarily agree with a median annual mass flux (out of 20 assessment years) as this implies that years with more extreme weather conditions are ignored in the leaching assessment.* SYN: The median annual mass flux was used as a vulnerability indicator because the intention of the field selection process was to identify fields that were more vulnerable	RMS AT: As highlighted several times we are of the opinion that a vulnerability metrics for site selection and site contextualisation can be entirely different. In case of site selection it is perfectly understandable to use a median mass flux as a robust metric to identify a site where leaching around this metric mass flow can be expected. However, site contextualisation is different from that. The site's vulnerability is also defined by climate variability as there are of course years having significantly higher rainfall as median years. Using a median mass flow broadly ignores	See expert consultation proposed at comment 4(48).

		typically to groundwater leaching, rather than only when extreme events happened. High percentile events cannot be guaranteed during a monitoring study and could not be enforced over such an extensive study. SYN believe that the use of the median is justified given the practicalities of conducting large-scale groundwater monitoring studies.	location specific weather variability. In other words: Focussing on the median annual mass flux only, a site with a median mass flux of X g/year without any variability in annual rainfall is considered equally vulnerable when compared to a site with the same median mass flux of X g/year albeit having a huge variability in annual rainfalls. We do not consider this correct. We suggest to discuss the most appropriate vulnerability metric for site contextualisation with MS's experts.	
4(102)	3CA B-8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	RMS AT: *The originally targeted leaching vulnerability (i.e., > 50th spatial percentile mass flux within the entire EU, see site selection procedure) for M2 and, particularly, for M3 has finally not been met in several cases. […] On basis of the leaching vulnerability assessment provided by the applicant, one may conclude that these 70 monitoring sites do not necessarily represent a realistic-worst case for groundwater monitoring as stated by the applicant.* SYN: The practicality of installing 70 groundwater monitoring locations across Europe means that it is not possible to ensure that all selected locations meet precise vulnerability criteria. Sites were selected based upon the vulnerability of 10km grid squares to leaching of M2 and M3. This size was chosen because it allowed for a reasonable pool of candidate farmers from which to select edge-of-field monitoring locations. It is known that only a	RMS AT: Please refer to comment 4(52).	See expert consultation proposed at comment 4(48).

		small percentage of growers are willing to participate in such an exercise which means that a large pool of candidates is needed. Even if SYN had conducted the selection at a finer resolution, differences between field soil and soil types appearing in a GIS data layer mean that a specific vulnerability cannot be guaranteed. The 50th centile groundwater leaching may not have been reached if it is assumed that all groundwater is at 1m depth. However, not all European groundwater is so shallow. SYN went to every effort to identify vulnerable sites with shallow groundwater and monitor them edge-of-field. SYN believes that this exercise has resulted in a set of monitoring locations that reflect worst-case exposure in the reality of vulnerable European groundwater beneath cereal growing regions. This can be seen in Comment #48 where 80% of the selected sites would be classified as having very high or high intrinsic groundwater vulnerability according to the DRASTIC map produced by JRC. In addition, SYN make a proposal to address any shortfall of modelled site vulnerability in Comment #47.		
4(103)	3CA B-8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	RMS AT: *Member States with a low number of protective monitoring sites (e.g., Ireland) may also have high numbers of relevant monitoring sites with a low leaching vulnerability similar to some FOCUS Zones. E.g., in Ireland 18 – 44 % of the monitoring sites considered relevant for this Member State have mass fluxes below the 50th spatial*	RMS AT: Thanks for further clarification. The applicant's approach to select "relevant" sites for individual MS is acknowledged and may serve as basis for further discussion.	Addressed.

		percentile mass flux calculated for Ireland (with the exception of M2). SYN: In the view of SYN, all of the monitoring locations are vulnerable, because they are placed in locations having shallow groundwater. The "relevant" classification for Member States was based on groundwater monitoring sites having climate conditions (temperature and rainfall based on MARS data) that are found in a Member State and was not based upon a specific leaching vulnerability criterion. In contrast, "protective" sites had climate conditions outside those found in a Member State but were placed in a FOCUS Zone found in the Member State and had a modelled median mass flux greater than the 90th percentile of the Member State distribution. SYN believe that the combination of Relevant and Protective sites provides a simple and understandable basis for discussion of the appropriateness of groundwater monitoring sites.		
4(104)	3CA B-8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	RMS AT: *The applicant did in no way reflect the monitoring sites leaching vulnerability assessment in the final assessment of the monitoring results (except of selecting protective sites […]). In view of the RMS AT, the site's leaching vulnerability is one additional aspect in the overall reliability of a monitoring site or of a set of, e.g., relevant monitoring sites for a Member State, beside hydraulic connectivity issues and actual application rates and frequencies.* SYN: SYN consider that every site has vulnerable groundwater in a	RMS AT: Thanks for further clarification. We consider any further information to assist the site's vulnerability assessment (apart of FOCUS-like modelling) helpful. In this sense, we are wondering whether less sophisticated, more pragmatic and substance independent approaches, e.g., the DRASTIC approach, may be equally effective if not superior. In short, the DRASTIC index is quantified by a linear combination of ratings and weights of the seven parameters: depth to groundwater (D), net recharge (R), aquifer media	Addressed.

		European context even if the target vulnerability may not have been reached considering chromatographic flow to 1m depth (several sites have percentiles above the 90th percentile for this quantity). Modelled vulnerability was only used to select "Protective Sites" for consideration at a Member State level and in this case a modelled vulnerability above the 90th percentile was needed to be considered "protective". Comment #48 shows how groundwater monitoring sites would be classified according to the DRASTIC methodology implemented by JRC. This showed that 80% of sites would be classified as having highly or very highly vulnerable intrinsic groundwater vulnerability (no sites were classified as having low vulnerability). It is not known what measure of vulnerability and which percentile can be used to include or exclude groundwater monitoring locations or how to apply correction factors to measured concentrations to ensure a specific vulnerability, although Comment #47 lays out a proposal. SYN would support a proposal from the RMS to assist the development of more targeted guidance.	(A), soil media (S), topography (T), impact of vadose zone (I) and hydraulic conductivity (C). The DRASTIC index is then given by Dr×Dw + Rr×Rw + Ar×Aw + Sr×Sw + Tr×Tw + Ir×Iw + Cr×Cw, where D, R, A, S, T, I and C are the acronyms of the seven parameters of the DRASTIC methodology and the subscripts w and r are the corresponding weights and ratings, respectively. Notice, that there are different versions of the DRASTIC approach (with different weightings) out there. We would like to ask MS's expert to decide on the need to evaluate the site's vulnerability according to the DRASTIC approach for confirmatory data purposes. Otherwise this issue can be addressed at AIR6.	
4(105)	3CA B-8.5.1.2.11 Assessing the monitoring sites' leaching vulnerability	RMS AT: *Probably a more intuitive (albeit less targeted) approach to check a monitoring site's leaching vulnerability is to simply compare it with the leaching vulnerability of the FOCUS Tier-1 standard scenario in the same FOCUS Zone.*	RMS AT: We agree that the approach suggested by us is less targeted then, e.g., a dedicated Tier-3b calculation. Nevertheless, we consider this (more) simple and (more) easily reproducible approach a pragmatic solution for regulatory daily use purposes. Also refer to comment 4(61).	Addressed.

		SYN: SYN do not agree that the approach mentioned by the RMS is necessarily correct. A FOCUS scenario is a single location regarded as vulnerable to leaching of groundwater for a wide variety of substances having different properties. The method followed by SYN establishes the complete distribution across the EU and thereby for each FOCUS Zone relevant for each compound and, although consistent with the Tier 1 modelling, provides a more accurate assessment of the modelled groundwater vulnerability with respect to chromatographic flow to 1m. It would therefore be more appropriate to compare Tier 3b concentrations with modelled site concentrations to estimate site vulnerability (see Comment #47)		
4(106)	3CA B-8.5.1.2.12 Contextualisation of monitoring sites	RMS AT: *It is noted that the applicant did not provide an assessment of the monitoring results on the level of Regulatory Zones.* SYN: SYN did not do this here because the focus of the assessment was the EU and Member State level.	RMS AT: Noted.	Addressed.
4(107)	3CA B-8.5.1.2.12 Contextualisation of monitoring sites	RMS AT: *In view of the RMS AT, the approach proposed by the applicant to define (climatically) appropriate monitoring sites on basis of FOCUS Zones and annual average temperature and precipitation, appears overly simplistic as it does not account for seasonal rainfall (which may drive leaching) and is, apparently, not restricted to the area of the target crop (cereals in this case) in the Member State. On overall, the RMS AT would have preferred a more targeted*	RMS AT: Please refer to comment 4(43).	Addressed.

		comparative assessment on basis of, e.g., long-term monthly average weather data (temperature and precipitation), restricted to the target crop area in the Member State. SYN: SYN used the FOCUS zones to determine whether a monitoring location was appropriate for a Member State. Many Member States also use this approach. In principle it would be possible to use the extent of cereals in a Member State and the MARS data to determine the ranges, by SYN believe that this would not make a substantive difference. Nevertheless, these data could be presented if the RMS requests them.		
4(108)	3CA B-8.5.1.2.12 Contextualisation of monitoring sites	RMS AT: *The applicant's definition of a protective monitoring site (exceeding the 90th percentile mass flux in this Member State) appears arbitrary and is probably related to the fact, that the applicant considers a spatial/temporal 90th percentile sample concentration, calculated from a set of relevant monitoring sites, an appropriate assessment endpoint also at the level of Member States. To the knowledge of the RMS AT there is no harmonized assessment goal available for monitoring studies, particularly at the level of Member States. […] In this respect, the criterion of a > 90th percentile mass flux for a protective monitoring may not be valid for other assessment endpoints.* SYN: In the absence of a harmonized protection goal SYN followed an approach that was simple and transparent. Whether this is an	RMS AT: Noted.	Addressed.

		acceptable approach or not would be a decision for individual Member States.		
4(109)	3CA B-8.5.1.2.12 Contextualisation of monitoring sites	RMS AT: *In view of the RMS AT, there is urgent need to develop an EU agreed and harmonized contextualisation approach as soon as possible. In the meanwhile, the RMS AT takes the applicant's listing of relevant monitoring sites for each Member State as given, and the RMS AT's assessments of the monitoring results is therefore also based on the applicant's lists of relevant monitoring sites.* SYN: SYN agree that there is a need to develop guidance. In the absence of such guidance SYN followed what they considered to be a reasonable and transparent means of contextualising monitoring sites that is consistent with Tier 1 modelling principles.	RMS AT: We agree that the applicant's approach for site contextualisation may serve as a basis for further discussion.	Addressed.
4(110)	3CA B-8.5.1.2.13 Accounting for actual application rates and application frequencies	RMS AT: *Actual application rates at the 70 monitoring sites are quite diverse […]. In view of the RMS AT this adds distinct uncertainties in the overall assessment of a monitoring study, particularly, whether assessment endpoints obtained from the monitoring results actually cover the intended use rate of 60 g/ha or not. […] the applicant did not reflect the actual pinoxaden application rates and frequencies in the final assessment of the monitoring results. […], the applicant considers the monitoring results indicative for the label use rate of 60 g/ha (see Sweeney, 2020).*	RMS AT: Please refer to comment (92).	Addressed.

		SYN: The position paper by Sweeney (2020) stated that sufficient sites in the pan-European monitoring study had applications at the maximum label rate, and that there was enough time for leachate resulting from those applications to have been detected, to understand the groundwater concentrations resulting from those applications. Pinoxaden is used on an as-needed basis for the control of black grass which does not induce pest pressure on an annual basis. This study therefore reflects typical farming practice for control of black grass in the EU. The results of this monitoring study are consistent with those from the German National federal well monitoring study where applications were made at the full national label rate of 58.5 g/ha to nearly all cereal fields in the vicinity of monitoring locations (Liss & Naeb 2020; for details: Comment #59)		
4(111)	3CA B-8.5.1.2.13 Accounting for actual application rates and application frequencies	RMS AT: *The RMS AT proposes a pragmatic and simple data processing approach, i.e., scaling the monitoring results with a monitoring site specific rate-normalization factor in order to bring them, on average, more in line with the intended use rate of 60 g/ha. This proposal is based on the simple consideration that, if a farmer would have had used pinoxaden at a certain monitoring site at a rate of, e.g., 1.3 times higher than actually used, all monitoring results would also have been 1.3 times higher than actually measured (ignoring non-linear sorption processes).* SYN: SYN agrees that the approach outlined by the RMS is a useful way	RMS AT: Noted.	Addressed.

<table>
<tr>
<td></td>
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<td>of scaling applications to the full label rate. This approach may scale applications made at the full rate upwards (depending on the number and level of applications) which may be overly conservative.</td>
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<tr>
<td>4(112)</td>
<td>3CA B-8.5.1.2.13 Accounting for actual application rates and application frequencies</td>
<td>RMS AT: According to Patterson (2016) and Bird (2019) […] one may conclude that the average travel time to groundwater is approx. 1 to 2 years. In this respect, the application period from 2014 – 2017 may be considered most relevant […]. Adding one additional year at the start/end of this period, to account for uncertainties […] gives an application period from 2013 – 2018, which may finally be considered most relevant. In the […] RMS AT's assessment, rate-normalization has been consistently based on arithmetic mean appl. rates from 2013 – 2018.

SYN: An approach, which bases correction factors only on previous applications (within the last 2-4 years) is considered more realistic. However, in the case of the Pan-European monitoring study, differences from using such an approach are minor:

<table>
<tr><td colspan="8">rate-normalization factor based on average of app. rates:</td></tr>
<tr><td colspan="8">2013-2018 (RMS AT)</td></tr>
<tr><td></td><td>M2</td><td>M3</td><td>M11</td><td>M52</td><td>M54</td><td>M55</td><td>M56</td></tr>
<tr><td>Number of rate-norma-lized residues > 0.1 µg/L</td><td>2</td><td>23</td><td>2</td><td>5</td><td>1</td><td>0</td><td>6</td></tr>
</table>
</td>
<td>RMS AT: We agree that selection of a (site specific) application period considered most relevant for the monitoring period is not straightforward and a matter for debate. However, as indicated by the applicant, the impact is considered minor in the case of the pinoxaden edge-of-field monitoring.

On overall, we suggest discussing the scaling approach of monitoring results (including the selection of the most appropriate application period) with MS's experts.</td>
<td>See expert consultation proposed at comment 4(48).</td>
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</table>

		Highest rate-norma-lized residues (µg/L) 0.127 0.469 0.155 0.258 0.152 0.078 0.123 **three preceding years (or more, if no applications in three preceding years)** M2 M3 M11 M52 M54 M55 M56 Number of rate-norma-lized residues > 0.1 µg/L 2 22 2 7 1 0 6 Highest rate-norma-lized residues (µg/L) 0.128 0.456 0.154 0.258 0.153 0.082 0.120 **between beginning of PUH (2013) and detect** M2 M3 M11 M52 M54 M55 M56 Number of rate-norma-lized residues > 0.1 µg/L 2 22 2 6 1 0 6 Highest rate-normalized residues (µg/L) 0.128 0.464 0.154 0.258 0.153 0.082 0.120		
4(113)	3CA B-8.5.1.2.13 Accounting for actual application rates and application frequencies	RMS AT: *The RMS AT is aware that this simple and pragmatic approach is clearly 'off-guidance'. Nevertheless, the RMS AT considers this approach sufficiently robust for regulatory decision making (at least in the case of a highly targeted edge-of-field monitoring study with sampling wells closely connected to treated fields with a well-documented use history). For demonstrative purposes and to allow further discussion amongst Member State's experts, the RMS AT's assessed the pinoxaden monitoring results also on basis of rate-normalized monitoring results.*	RMS AT: Noted.	Addressed.

		SYN: The applicant welcomes the effort to present endpoint metrics using rate-normalized concentrations in addition to those derived from measured concentration values. Overall, it can be concluded that even using rate-normalized concentrations, no unacceptable risk to groundwater of pinoxaden metabolites is expected.		
4(114)	3CA B-8.5.1.2.14 Minimum number of (relevant) monitoring sites required	RMS AT: *The applicant presented monitoring assessment endpoints for each set of relevant monitoring sites irrespective of the number of monitoring sites included in these assessments. Notice that in the case of the FOCUS Zones Châteaudun, Kremsmünster, Porto and Sevilla only 1 to 3 monitoring sites are accounted for. Low numbers of relevant monitoring sites (n ≤ 7) are also given for the FOCUS Zone Piacenza and some Member States, depending on the metabolite assessed […]* SYN: No guidance is available on the number of groundwater monitoring sites needed and how to interpret the data to demonstrate safe uses at a FOCUS Zone level. SYN presented data as a 90th percentile to have a consistent way of comparing and summarising concentrations. Sweeney (2020) has proposed a way in which monitoring data can be treated like FOCUS modelling data to establish a FOCUS equivalent concentration (FEC). This approach groups measurements into "FOCUS years" (maximum measurement in a year represents monitoring in that year) and places a minimum of 20	RMS AT: The number of sites needed for an assessment should be discussed with MS's experts. We are aware that there are many different approaches on how to assess such a kind of monitoring study. Notice that we do not necessarily support the so-called "FOCUS equivalent concentration (FEC)" approach introduced by the applicant, as long as the number of sites and the number of years in this approach have the same weight (e.g., 2 sites with 10 years have the same weight as 10 sites with 2 years). In our understanding, the site's vulnerability is to a larger extend driven by "hard" facts at the monitoring site (soil properties, vadose zone, depth to groundwater, impermeable layers, etc.) and to a lesser extend driven by the site's weather conditions. In this respect, we would prefer giving more weight to the number of sites and less weight to the number of monitoring years. A pragmatic solution would be, e.g., that the number of sites in the FEC approach has to be larger than the number of years. Thus, for 20 FEC years (which may be conceptual similar to a FOCUS Tier-1	Addressed.

years on the amount of data needed to demonstrate a pass at a FOCUS Zone level. Using this approach and using the maximum concentration across all wells to represent a measurement, the following Table is obtained for pinoxaden and its metabolites.

Zone	PNX	M2	M3	M11	M52	M54	M55	M56	FOCUS years
C	-	-	-	-	-	-	-	-	10
H	0.0075	0.0105	0.026883	0.012514	0.0075	0.0075	0.0125	0.028135	165
K	-	-	-	-	-	-	-	-	15
Pi	0.0075	0.0075	0.0125	0.0075	0.020165	0.0075	0.0075	0.0075	35
Po	-	-	-	-	-	-	-	-	15
S	-	-	-	-	-	-	-	-	5
T	0.0075	0.0075	0.0125	0.011053	0.043855	0.0075	0.0075	0.0075	105

This Table shows that there are enough data to calculate a FOCUS Equivalent Concentration (FEC) for Zones Hamburg, Piacenza and Thiva and the FEC for all these zones are well below the parametric limit of 0.1 µg/L. Zones Porto and Kremsmunster would require two more years of data and Chateaudun and Sevilla would require more time – effectively never for Sevilla as only one site is present.

Application of this methodology to the concentration record scaled to the maximum application rate and applying a 9.2d storage stability half-life for metabolite M55 gives the following Table (concentrations all in µg/L).

FOCUS Zone	PNX	M2	M3	M11	M52	M54	M55	M56
C	-	-	-	-	-	-	-	-
H	0.01125	0.01539	0.033627	0.024	0.015	0.015135	0.020392	0.037563
K	-	-	-	-	-	-	-	-
Pi	0.0089	0.0089	0.01257	0.0098	0.02031	0.01043	0.0098	0.01283
Po	-	-	-	-	-	-	-	-
S	-	-	-	-	-	-	-	-
T	0.00879	0.00959	0.015575	0.01617	0.041256	0.015	0.011765	0.01153

assessment) a minimum of 5 sites (with 4 years each) would be needed. We agree to use the annual maximum concentration for this approach for conservative reasons.

In the case of EFSA'S PEA approach, is appears sensitive to specify a minimum number of sites needed.

We would like to ask the MS's expert to decide on the need to assess the monitoring data on basis of alternative approaches (e.g., FEC or PEA) for confirmatory data purposes. Otherwise such assessments could be provided for AIR6.

Even with these worst-case assumptions the FECs for FOCUS zones Hamburg, Piacenza and Thiva are far below 0.1 µg/L. Details of this methodology can be provided if requested by the RMS.

EFSA (2011) proposed an approach based upon the number of exceedances observed in a study. This "percent exceedance approach" (PEA) required that less than 5% of measurements could be above the relevant parametric limit. Using the raw data from the study (maximum concentration across all wells) gives the following Table (values all in %).

FOCUS Zone	PNX	M2	M3	M11	M52	M54	M55	M56
chateaudun	0	0	0	0	0	0	0	0
hamburg	0	0	0	0	0	0	0	0
kremsmunster	0	0	0	0	0	0	0	0
piacenza	0	0	0	0	0	0	0	0
porto	0	0	0	0	1.8	0	0	0
sevilla	0	0	0	0	0.0	0	0	0
thiva	0	0	0	0	0.3	0	0	0

The only FOCUS zones where exceedances were observed were in Porto and Thiva for metabolite M52 and the level of exceedance of the relevant regulatory trigger is low. Scaling concentrations to the maximum label rate and using worst-case assumptions for the storage stability of M55 gives the following Table (all values in %).

	PNX	M2	M3	M11	M52	M54	M55	M56
chateaudun	0	0	0	0	0	0	0	0
hamburg	0	0	0	0	0	0	0.1	0
kremsmunster	0	0	0	0	0	0	0	0
piacenza	0	0	0	0	0	0	0	0
porto	0	0	0	0	1.8	0	1.8	0
sevilla	0	0	0	0	0	0	0	0
thiva	0	0.53	0	0	1.1	0	0	0

This Table shows that the level of exceedances of the relevant regulatory groundwater trigger

		remains very low even using worst-case assumptions. Although there is no guidance how to calculate a regulatory endpoint the level of exceedance for pinoxaden and its metabolites is extremely low and beneath any reasonable level of concern. Reference: Sweeney 2020 Proceedings of the 22nd Fresenius AGRO conference		
4(115)	3CA B-8.5.1.2.13 Accounting for actual application rates and application frequencies	RMS AT: *The RMS AT is not in the position to conclude on a definitive minimum number of (relevant) monitoring sites to be included in an assessment of a monitoring study for regulatory decision making. However, on basis of the targeted pinoxaden edge-of-field monitoring study, considering uncertainties in hydraulic connectivity, leaching vulnerability, contextualisation, extreme sites, etc., the RMS AT considers at least 10 (preferably more) monitoring sites as a minimum requirement to derive sufficiently robust endpoints for regulatory decision making at each assessment levels. Assessments for large FOCUS Zones or large Member States may even require more sites. In this sense, assessment endpoints derived for the FOCUS Zones Châteaudun, Kremsmünster, Piacenza, Porto and Sevilla, for the Regulatory Zone North as well as for some metabolites in Denmark, Estonia, Latvia and Sweden, are considered less reliable and are therefore not recommended by the RMS AT for regulatory decision making.*	RMS AT: Please refer to comment 4(114).	Addressed.

		SYN: SYN agree that guidance is needed on this matter and propose that the FOCUS Equivalent Concentration (FEC) and Percent Exceedance Approach (PEA) are starting points for consideration on the number or sites needed and amount of data required to demonstrate safe uses at a European level (see Comment #38).		
4(116)	3CA B-8.5.1.2.15 Percentile calculation approach	RMS AT: *[…], the applicant's approach to calculate a given percentile sample concentration is not supported by the RMS AT. From a pure statistical point of view, a percentile calculation should always be based on a bias-free and consistent dataset, e.g., on individual annual maximum or individual annual average concentrations obtained from a set of (relevant) monitoring sites for a consistent period (e.g., 2016 – 2019 in the case of the pinoxaden monitoring study).* SYN: SYN agrees that an unbiased percentile calculation would be beneficial. For this reason, the use of maximum value of annual averages in each site is agreed as an adequate metric. Sampling rounds not uniformly performed in all sites can be then removed from the analysis by using again only the maximum value. This will represent a conservative approach, which also guarantees the uniformity of the dataset used in the analysis because all sites will have the same amount of data.	RMS AT: Noted. Notice that we do not necessarily agree with the *maximum of the annual average concentrations* at each site as the most appropriate metric for percentile calculations. MS's experts have to agree on the metric as well as on the percentile approach first.	Addressed.
4(117)	3CA B-8.5.1.2.15 Percentile calculation approach	RMS AT: *In order to calculate a certain percentile sample concentration, the applicant used the EXCEL function percentile.inc() […].*	RMS AT: Noted. Further guidance on the most appropriate percentile calculation method is needed.	Addressed.

		[…] It may be noted that a given set of monitoring sites (with associated fields) may be considered a subset of all potential monitoring sites in an assessment area. In this sense, a percentile calculation on basis of, e.g., the Weibull plotting position (percentile.exc()) may indeed be more adequate. In view of missing guidance the RMS AT follows the applicant's approach using percentile.inc() […]. SYN: EXCEL function *percentile.inc()* was used as a pragmatic choice for the analysis. The applicant acknowledges that the method used for percentile calculation impacts the outcome, especially for small populations of samples. For this reason, Hazen percentile method is proposed going forward. This is in line with recommendations in FOCUS (2014).	Also refer to comment 4(64).	
4(118)	3CA B-8.5.1.2.16 Monitoring assessment endpoints	RMS AT: *The limited protectiveness of a 90th spatial/temporal percentile concentration in real-world groundwater may still be acceptable to demonstrate 'significant safe use areas' in the EU or in a FOCUS Zone. However, Member States may not necessarily accept such a limited protectiveness for real-world groundwater in their territories, depending on their groundwater protection goal.* SYN: The relevance assessment for GW metabolites is laid down in Commission Regulation 284/2013, and hence can be considered applicable mainly for product approvals, as well as representative	RMS AT: Noted.	Addressed.

		uses in active substance approval. For the latter, however, the principle of 'at least one safe use' in a significant area (FOCUS, 2014) should always be considered.		
4(119)	3CA B-8.5.1.2.16 Monitoring assessment endpoints	RMS AT: *In order to allow further discussion amongst Member States, the RMS AT decided to assess the targeted pinoxaden edge-of-field monitoring study on basis of different assessment endpoints covering a wider range of conservatism and protectiveness. Notice that in the case of the targeted pinoxaden edge-of-field monitoring study, the conclusion, whether the pinoxaden metabolites exceed 0.1 µg/L or not, is solely depending on the assessment endpoint (with the exception of M3).* SYN: The applicant appreciates the effort by RMS AT to provide different endpoint metrics. This extended view gives further confidence to the conclusion that exceedances of pinoxaden metabolites above 0.1 µg/L are highly unlikely, no matter from which endpoint metric perspective the data are being interpreted. The metabolite M3 is concluded to be a non-relevant metabolite, hence a slightly higher number of measurements above 0.1 µg/L should not give reason for concern.	RMS AT: Noted.	Addressed.
4(120)	3CA B-8.5.1.2.18 Reliability assessment for individual monitoring sites	RMS AT: *Site PXDIT-1254 is the one and only site located in the FOCUS Zone Sevilla. Langridge & Schofield (2020) concluded that this site has extreme (> 90°) variation in the groundwater flow direction and the (only) sampling well at this site is not considered in the down-hydraulic*	RMS AT: Noted.	Addressed.

		gradient […] on several […] occasions […]. Andrews et al. (2020) concluded that the sampling well is actually located in the up-hydraulic gradient of the treated field. From Hoogeweg et al. (2000, 2000a and 2000b) it can be deduced that the mass flux of M3, M11 and M52 at PXDIT-1254 is around the 50th spatial percentile of the mass flux distribution in the FOCUS Zone Sevilla. And, finally there have been only two applications of 30 g/ha in 2014 and 2015. Nonetheless, the applicant considers the 90th percentile sample concentration, calculated for the FOCUS Zone Sevilla on basis of this one and only monitoring site located in this FOCUS Zone, sufficient to demonstrate 'safe use' for the FOCUS Zone Sevilla (for the intended application rate of 60 g/ha applied each year). SYN: See SYN response to Comment #38 on the number of years of data that might be needed to demonstrate safe uses at a European level. SYN agree that safe uses across a Zone are unlikely to be demonstrated from a single groundwater monitoring location.		
4(121)	3CA B-8.5.1.2.18 Reliability assessment for individual monitoring sites	RMS AT: *[…], there is one situation, where the applicant indicated that the assessment endpoint may not be entirely reliable, and this is the applicant's assessment for the FOCUS Zone Kremsmünster, which is the only case where the 90th percentile sample concentration of a pinoxaden metabolite (M3 in this case) is > 0.1 µg/L (0.142 µg/L according to the applicant's approach). As this is due*	RMS AT: Noted.	Addressed.

		to a single extreme monitoring site (PXDDE-1561) in a set of only 3 monitoring sites located in this FOCUS Zone, the applicant came to the conclusion that the assessment for this FOCUS Zone may not be sufficiently reliable. Consequently, the 90th percentile sample concentration of 0.142 µg/L for M3 obtained for the FOCUS Zone Kremsmünster was excluded from further considerations. SYN: Changes to the attribution of FOCUS Zones appropriate to monitoring sites occurred in 2014 when MARS weather data changed from a 50km grid level to a 25km grid level. This meant that 15 sites that had previously been attributed to Kremsmünster Zone at the start of the programme were changed to other Zones. This change in attribution could not have been foreseen by SYN at the time of study initiation. Refer to Comment #38 on a possible approach to the amount of data needed to demonstrate safe uses at a FOCUS zone level. Additional monitoring data for the Kremsmünster Zone are available from the German National monitoring programme (see Comment #58). Note that the relevant regulatory endpoint for metabolite M3 is 10 µg/L and the measurement of 0.142 µg/L needs to be viewed in this context.		
4(122)	3CA B-8.5.1.2.18 Reliability assessment for individual monitoring sites	RMS AT: *[…] there is almost no individual monitoring site without certain limitations and these limitations may be even more pronounced in a set of (relevant)*	RMS AT: We agree that it is impossible to setup a monitoring fulfilling all requirements needed for regulatory decision taking at each site. For that reason, any kind of limitation should be adequately	Addressed.

		monitoring sites depending on its composition. SYN: The practicalities of establishing a programme of this size should be considered. SYN followed an open and transparent process, using agreed groundwater models and parameterisation to identify 70 monitoring locations across Europe. It is an extremely difficult task to have enough monitoring sites in all FOCUS Zones and at the same time having a compilation of the requested worst-case properties at each site. It may therefore be impossible in the real world to identify the requested number of sites which also satisfy the requested compilation of worst-case criteria.	addressed (which has not been done). By the way, we do not consider the (regulatory) request for adequate hydraulic connectivity, adequate vulnerability, shallow groundwater and actual applications close to the intended one a "*compilation of worst-case criteria*."	
4(123)	3CA B-8.5.1.2.18 Reliability assessment for individual monitoring sites	RMS AT: *[Table RMS-21] FOCUS Tier-3b PECgw values (µg/L) (90th, 95th, 97th and 99th spatial/temporal percentile of the annual average concentrations) at 1 m soil depth (20 assessment years) calculated for the area of winter wheat in each FOCUS Zone (provided by the applicant) and on basis of the monitoring sites located in each FOCUS Zone (calculated by the RMS AT on basis of data provided by the applicant).* SYN: Table RMS-21 compares the modelled Tier 3b PECgw for the whole winter wheat area in the EU and for FOCUS Zones with the modelled concentrations for the groundwater monitoring locations. This Table shows that at the 90th and 95th percentile level the FOCUS Zones in which most groundwater monitoring sites are located (Hamburg 33 sites,	RMS AT: In principle, we agree with the applicant approach demonstrated in the comment to quantify the minimum percentile needed from a set of (relevant) monitoring sites to cover the true, e.g., 90th percentile in this assessment area. However, we do not necessary agree with the so-called "FOCUS equivalent concertation" (FEC) for reason outlined in 4(114). We suggest to discuss the applicably of this approach together with the applicably of the FEC approach with MS's experts.	See expert consultation proposed at comment 4(48).

Piacenza 7 sites and Thiva 23) the modelled concentration for the monitoring sites exceeds he Tier 3b concentration for metabolites M2, M3, M11, M52, M54 - exception for M2 at Thiva where the 95th percentile modelled concentration is <0.001 µg/L and that for the whole wheat area is 0.001µg/L. It can be concluded therefore that the monitoring locations have a greater vulnerability than the Tier 3b calculations for these metabolites. The situation for metabolites M55 and M56 is more complicated because the distribution for these metabolites is so narrow that most locations have a similar vulnerability.

The comparison between Tier 3b concentrations and modelled concentrations for the sites is useful. The Table below shows the percentile required for the concentration modelled for the groundwater scenarios to exceed the 90th percentile Tier 3b concentration for the zone (only 90th ,95th,97th and 99th percentiles considered).

Zone	M2	M3	M11	M52	M54	M55	M56
EU	90	90	90	90	90	99	97
Hamburg	90	90	90	90	90	95	90
Piacenza	90	90	90	90	90	99	95
Thiva	95	90	90	90	90	95	95

This information can be used with the Focus Equivalent Concentration (FEC) approach outlined in Comment #38 to calculate a FEC appropriate to the difference between Tier 3b concentrations and site modelled concentrations. For example, for metabolite M55 in Piacenza a 99th percentile concentration would be required for the site concentrations to

exceed the 90th percentile concentration for the Zone. A 99th percentile concentration from the monitoring data would therefore be required to calculate the FEC. Whereas for metabolite M54 only a 90th percentile would be required. This is a highly conservative approach because the FEC method uses the maximum monitored concentration in a year to represent a "FOCUS year". A 99th percentile of FOCUS year calculations will therefore exceed the 99th percentile of the monitoring data.

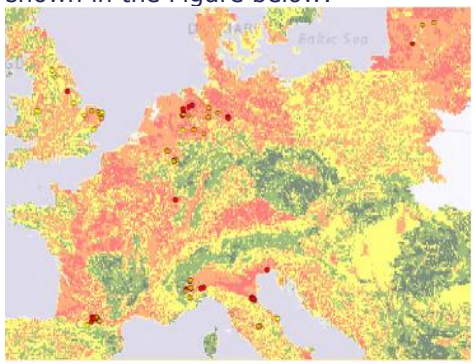
Using this approach, the following Table of FECs is obtained (monitoring data scaled for maximum applications and M55 concentrations adjusted for storage stability using the most conservative half-life of 9.2d) for the zones having enough FOCUS years to calculate a FEC according to this approach (units of µg/L).

Scenario	M2	M3	M11	M52	M54	M55	M56
EU	0.015	0.027	0.021	0.020	0.015	0.062	0.055
hamburg	0.015	0.034	0.024	0.015	0.015	0.030	0.038
piacenza	0.009	0.013	0.010	0.020	0.010	0.015	0.016
thiva	0.015	0.016	0.016	0.041	0.015	0.016	0.014

This Table shows that even by this extremely conservative measure of combining Tier 3b concentrations and concentrations modelled for the groundwater monitoring locations in combination with the FEC approach concentrations remain well below the relevant regulatory trigger for all pinoxaden metabolites. Although this approach is not guidance it may prove a useful starting point for a method to interpret monitoring data on the basis of modelled vulnerability.

4(124)		RMS AT: *On basis of this highly targeted contextualisation exercise one may concluded that individual sets of monitoring sites located in a certain FOCUS Zone are on overall not sufficiently vulnerable to allow a meaningful calculation of, e.g., a 90th, 95th, 97, or 99th spatial/percentile of annual average concentrations obtained from monitoring results at these sites. This is particularly true for M55 and M56 in almost all FOCUS Zones but also for the entire EU.* SYN: The narrowness of the distributions for M55 and M56 result from modelling the entire EU cereals area for these metabolites using environmental fate data appropriate to Tier 1 modelling. These data suggest that environmental conditions are almost irrelevant to the level of leaching of these metabolites to 1m. It would be incorrect to assume the groundwater monitoring locations are not conservative for these metabolites because every location is essentially of the same vulnerability to chromatographic flow at 1m according to modelling. See Comment #47 for a method to estimate FOCUS zone concentrations that considers variations of percentile vulnerabilities for each metabolite at a FOCUS zone level. In the absence of any guidance on the calculation of groundwater vulnerability SYN decided to use a modelling approach to be consistent with Tier 1 modelling. However, this is not the only approach that can be	RMS AT: We highly appreciate any further information provided on the site's leaching or groundwater vulnerability, e.g., applying the DRASTIC approach. We would like to ask the MS's experts to decide on the need evaluating the DRASTIC approach provided by the applicant for confirmatory data purposes. Otherwise, these additional data can be addressed at AIR6. Also refer to comment 4(104).	Addressed.

taken. The DRASTIC score (Aller et al, 1985) is commonly used to estimate groundwater vulnerability world-wide and this exercise was performed by JRC to estimate the intrinsic vulnerability of European groundwater. DRASTIC is different to the approach used by SYN because it uses additional criteria, such as aquifer characteristics, to calculate the overall vulnerability of groundwater, whereas the approach used by SYN is more appropriate to vulnerability arising from chromatographic flow, but is consistent with Tier 1 modelling. SYN have used the geolocations of the 70 groundwater monitoring sites to place them on the JRC map of intrinsic groundwater vulnerability. This is shown in the Figure below:



The following Table shows the attribution of sites according to the JRC scheme.

Member State	Red Very high Vulnerability	Orange High Vulnerability	Yellow Moderate Vulnerability
France	5	5	3
Germany	7	12	1
Italy	9	9	2
Lithuania	1	2	-
UK	1	5	8
Total	23	33	14

This Table shows that 56 (80%) of the groundwater monitoring sites are situated in areas of high or very high intrinsic groundwater vulnerability according to the JRC DRASTIC map. Unfortunately, the individual data layers are not available from JRC. Nevertheless, SYN has performed its own exercise to reproduce the JRC map using appropriate data layers. The vulnerability of each site according to the individual DRASTIC data layers can be assessed using these data along with the percentile of the overall DRASTIC score. These data can be made available if requested by the RMS.

In summary SYN consider that every effort has been made to identify groundwater monitoring sites that are vulnerable to leaching. Sites may appear to be more or less vulnerable according to the methodology used to estimate vulnerability. However, SYN has monitored 70 different groundwater monitoring locations having shallow groundwater and have monitored them quarterly for 5 years. SYN believes that this is an appropriate study to estimate the potential of pinoxaden and its metabolites to leach to groundwater under realistic farming conditions appropriate to the control of black grass in Europe.

Reference: https://water.jrc.ec.europa.eu/portal/apps/webappviewer/index.html?id=81c72a69914148b9be1f7ff6b429effb (checked in 2022).

4(125)	3CA B-8.5.1.2.18 Reliability assessment for individual monitoring sites	SYN: Table RMS-21 compares the modelled Tier 3b PECgw for the whole winter wheat area in the EU and for FOCUS Zones with the modelled concentrations for the groundwater monitoring locations. This Table shows that at the 90th and 95th percentile level the FOCUS Zones in which most groundwater monitoring sites are located (Hamburg 33 sites, Piacenza 7 sites and Thiva 23) the modelled concentration for the monitoring sites exceeds he Tier 3b concentration for metabolites M2, M3, M11, M52, M54 - exception for M2 at Thiva where the 95th percentile modelled concentration is <0.001 µg/L and that for the whole wheat area is 0.001µg/L. It can be concluded therefore that the monitoring locations have a greater vulnerability than the Tier 3b calculations for these metabolites. The situation for metabolites M55 and M56 is more complicated because the distribution for these metabolites is so narrow that most locations have a similar vulnerability. The comparison between Tier 3b concentrations and modelled concentrations for the sites is useful. The Table below shows the percentile required for the concentration modelled for the groundwater scenarios to exceed the 90th percentile Tier 3b concentration for the zone (only 90th ,95th,97th and 99th percentiles considered).	RMS AT: Please refer to comment 4(123)	See expert consultation proposed at comment 4(48).

Zone	M2	M3	M11	M52	M54	M55	M56
EU	90	90	90	90	90	99	97
Hamburg	90	90	90	90	90	95	90
Piacenza	90	90	90	90	90	99	95
Thiva	95	90	90	90	90	95	95

This information can be used with the Focus Equivalent Concentration (FEC) approach outlined in Comment #38 to calculate a FEC appropriate to the difference between Tier 3b concentrations and site modelled concentrations. For example, for metabolite M55 in Piacenza a 99th percentile concentration would be required for the site concentrations to exceed the 90th percentile concentration for the Zone. A 99th percentile concentration from the monitoring data would therefore be required to calculate the FEC. Whereas for metabolite M54 only a 90th percentile would be required. This is a highly conservative approach because the FEC method uses the maximum monitored concentration in a year to represent a "FOCUS year". A 99th percentile of FOCUS year calculations will therefore exceed the 99th percentile of the monitoring data.

Using this approach, the following Table of FECs is obtained (monitoring data scaled for maximum applications and M55 concentrations adjusted for storage stability using the most conservative half-life of 9.2d) for the zones having enough FOCUS years to calculate a FEC according to this approach (units of µg/L).

Scenario	M2	M3	M11	M52	M54	M55	M56
EU	0.015	0.027	0.021	0.020	0.015	0.062	0.055
hamburg	0.015	0.034	0.024	0.015	0.015	0.030	0.038
piacenza	0.009	0.013	0.010	0.020	0.010	0.015	0.016
thiva	0.015	0.016	0.016	0.041	0.015	0.016	0.014

This Table shows that even by this extremely conservative measure of combining Tier 3b concentrations and

		concentrations modelled for the groundwater monitoring locations in combination with the FEC approach concentrations remain well below the relevant regulatory trigger for all pinoxaden metabolites. Although this approach is not guidance it may prove a useful starting point for a method to interpret monitoring data on the basis of modelled vulnerability.		
4(126)	3CA B-8.5.1.2.19 Results of the RMS AT's assessment of the targeted pinoxaden edge-of-field monitoring study	RMS AT: [Table RMS-22] SYN: Using the number above 0.1 µg/L for metabolites that are not relevant (trigger of 10 µg/L) is not appropriate for metabolites M3, M11, M54 and M56. Using number of residues above trigger would be a better metric.	RMS AT: To our understanding, the relevance assessment for the pinoxaden metabolites is not agreed so far.	Comparison to 0.1 µg/L is needed until a final outcome is available on the relevance of metabolites for groundwater.
4(127)	3CA B-8.5.1.2.19 Results of the RMS AT's assessment of the targeted pinoxaden edge-of-field monitoring study	RMS AT: [Table RMS-26]: maximum concentrations SYN: SYN do not agree to the use of a maximum concentration for the purposes of regulatory decision making on groundwater monitoring data. This approach is biased towards most extreme conditions, and effectively penalises applicants for taking more data which is against sound risk assessment procedure. Based on >100 sites (including national monitoring), highest monitored concentrations are considerably lower than in FOCUS Tier-1 modelling, which indicates that exceedances in real agronomic settings are very unlikely.	RMS AT: Noted. We suggest to discuss the most appropriate endpoints from such a type of edge-of-field monitoring with MS's experts. This may include alternative approaches, e.g. the FOCUS Equivalent Concentration (FEC) or the Percentage Exceedance Approach (PEA).	See expert consultation proposed at comment 4(48).
4(128)	B8 KIIA 7.12/12 Langridge & Schofield, 2020	RMS AT: *On request of the RMS AT, the applicant provided the pinoxaden use history data in a dedicated EXCEL sheet giving details on the actual application rate (g/ha) and*	RMS AT: Thanks for clarification. It was also our understanding that the EXCEL file provided by the applicant is the most referable source for the pinoxaden use history.	Addressed.

		application date. It is noted that the pinoxaden use history data given in the report appears not to be complete as the EXCEL sheet, provided by the applicant, accounts for additional applications, which are nowhere else documented in the dossier. SYN: The difference in pesticide use history (PUH) between the Excel file submitted and the information in Langridge and Schofield (2020) is that in the report only the PUH information collected by Ramboll since the beginning of the monitoring program is included. In the Excel file also the Pinoxaden use history collected during the study design phase was included, that was performed by Arcadis, and is included in White and Hamer (2016). It is concluded that the excel file is the most referable document as it contains all the PUH since the initiation of the groundwater monitoring efforts.		
4(129)	B8 KIIA 7.12/38 Andrews et al., 2020 A	RMS AT: *The RMS AT's evaluator has to admit, that he has neither experience with these kinds of measurements nor is he in the position to conclude on any consequences arising from the obtained results. The applicant is asked to more deeply reflect the implications of the groundwater flow velocity assessment on the reliability of the monitoring results at each monitoring site.* SYN: The study shows that the majority of sites has velocity modes between 1-100 m/year, which should be sufficient in most cases to cover	RMS AT: We appreciate additional information announced by the applicant. We would like to ask MS's expert to consider the need evaluating new information on the impact of horizontal travel time on the reliability of the monitoring results for confirmatory data purposes. Otherwise these new information should be assessed at AIR6.	Addressed.

		the distance between the field edge and the sampling well within a monitoring period of 4 years. With this, it is likely that reliability of the obtained monitoring results is not adversely affected by hydraulic conductivity. However, to elucidate the situation further for all 70 monitoring sites, a detailed assessment can be provided upon request.		
4(130)	B8 KIIA 7.12/15 Andrews et al., 2020	RMS AT: *The extensive elucidation activities conducted at this monitoring site did not give any indication that isolated findings of pinoxaden metabolites at site PXDIT-1208 are due to, e.g., shortcuts or activities other than good agriculture practice. Therefore, there is no need to omit results obtained at this monitoring site in the final assessment.* SYN: It is noted that the single detect of M52 at a concentration of 0.162 µg/L at site PXDIT-1208 was likely caused by an intense rainfall event shortly after application causing the groundwater table to rise, catching residues close to the surface into the saturated zone.	RMS AT: Intense rainfall shortly after application may happen and do not necessarily contradict good agricultural practice.	Addressed.
4(131)	B8 KIIA 7.12/26 Hoogeweg et al., 2020	RMS AT: *[…] mass flux distributions of most of the pinoxaden metabolites (with the exception of M2 and M52) are extremely 'flat' covering only a limited range in magnitude. Consequently, the same is true for the site-specific mass flux calculations […] E.g., in the case of M55 and M56 the monitoring site with the highest leaching vulnerability (100th spatial percentile mass flux) has a mass flux which is only 2.4 and 3.2 times higher than the monitoring sites with*	RMS AT: From our point of view, the reliability of a 1-m FOCUS-like leaching model for assessing the site's leaching vulnerability, particularly if vulnerability distributions are extremely flat (indicating almost no differences in vulnerability all over the EU), should be discussed with MS's experts. MS's experts to discuss the reliability of a 1-m FOCUS-like leaching model for assessing the site's leaching	See expert consultation proposed at comment 4(48).

		the lowest leaching vulnerability […]. In view of the RMS AT, leaching vulnerabilities deduced from such 'flat' mass flux distributions appear meaningless with respect to real-world leaching vulnerabilities at the monitoring sites and this may have implications on the reliability of the overall contextualisation approach […] SYN: SYN note the narrowness of the mass flux distributions of M55 and M56, however these were calculated by modelling the entire EU using endpoints appropriate to pinoxaden and its metabolites. The GeoPEARL (4R) model is the same as the FOCUS PEARL 4.4.4 model used for evaluations at a Member State and European level. The model therefore indicates that there is little difference between sites across Europe regarding leaching to 1m depth for these metabolites. It is a matter of conjecture whether this represents the true picture of potential groundwater exposure presented by these metabolites. The DRASTIC approach to characterise sites also indicated (see Comment #48) that sites vulnerable to groundwater contamination were selected. This approach is independent of the modelling approach outlined by SYN.	vulnerability to be used comparing sites and setting sites into context. MS's experts to discuss whether other approaches (e.g., the DRASTIC approach or similar index approaches) should be accounted as well or may serve as suitable alternatives.	
4(132)	B8 KIIA 7.12/39 Sweeney, 2020	RMS AT: *The RMS AT agrees with the study author that these 24 sites have at least one application from 2013 – 2016 at maximum label rate, which make these sites of course more reliable with respect to the maximum label rate of 60 g/ha. However, there are 46 sites (two thirds of all sites)*	RMS AT: Noted. Please also refer to comment 4(92).	See expert consultation proposed at comment 4(48).

		where this is not the case. It is also noted that only 1 out of the 5 monitoring sites with pinoxaden residues > 0.1 µg/L is amongst these 24 sites. The other 4 sites with findings of pinoxaden metabolites > 0.1 µg/L have application rates significantly less than the maximum label rate. In conclusion, the RMS AT is not of the opinion that the targeted pinoxaden edge-of-field monitoring study as a whole […] is adequately covering the maximum label rate of 60 g/ha. SYN: SYN consider that the monitoring study reflects farming practice for control of black grass at the full label rate of 60g/ha. The scaling approach outlined by the RMS is a useful way to scale results to the full label rate, and even with this approach, concentrations are still below the parametric limit for most metabolites. Over 90% of the overall data are <LOD and it is difficult to see how the increase in rate could have caused exceedances not observed in the current study. The monitoring study conducted in Germany had applications at the full label rate and essentially had the same conclusions. (see Comment #59)		
4(133)	B8 KIIA 7.12/42 Ford, 2020 France National Monitoring Program	RMS AT: *Possibly, isolated findings of pinoxaden (> LOD but < LOQ) and of its hydrolysis product M2 in the French national monitoring programme may be attributed to the karstic properties of the monitoring sites with rapid transport via fissures in the underlying limestone. For unknown reasons, pinoxaden and M2*	RMS AT: Noted.	Addressed.

		were most frequently found in the 6/2016 and 9/2016 samples all over the French National monitoring study. SYN: It should be noted that all detects of parent pinoxaden (n=7) and most of the findings of M2 in 6/2016 and 9/2016 were below the LOQ (n=11), and that the maximum concentration of M2 ever measured in the period of the monitoring from 2015 to the end of 2019 was at a concentration of 0.037 µg/L in 12/2017.		
4(134)	B8 KIIA 7.12/42 Ford, 2020 France National Monitoring Program	RMS AT: *[…] the French national monitoring programme is clearly the least targeted one, with large and poorly defined catchment areas […]. There is also no dedicated hydraulic connectivity assessment available […], albeit the sites are considered vulnerable […] representing karstic areas in many cases. It is also noted that the groundwater levels for several monitoring sites are not reported (or validated). Despite these limitations, the RMS AT is of the opinion that the French national monitoring programme provides further indication that metabolites of pinoxaden are unlikely to exceed 0.1 µg/L in groundwater.* SYN: The applicant agrees with the conclusion by RMS AT that the French national monitoring program, despite its limitations, provides further weight-of-evidence that metabolites of pinoxaden are unlikely to exceed 0.1 µg/L in groundwater.	RMS AT: Noted.	Addressed.
4(135)	B8 KIIA 7.12/42 Resseler et al., 2020	RMS AT: *The documentation of the German National pinoxaden monitoring program, including site*	RMS AT: The additional vulnerability assessment of the monitoring sites in the German national monitoring	Addressed.

German National Federal Well Monitoring Program	*characteristics, hydraulic connectivity assessment and pinoxaden use history, is highly detailed, extensive and well prepared.* SYN: SYN would like to provide a vulnerability ranking for the monitoring sites of the German National Federal wells monitoring program based on DRASTIC and information on the wells available in the FOCUS Kremsmünster zone. The sites in Germany (in total 22 wells) are distributed across the four vulnerability classes of DRASTIC as follows: Very high vulnerability (red): 7 sites (32%) High vulnerability (orange): 11 sites (50%) Medium vulnerability (yellow): 3 sites (14%) Low vulnerability (green): 1 site (0.5%) According to the DRASTIC method 82% of the sites in Germany can be assigned to the classes of high or very high vulnerability. The table below shows the individual ranking results for each of the wells in Germany.	program on basis of the DRASTIC approach is appreciated. On overall, we highly welcome any further information on the site's groundwater vulnerability outside of the usual "FOCUS 1-m modelling world". As already outlined several times in the DAR, a 1-m FOCUS-like leaching model may not be necessarily the most appropriate tool to assess the site's vulnerability with respect to real-world conditions. A more condensed view of different approaches (including, e.g., the DRASTIC or similar approaches) may help to decrease uncertainties in assessment of the site's leaching vulnerability. MS's expert to discuss the need to evaluate new information announced (DRASTIC approach, alignment of sites in the German national monitoring program to FOCUS zones) in context of confirmatory data or AIR6.

one	Vulnerability
Bexten	very high
Brekendorf	very high
Kirchham	very high
Kittlitz	very high
Postmuenster	very high

Simbach Stoelln	very high
Tabeckendorf	very high
Asing	high
Flechum	high
Grosse-Luetke	high
Rheinau-Freistett	high
Rheinhausen-Oberhausen	high
Rohlstorf	high
Schlamersdorf	high
Soenderby	high
Suesel-Vinzier	high
Torgelow	high
Veltrup	high
Biblis	moderate
Gross-Rohrheim	moderate
Maria Einsiedel	moderate
Lelkendorf	low

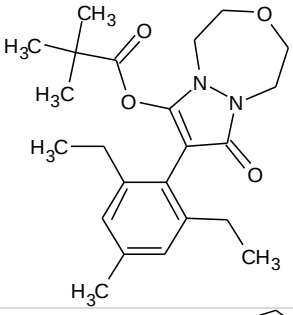
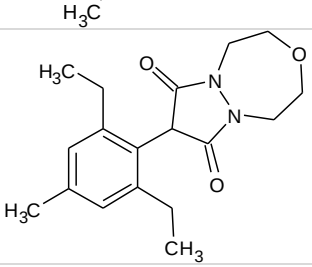
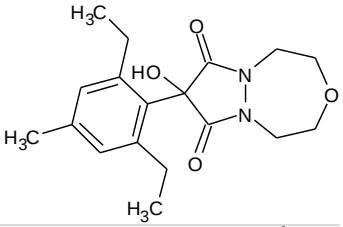
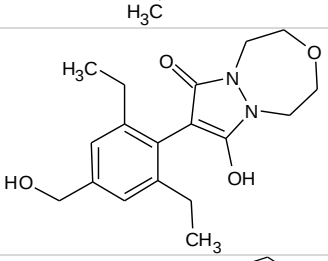
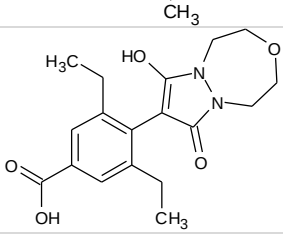
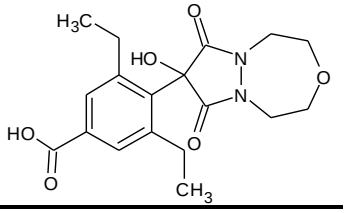
In addition, it should be noted that many sites of the German national monitoring can be attributed to the Hamburg and Kremsmünster FOCUS zones. Particularly for the latter, this may be worthwhile to consider in more depth, as the Pan-EU monitoring program does not represent the Kremsmünster scenario particularly well. An evaluation of how the 22 sites of the German national monitoring program can be attributed to FOCUS zones shows that 7 sites (Brekendorf, Kirchham, Tabeckendorf, Postmuenster, Simbach, Schlamersdorf, Soenderby) belong to the FOCUS zone Kremsmünster.

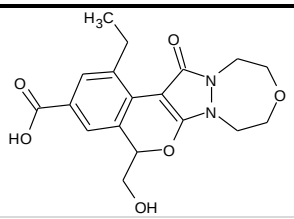
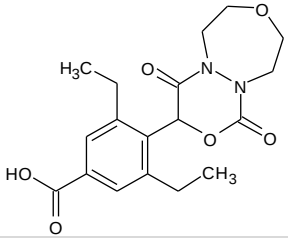
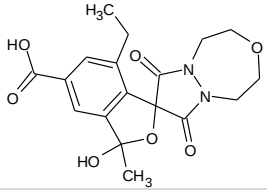
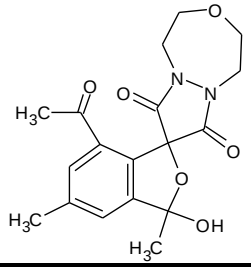
4(136)	B8 KIIA 7.12/42 Resseler et al., 2020 German National Federal Well Monitoring Program Table RMS 100	RMS AT: [Table RMS-100] Pinoxaden application history in the 45° segment – RMS AT assessment SYN: The applicant would like to note that in the German National Federal wells monitoring program farmers were incentivized to proactively apply pinoxaden on their cereals fields by providing products free of charge to them, thus also creating an incentive to prioritize cropping of cereals over other crops. With that, it is reasonable to assume that the monitoring program in Germany covers an "unrealistically" high area with applications during the study period and SYN would like to provide additional information on the product use: The arithmetic average of the percentage of cereal field area treated with pinoxaden was 89% (median 94%) of the total available cereal area in the delineated sub-catchment (treated areas are shown in Table RMS 100/Liss & Naeb 2020). The total number of treatable cereal fields was 477, from which 407 fields (85%) were treated. In the vast majority these 407 treatment events were performed by applying the maximum registered label rate of 58.5 g PXD/ha: Only 14 fields out of 407 fields treated received less than the maximum registered rate (calculated across the monitoring period 2014 - 2019). The applicant offers to provide a new GIS based evaluation on these details of application areas and rates (based on	RMS AT: This condensed overview on the actual application of pinoxaden in the 45° segments (39.3 ha area) in the German national monitoring program is appreciated. We agree that the percentage of treatable (i.e., cereal) fields in this monitoring program was particularly high. However, considering the percentage of cereal fields located in the 45° segment, the percentage of total area annually treated in the 39.3 ha area comes down to 0 – 89 % with a median of 20 %. Irrespective of the percentage finally treated, the RMS AT agrees with the applicant that the German national monitoring represents typical cereal farming practices with extensive pinoxaden use. MS's expert to discuss the need to evaluate new information announced (new GIS data on the pinoxaden application in the German national monitoring program) in context of confirmatory data or AIR6.	Addressed.

		the submitted GLP reports) on request or for the new AIR submission. This national federal well monitoring study, conducting also monthly samplings, showed no exceedances of any trigger. Connectivity was proven. It may therefore be concluded that even under such an "unrealistic" high use pressure with yearly applications safe uses for PXD exist in FOCUS Hamburg and Kremsmünster zones.		
4(137)	B8.5.5 RMS AT's summary of monitoring data for pinoxaden and its metabolites	RMS AT: *The RMS AT agrees with the applicant that the overall monitoring results provided […] give strong evidence that the exposure of the pinoxaden metabolites to groundwater is low, and it is highly unlikely that pinoxaden metabolites will exceed the regulatory threshold of 0.1 µg/L under typical pinoxaden use conditions across the EU. […] highly isolated exceedances of 0.1 µg/L of pinoxaden metabolites, particularly in shallow groundwater below or close to treated fields, may occur […]. These conclusions are basically valid at the level of the entire EU, FOCUS Zones and Member States.* SYN: The applicant welcomes the conclusion by RMS AT that, albeit the occurrence of single exceedances above 0.1 µg/L in shallow groundwater, it is highly unlikely that pinoxaden metabolites will exceed the regulatory threshold of 0.1 µg/L under typical pinoxaden use conditions (this threshold is also not appropriate for metabolites M3, M11, M54 and M56).	RMS AT: Noted. MS's expert to discuss the most appropriate endpoints to be derived from a dedicated edge-of-field monitoring campaign at the level of the EU and individual MS.	See expert consultation proposed at comment 4(48).

		In conclusion, the Pan-European monitoring program has demonstrated the safe use of pinoxaden in significant cereal growing regions in Europe in accordance with FOCUS (2014). Taking into account the 90th percentile over all individual samples according to FOCUS guidance (FOCUS, 2014), but also looking at maximum annual average or the 90th spatial/temporal percentile of the sites' annual average concentrations, none of the metabolites are observed above the parametric limit of 0.1 µg/L, which may trigger a non-relevance assessment according to the EC guidance document SANCO/221/2000 –rev.10 final.		
4(138)	B8.5.5 RMS AT's summary of monitoring data for pinoxaden and its metabolites	RMS AT: *On overall, the RMS AT highly recommends to develop more targeted regulatory guidance on how to conduct, evaluate and assess such monitoring studies at the level of the entire EU (for active substance approval) and at the level of Member States (for product registration).* SYN: The applicant shares the need for development of regulatory guidance on groundwater monitoring studies to facilitate conduct and evaluation of such studies. The applicant would like to thank RMS Austria for the enormous effort and commitment in evaluating this GW monitoring program, and the additional analyses and calculations provided, which aid the interpretation of the monitoring data greatly.	RMS AT: This feedback is highly appreciated.	Addressed.

Appendix B – Used compound codes

Code/trivial name[a]	Chemical name/SMILES notation[b]	Structural formula[©c]
pinoxaden	8-(2,6-diethyl-4-methylphenyl)-7-oxo-1,2,4,5-tetrahydro-7H-pyrazolo[1,2-d][1,4,5]oxadiazepin-9-yl 2,2-dimethylpropanoate CC(C)(C)C(=O)OC1=C(C(=O)N2CCOCCN21)c1c(CC)cc(C)cc1CC MGOHCFMYLBAPRN-UHFFFAOYSA-N	
M2	8-(2,6-diethyl-4-methylphenyl)tetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9(8*H*)-dione CCc1cc(C)cc(CC)c1C1C(=O)N2CCOCCN2C1=O QHUWVQWAKAJLTJ-UHFFFAOYSA-N	
M3	8-(2,6-diethyl-4-methylphenyl)-8-hydroxytetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9(8*H*)-dione CCc1cc(C)cc(CC)c1C1(O)C(=O)N2CCOCCN2C1=O XTDSHACLOHQSIG-UHFFFAOYSA-N	
M4	8-[2,6-diethyl-4-(hydroxymethyl)phenyl]-9-hydroxy-1,2,4,5-tetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-7-one CCc1cc(CO)cc(CC)c1C=1C(=O)N2CCOCCN2C=1O WGVDNRLFXQNIMF-UHFFFAOYSA-N	
M6	3,5-diethyl-4-(9-hydroxy-7-oxo-1,2,4,5-tetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-8-yl)benzoic acid O=C(O)c1cc(CC)c(C=2C(=O)N3CCOCCN3C=2O)c(CC)c1 IGUXRAORVWEOEM-UHFFFAOYSA-N	
M11	3,5-diethyl-4-(8-hydroxy-7,9-dioxohexahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-8-yl)benzoic acid O=C(O)c1cc(CC)c(c(CC)c1)C1(O)C(=O)N2CCOCCN2C1=O TYFDZZRIQWKTIX-UHFFFAOYSA-N	

M52	1-ethyl-5-(hydroxymethyl)-14-oxo-8,9,11,12-tetrahydro-5*H*,14*H*-[2]benzopyrano[3',4':3,4]pyrazolo[1,2-*d*][1,4,5]oxadiazepine-3-carboxylic acid O=C(O)c1cc2c(C=3C(=O)N4CCOCCN4C=3OC2CO)c(CC)c1 LOMMJLDVYWDSCR-UHFFFAOYSA-N	
M54	4-(1,4-dioxohexahydro-1*H*-[1,3,4]oxadiazino[3,4-*d*][1,4,5]oxadiazepin-3-yl)-3,5-diethylbenzoic acid O=C(O)c1cc(CC)c(c(CC)c1)C1OC(=O)N2CCOCCN2C1=O DMAYIZFOQDBUEV-UHFFFAOYSA-N	
M55	7-ethyl-3-hydroxy-3-methyl-7',9'-dioxo-1',2',4',5'-tetrahydro-3*H*,7'*H*,9'*H*-spiro[[2]benzofuran-1,8'-pyrazolo[1,2-*d*][1,4,5]oxadiazepine]-5-carboxylic acid O=C(O)c1cc(CC)c2c(c1)C(C)(O)OC21C(=O)N2CCOCCN2C1=O YMOZJKIMMVZGEL-UHFFFAOYSA-N	
M56	7-acetyl-3-hydroxy-3,5-dimethyl-1',2',4',5'-tetrahydro-3*H*,7'*H*,9'*H*-spiro[[2]benzofuran-1,8'-pyrazolo[1,2-*d*][1,4,5]oxadiazepine]-7',9'-dione CC(=O)c1cc(C)cc2c1C1(OC2(C)O)C(=O)N2CCOCCN2C1=O NTVGVBNYCCFRPZ-UHFFFAOYSA-N	

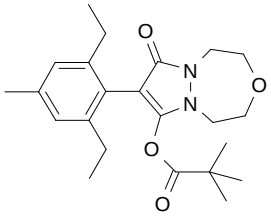
(a): The compound name in bold is the name used in the conclusion.
(b): ACD/Name 2021.1.3 ACD/Labs 2021.1.3 (File Version N15E41, Build 123232, 07 Jul 2021)
(c): ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 28 Aug 2021)

Appendix C – List of endpoints

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Pinoxaden (ISO published)
Function (*e.g.* fungicide)	Herbicide
Rapporteur Member State	UK (after Brexit AT)
Co-rapporteur Member State	n/a

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	8-(2,6-diethyl-4-methylphenyl)-7-oxo-1,2,4,5-tetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-9-yl 2,2-dimethylpropanoate 1979 Rules: 8-(2,6-diethyl-*p*-tolyl)-1,2,4,5-tetrahydro-7-oxo-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-9-yl 2,2-dimethylpropionate
Chemical name (CA) ‡	8-(2,6-diethyl-4-methylphenyl)-1,2,4,5-tetrahydro-7-oxo-7*H*-pyrazolo[1,2-*d*] [1,4,5] oxadiazepin-9-yl 2,2-dimethylpropanoate
CIPAC No ‡	776
CAS No ‡	243973-20-8
EC No (EINECS or ELINCS) ‡	Not yet available
FAO Specification (including year of publication) ‡	None on website
Minimum purity of the active substance as manufactured ‡	970 g/kg
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Toluene max. content 1 g/kg
Molecular formula ‡	$C_{23}H_{32}N_2O_4$
Molecular mass ‡	400.5 g/mol
Structural formula ‡	

- **Summary of representative uses evaluated (pinoxaden) initially submitted for Annex I approval**

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as g/L (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Wheat, Winter	North EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Up to 0.045 kg as/ha in autumn
Barley, Winter	North EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Up to 0.045 kg as/ha in autumn
Barley, Spring	North EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	
Rye	North EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Up to 0.045 kg as/ha in autumn
Triticale	North EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Up to 0.045 kg as/ha in autumn
Wheat, Winter	South EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	
Barley, Winter	South EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	
Durum	South EU	A-12303C (+ A-12127R*)	F	Grassweeds	EC	NOA 407855 - 100	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.045	-	

* Application always made with adjuvant A-12127R at 0.5% concentration of spray solution, or in some countries 3:1 ratio with A-12303C dose rate.

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).
(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr).
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR) (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989 (f) All abbreviations used must be explained (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench (h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated	(k) Indicate the minimum and maximum number of application possible under practical conditions of use (l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha (m) PHI - minimum pre-harvest interval

- **Summary of representative uses evaluated (pinoxaden) submitted in course of Confirmatory Data submission**

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as g/L (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Wheat, Winter	North EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Do not apply in autumn
Barley, Winter	North EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Do not apply in autumn
Barley, Spring	North EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Do not apply in autumn
Rye	North EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Do not apply in autumn
Triticale	North EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Do not apply in autumn
Wheat, Winter	South EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Do not apply in autumn
Barley, Winter	South EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.06	-	Do not apply in autumn
Durum	South EU	A13814D	F	Grassweeds	EC	NOA 407855 - 60	Foliar broadcast	Up to GS39	1	-	-	100-400	0.03-0.045	-	Do not apply in autumn

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).
(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr).
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) Indicate the minimum and maximum number of application possible under practical conditions of use

(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989 (f) All abbreviations used must be explained (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench (h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated	(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha (m) PHI - minimum pre-harvest interval

Methods of Analysis

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Provisionally: Sum of M4 and M6 expressed as parent pinoxaden (to include free and conjugated residues of M4 and M6)
Food of animal origin		None strictly needed
Soil		NOA 407854 (M2), NOA 447204 (M3)
Water	surface	NOA 407854 (M2)
	drinking/ground	Pinoxaden (NOA 407855), NOA 407854 (M2), SYN 546105 (M52), SYN 546107 (M55). Whether NOA 447204 (M3), SYN 546106 (M54), SYN 546108 (M56) SYN 504574 (M11) will need to be included in the monitoring definition remains open.
Air		Pinoxaden (NOA 407855)

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Method REM 199.03. Off line SPE, extraction by relfux with HCl Analytes: M4 and M6 (free and conjugated) M4 Q1 *m/z* was 333.25 and Q3 *m/z* was 101.5 M6 Q1 *m/z* was 345.16 and Q3 *m/z* was 173.15 The LOQ for cereal grains (dry commodities) was 0.01 mg/kg for each metabolite of pinoxaden. The LOQ for each metabolite in cereal whole plants (high water content matrix), ears, stalks and straw was 0.02 mg/kg. ILV data are available. Confirmatory method for the determination of free and conjugated metabolites M4 and M6 in high water and dry matrices and complete validation for the determination of metabolites M4 and M6 (free and conjugated) in high oil and high acid content commodities are required. The Quechers methodology with LC-MS/MS has been applied to determination of free M4 and M6 in a range of commodity types (barley, lettuce, oilseed rape seeds and orange) (ILV data is not currently available as the validation report was for a single laboratory) LOQ 0.01 mg/kg for each analyte. Validation is available for both primary and confirmatory transitions.

Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Not strictly required as no MRLs have been set for products of animal origin. A suitable method of analysis (and ILV) is available for the analytes M4 and M6 (method code T001530-03). Following acid reflux, clean up and analysis by HPLC MS/MS. LOQ M4: 0.01 mg/kg for milk and 0.02 mg/kg for animal tissues and eggs LOQ M6: 0.01 mg/kg for milk and 0.02 mg/kg for animal tissues and eggs
Soil (analytical technique and LOQ)	LC-MS/MS methods submitted for pinoxaden, M2 and M3 (validation submitted for both primary and confirmatory transitions) with LOQs of 0.5 µg/kg for each analyte.
Water (analytical technique and LOQ)	LC-MS/MS methods submitted for pinoxaden, M2 and M3, M11, M52, M54, M55 (validation submitted for both primary and confirmatory transitions) with LOQs of 0.05 µg/L for each analyte in surface, ground and drinking water.
Air (analytical technique and LOQ)	Method A.13.S267 (LC-MS/MS): Sampling conditions: 35ºC and 79% humidity Parent NOA 407855 (M1) degrades into the hydrolysis product NOA 407854 (M2) and to a lesser extent the oxidation product NOA 447204 (M3) The LOQ was 1 µg/m^3 Sampling conditions: ambient Samples were analysed immediately to avoid hydrolysis of pinoxaden to M2 and M3 LOQ: 1 µg/m^3 for pinoxaden (4 hrs sampling time for air flow time of 1 L/min).
Body fluids and tissues (analytical technique and LOQ)	Not relevant since pinoxadene is neither classified as toxic or very toxic

Impact on Human and Animal Health

Other toxicological studies (Annex IIA, point 5.8)

Studies performed on metabolites or impurities ‡	For M3, an LD50 of 1089 mg/kg bw was identified in the acute oral toxicity study. In the dietary repeat dose toxicity studies, effects on body weight, food consumption and liver were observed. A NOAEL of 67 mg/kg bw/d was identified in the 28-day study and a NOAEL of 99 mg/kg bw/day was established from the 90-day study. M3 was not mutagenic in bacterial cells or in mammalian cells *in vitro*. It was weakly clastogenic in lymphocytes *in vitro*. However, no genotoxic activity was seen in either a mouse bone marrow micronucleus study or a rat liver UDS assay *in vivo*. Bone marrow exposure was confirmed due to plasma analysis in an additional study. Overall, on the basis of these data, it can be concluded that M3 is not mutagenic *in vivo*; however, compared to pinoxaden, M3 appears to be approximately 10-times more toxic, as an oral LD50 of 1089 mg/kg bw was estimated for M3 compared to an oral LD50 > 5000 mg/kg bw for pinoxaden and NOAEL values of 67 and 99 mg/kg bw/day were identified for M3 in dietary 28-day and 90-day dietary studies compared to NOAEL values of 610 and 466 mg/kg bw/day for pinoxaden are proposed by the RMS. Peer review proposed to discuss NOAEL setting and ADI setting.Hence, RMS proposed a specific ADI has been set for M3, by reducing the parent ADI by 10, to obtain a value of 0.01 mg/kg bw/day. A developmental study in rabbits was performed to address the hazard derived from pinoxaden (classified as Reprotoxic, Category 2, H361d). Peer review proposed to discuss groundwater relevance of M3. For M6, an LD50 of >2000 mg/kg bw was identified in the acute oral toxicity study. In the dietary repeat dose toxicity studies, no effects were seen up to the limit dose.

A NOAEL of > 1000 mg/kg bw/d was identified from both the 28-day and 90-day studies. M6 was not mutagenic in bacterial cells and was not mutagenic or clastogenic in mammalian cells *in vitro*. Overall, on the basis of these data, it can be concluded that M6 is not mutagenic and that it is less toxic than the parent. Hence, the use of the parent ADI in the dietary risk assessment for M6 represents a conservative approach.

For M10, an LD50 of >2000 mg/kg bw was identified in the acute oral toxicity study. M10 was not mutagenic in bacterial cells *in vitro*. It was not clastogenic to lymphocytes *in vitro* but it gave a positive response in the mouse lymphoma cell assay. However, no genotoxic activity was seen in either a mouse bone marrow micronucleus study or a rat liver UDS assay *in vivo*. Overall, on the basis of these data, it can be concluded that M10 is not mutagenic *in vivo* and that it is less toxic than the parent. Hence, the use of the parent ADI in the dietary risk assessment for M10 represents a conservative approach.

For M11 genotoxicity studies examining *in vitro* bacterial mutation, *in vitro* gene mutation in mammalian cells, and *in vivo* micronucleus formation (bone marrow exposure was confirmed due to plasma analysis in an additional study) demonstrated that metabolite M11 is not genotoxic. Peer review proposed to discuss grouping approach.

For M52 genotoxicity studies examining *in vitro* bacterial mutation, *in vitro* gene mutation in mammalian cells, and *in vivo* micronucleus formation (bone marrow exposure was confirmed due to plasma analysis in an additional study) demonstrated that metabolite M52 is not genotoxic. No conclusion regarding developmental toxicity can be drawn, as no data has been generated to address this endpoint for M52.

For M54 genotoxicity studies examining *in vitro* bacterial mutation, *in vitro* gene mutation in mammalian cells, and *in vivo* micronucleus formation (bone marrow exposure was confirmed due to plasma analysis in an additional study) demonstrated that metabolite M54 is not genotoxic. Peer review proposed to discuss grouping approach.

For M55 genotoxicity studies examining *in vitro* bacterial mutation, *in vitro* gene mutation in mammalian cells, *in vivo* unscheduled DNA synthesis, and *in vivo* micronucleus formation (bone marrow exposure was confirmed due to plasma analysis in an additional study) have been investigated. M55 was positive in a bacterial reverse mutation assay and the follow-up *in vivo* Comet assay had an equivocal/positive outcome in the duodenum of male rats. Overall no conclusion regarding the mutagenic potential and hence the genotoxicity of M55 can be drawn and the metabolite is considered as

relevant. Peer review proposed to discuss grouping approach. For M56 genotoxicity studies examining *in vitro* bacterial mutation, *in vitro* gene mutation in mammalian cells, and *in vivo* micronucleus formation (bone marrow exposure was confirmed due to plasma analysis in an additional study) demonstrated that metabolite M56 is not genotoxic. Peer review proposed to discuss grouping approach.

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

Substance classified (Pinoxaden)	<u>Classification of the active substance on the basis of toxicological properties in accordance with the CLP Regulations</u> Hazard pictogram: Signal word: Warning Hazard statements: Acute Tox 4; H332 (Harmful if inhaled) Skin Irrit 2; H315 (Causes skin irritation) Eye Irrit 2; H319 (Causes serious eye irritation) STOT SE 3; H335 (May cause respiratory irritation) Skin Sens 1A; H317 (May cause an allergic skin reaction) Repr Cat 2; H361d (Suspected of damaging the unborn child) <u>Classification of the active substance on the basis of toxicological properties in accordance with the DSD</u> Hazard symbol: **Xn** Indication of danger: Harmful Risk phrases: R20: Harmful by inhalation R36/37/38: Irritating to eyes, respiratory system and skin R43: May cause sensitisation by skin contact. R63: Possible risk of harm to the unborn child Safety phrases: S36/37/39: 'Wear suitable protective clothing, gloves and eye/face protection' S46: 'If swallowed, seek medical advice immediately and show this container or label'

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

Mineralization after 100 days ‡	4.3 – 37.5 % AR after 119 – 120 d, [^{14}C-phenyl]-label (n[11] = 8) 13.8 – 47.6 % after 100 – 120 d, [^{14}C-pyrazole]-label (n = 5) 43.9 % after 100 d, [^{14}C-oxadiazepin]-label (n = 1)
Non-extractable residues after 100 days ‡	32.4 – 63.4 % AR after 119 – 120 d, [^{14}C-phenyl]-label (n = 8) 32.0 – 39.7 % after 100 – 120 d, [^{14}C-pyrazole]-label (n = 5) 36.1 % after 100 d, [^{14}C-oxadiazepin]-label (n = 1)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	NOA 407854 (M2): 10.8 – 89.7 % AR at 1 – 3 d (n = 8) NOA 447204 (M3): 5.4 – 30.6 % AR at 7 – 120 d (n = 8) No other metabolites > 5 % AR

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡

Mineralization after 100 days	0.1 % after 119 d, [^{14}C-phenyl]-label (n = 1)
Non-extractable residues after 100 days	2.2 % after 119 d, [^{14}C-phenyl]-label (n = 1)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	NOA 407854 (M2): 94.4 % AR after 68 d, [^{14}C-phenyl]-label (n = 1)

Soil photolysis ‡

Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	NOA 407854 (M2): 78.7 – 67.4 % at 9 – 24 hours (n = 3) NOA 447204 (M3): 15.3 – 43.2 % at 6 – 14 d (n = 3) SYN 515622: max. 20.4 % AR at 6 d NOA 437397: max. 6.7 %

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

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type	X[12]	pH	t. °C / % MWHC	DT_{50}/DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Gartenacker, Loam/silt loam		7.23	20°C / 40%	0.13/0.44	0.08	12.7	SFO
Gartenacker, Silt loam		7.32	20°C / 40%	0.23/0.76	0.16	5.0	SFO
Plaza, Loamy sand		8.00	25°C / 75% FMC	0.15/0.48	0.21	8.9	SFO
Plaza, Loamy sand		7.70	25°C / 75% FMC	0.23/0.75	0.29	6.6	SFO

[11] n corresponds to the number of soils.
[12] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

Plaza, Loamy sand		7.70	25°C / 75% FMC	0.19/0.62	0.24	4.4	SFO
Birkenheide, Sandy Loam		6.04	20°C / 40%	1.05/3.48	0.70	10.0	SFO
Borstel, Loamy sand		5.10	20°C / 40%	2.30/7.63	-	17.1	SFO
Borstel, Weak loamy sand		6.70	20°C / 40%	0.43/1.43	-	19.2	SFO
Marsillargues, Silty clay loam		7.90	20°C / 40%	0.39/1.31	0.30	4.6	SFO
Marsillargues, Silty loam		7.00	20°C / 40%	0.37/1.21	0.27	12.8	SFO
18 Acres, Sandy clay loam		5.80	20°C / 40%	0.76/2.54	0.81	6.8	SFO
Pappelacker, Sand		6.70	20°C / 40%	0.10/0.33	-	24.4	SFO
Welver-Borgeln, Silt loam		6.70	20°C / 40%	0.24/0.80	-	18.6	SFO
Geometric mean					**0.34**		

FMC: Field moisture capacity (1/3 bar)

NOA 407854 (M2)	Aerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Gartenacker, Loam/silt loam		7.23	20°C / 40%	15.8/54.4	0.8	10.3	11.7	SFO-SFO
Gartenacker, Silt loam		7.32	20°C / 40%	12.3/41.0	0.77	8.4	12.3	SFO-SFO
Plaza, Loamy sand		8.00	25°C / 75% FMC	6.1/20.2	1	8.4	9.6	SFO-SFO
Plaza, Loamy sand		7.70	25°C / 75% FMC	2.4/7.9	1	3.1	8.8	SFO-SFO
Plaza, Loamy sand		7.70	25°C / 75% FMC	3.0/10.0	0.88	3.8	5.9	SFO-SFO
Marsillargues, Silty clay loam		7.90	20°C / 40%	42.2/140.1	0.9	32.9	4.5	SFO-SFO
Marsillargues, Silty loam		7.00	20°C / 40%	57.8/192.1	0.93	41.7	3.5	SFO-SFO
Pappelacker, Sand		6.70	20°C / 40%	53.3/176.9	0.97	53.3	7.6	SFO-SFO
Arithmetic mean					**0.91**			
Geometric mean						**17.1**		

FMC: Field moisture capacity (1/3 bar)

NOA 447204 (M3)	Aerobic conditions Alkaline/neutral soils (parent dosed)							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Plaza, Loamy sand		8.00	25°C / 75% FMC	36.9/122.6	0.25	50.9	16.9	SFO-SFO
Plaza, Loamy sand		7.70	25°C / 75% FMC	50.6/168.0	0.21	64.8	8.6	SFO-SFO
Plaza, Loamy sand		7.70	25°C / 75% FMC	39.6/131.6	0.26	50.7	17.5	SFO-SFO
Marsillargues, Silty clay loam		7.90	20°C / 40%	117.0/388.7	0.38	91.3	12.2	SFO-SFO

Marsillargues, Silty loam		7.00	20°C / 40%	103.4/343.4	0.32	74.6	8.2	SFO-SFO
Arithmetic mean					**0.30**			
Geometric mean						**67.4**		
NOA 447204 (M3)	Aerobic conditions Acidic soils (metabolite dosed)							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Krone, Silt loam		6.01	20 °C, pF2	387.2/1286.3	n.a.	387.2	1.4	HS
18 Acres, Sandy clay loam		6.13	20 °C, pF2	129.7/430.8	n.a.	129.7	3.9	SFO
Borstel, Loamy sand		4.95	20 °C, pF2	179.0/594.6	n.a.	179.0	4.6	SFO
Arithmetic mean					**n.a.**			
Geometric mean						**208**		

n.a. denotes not applicable (metabolite dosed study)

M11	Aerobic conditions							
Soil type	X[1]	pH ($CaCl_2$)	t. °C/% MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Gartenacker Silt loam		7.21	20 °C / pF 2.0	7.7 / 25.5	n.a.	7.7	5.6	SFO
18 Acres Sandy clay loam		5.68	20 °C / pF 2.0	9.6 / 75.1	n.a.	22.6[(a)]	4.3	FOMC
Marsillargues Silty clay loam		7.55	20 °C / pF 2.0	9.3 / 30.8	n.a.	9.3	2.7	SFO
Arithmetic mean					**n.a.**			
Geometric mean						**11.7**		
pH dependence, Yes or No						Not applicable (small dataset)		

n.a. denotes not applicable (metabolite dosed study)
[a] Pseudo SFO-DegT50: FOMC-DegT90 / 3.32

M52	Aerobic conditions							
Soil type	X[1]	pH ($CaCl_2$)	t. °C/% MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Gartenacker Silt loam		7.21	20 °C / pF 2.0	0.7 / 28.1	n.a.	8.4[(a)]	6.2	FOMC
18 Acres Sandy clay loam		6.14	20 °C / pF 2.0	1.1 / 18.7	n.a.	5.6[(a)]	5.9	FOMC
Marsillargues Silty clay loam		7.60	20 °C / pF 2.0	1.0 / 26.3	n.a.	12.6[(b)]	2.5	HS
Arithmetic mean					**n.a.**			

Geometric mean					**8.4**		
pH dependence, Yes or No					Not applicable (small dataset)		

n.a. denotes not applicable (metabolite dosed study)
(a) Pseudo SFO-DegT50: FOMC-DegT90 / 3.32
(b) HS slow phase rate (k_2)

M54	Aerobic conditions							
Soil type	X[1]	pH ($CaCl_2$)	t. °C/% MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Gartenacker Silt loam		7.21	20 °C / pF 2.0	4.9 / 16.4	n.a.	4.9	5.4	SFO
18 Acres Sandy clay loam		5.68	20 °C / pF 2.0	9.3 / 30.9	n.a.	9.3	5.5	SFO
Marsillargues Silty clay loam		7.55	20 °C / pF 2.0	9.3 / 30.9	n.a.	9.3	7.0	SFO
Arithmetic mean					**n.a.**			
Geometric mean						**7.5**		
pH dependence, Yes or No						Not applicable (small dataset)		

n.a. denotes not applicable (metabolite dosed study)

M55	Aerobic conditions							
Soil type	X[1]	pH ($CaCl_2$)	t. °C/% MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Gartenacker Silt loam		7.21	20 °C / pF 2.0	9.6 / 31.9	n.a.	9.6	7.1	SFO
18 Acres Sandy clay loam		6.14	20 °C / pF 2.0	75.4 / 321	n.a.	106[(a)]	1.1	DFOP
Marsillargues Silty clay loam		7.60	20 °C / pF 2.0	5.3 / 17.5	n.a.	5.3	8.6	SFO
Arithmetic mean					**n.a.**			
Geometric mean						**17.5**		
pH dependence, Yes or No						Not applicable (small dataset)		

n.a. denotes not applicable (metabolite dosed study)
(a) DFOP slow phase rate (k_2)

M56	Aerobic conditions							
Soil type	X[1]	pH ($CaCl_2$)	t. °C/% MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Gartenacker Silt loam		7.15	20 °C / pF 2.0	39.1 / 130	n.a.	39.1	7.5	SFO
18 Acres Sandy clay loam		6.08	20 °C / pF 2.0	110 / 366	n.a.	110	4.7	SFO

M56	Aerobic conditions							
Soil type	X[1]	pH ($CaCl_2$)	t. °C/% MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	Chi^2 error (%)	Method of calculation
Marsillargues Silty clay loam		7.52	20 °C / pF 2.0	76.1 / 375	n.a.	129([b])	2.7	HS
Arithmetic mean					**n.a.**			
Geometric mean						**82.2**		
pH dependence, Yes or No						Not applicable (small dataset)		

n.a. denotes not applicable (metabolite dosed study)
(a) HS slow phase rate (k_2)

Field studies ‡

A reliable DT50 could not be established for pinoxaden from field data due to the rapid degradation and too few data points

NOA 407854 (M2) Modelling	Aerobic conditions								
Soil type	Location		pH	Depth (cm)	DT_{50} (d) actual	DT_{90} (d) actual	Chi^2 error (%)	DT_{50} (d) Norm.	Method of calculation
Silt loam	Rignano Scalo, Italy (Tribolet, 2003a)		7.02	-	-	-	11.1	0.85	SFO
Silt loam	Rignana Scalo, Italy (Tribolet, 2003b)		7.1	-	-	-	5.41	2.04	SFO
Silty clay loam	Bagnarola di Budrio, Italy (Tribolet, 2003d)		7.29	-	-	-	10.47	14.8	SFO
Silt loam	Tamarite de litera, Spain (Tribolet, 2003e)		7.30	-	-	-	15.5	2.84	SFO
Loam	Tamarite de litera, Spain (Tribolet, 2003f)		7.54	-	-	-	6.71	0.85	SFO
Loamy sand	Alcala de Guadaria (Tribolet, 2003g		7.59	-	-	-	9.78	7.24	SFO
Clay loam	Rohlstorf, Germany, sub-study 2 (Stolze, 2003a)		7.00	-	-	-	13.0	0.99	SFO
Clay loam	Rohlstorf, Germany, sub-study 4 (Stolze, 2003a)		7.00	-	-	-	2.21	2.37	SFO
Clay loam	Stein, Switzerland (Sandmeier, 2001)		7.18	-	-	-	0.95	1.3	SFO
Geometric mean					-	-		**2.23**	

M3 Modelling	Aerobic conditions Acidic soils								
Soil type	Location		pH $CaCl_2$	Depth (cm)	DT_{50} (d) Norm	DT_{90} (d) Norm	Chi^2 error (%)	DT_{50} (d) Norm.	Method of calculation
Sandy loam	Xinzo de Limia, Spain		4.52	0 - 100	20.5	159	17.3	47.9[(a)]	FOMC

Loamy sand	Bossel, Germany	6.27	0 - 100	88.0	292	23.0	88.0	SFO
Loam	Barry D'Islemade, France	5.43	0 - 100	28.6	94.9	24.3	28.6	SFO
Geometric mean				-	-		**49.4**	

(a) Pseudo DegT50: FOMC-DegT90 / 3.32

pH dependence ‡ (yes / no) (if yes type of dependence)	No
Soil accumulation and plateau concentration ‡	N/A

Laboratory studies ‡

Parent	Anaerobic conditions						
Soil type	X[13]	pH	t. °C/% MWHC	DT_{50}/DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Gartenacker, Loam/silt loam		7.23	20 °C/40 %	0.2/0.6	Not calculated	unknown	SFO

NOA 407854 (M2)	Anaerobic conditions							
Soil type	X[1]	pH	t. °C/% MWHC	DT_{50}/DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Gartenacker, Loam/silt loam		7.23	20 °C/40 %	Stable	-	-	-	-

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Pinoxaden							
Soil Type (USDA)	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Borstel, Sandy loam	1.0	5.1	-	-	1.7	173	0.99
Marsillargues, Silty clay loam	1.4	7.3	-	-	4.4	323	1.025
Gartenacker, Silt loam	2.4	7.2	-	-	2.9	121	1.029
18 Acres, Sandy clay loam	2.5	5.8	-	-	4.6	180	1.054
Plaza, Loamy sand	1.2	7.0	-	-	4.9	403	0.93
Northwood, Loam	3.0	6.4	-	-	13.4	453	1.12
Ephrata, Sand	0.35	6.7	-	-	1.04	299	0.98
Minto, Loam	3.2	7.5	-	-	10.9	337	1.03
Larned, Silty clay loam	1.0	5.6	-	-	8.9	852	1.07
Median						**323**	**1.03**
Geometric mean						**299**	

[13] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

Arithmetic mean			**1.03**
pH dependence, Yes or No	**No**		

NOA 407854 (M2)							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc[b] (mL/g)	1/n
Wisborough Green, Silty clay loam	2.5	4.8	-	-	0.1	4.0	0.99
Borstel,	1.4	4.9	-	-	0 [a]	0 [a]	1 [a]
18 Acres, Sandy clay loam	2.9	5.9	-	-	0.32	11	0.79
Gartenacker,	2.3	7.1	-	-	0 [a]	0 [a]	1 [a]
Marsillargues	0.58	7.8	-	-	0 [a]	0 [a]	1 [a]
Birkenheide, Sandy loam	0.9	6.0	-	-	0.47	51.9	0.96
Plaza, Loamy sand	1.2	7.0	-	-	0.06	5.2	1.019
Northwood, Loam	3.0	6.4	-	-	0.18	6.0	0.976
Ephrata, Sand	0.35	7.0	-	-	0.098	23	1.029
Minto, Loam	3.2	7.5	-	-	0.14	4.2	0.988
Larned, Silty clay loam	1.0	5.6	-	-	0.28	27	0.975
18 Acres, Sandy clay loam	2.9	5.9	-	-	0.49	17	0.90
Wisborough Green, silty clay loam	2.9	4.8	-	-	0.32	11	0.99
Maine, Clay loam	2.6	5.0	-	-	0.14	6	0.96
Pappelacker,	1.14	6.7	-	-	0 [a]	0 [a]	1 [a]
Welver-Borgeln, Silt loam	2.02	6.7	-	-	0.19	10	0.93
Median					**0.18**	**6**	**1**
Geometric mean[(b)]						**7.97**	
Arithmetic mean							**0.97**
pH dependence (yes or no)			**No**				

(Note: [a] it was not possible to calculate a 1/n or adsorption coefficient, since little or no adsorption was observed during the study. For the purposes of calculating a median value for these parameters, a Kf/Kfoc value of zero has been assigned to soils with little or no adsorbance. The median Kfoc of 6 mL/g used in groundwater modelling.)
(b): Following the approach of Habib (2012), the calculated geometric mean value of non-zero values was multiplied with 12/16 to account for the number of soils for which Kf and Kfoc values were reported as 0 mL/g.

NOA 447204 (M3)							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Borstel, Sandy loam	1.0	5.1	-	-	0.38	37.8	1.046
Gartenacker, Silt loam	1.4	7.3	-	-	0.62	26.2	1.028
Marsillargues, Silty clay loam	2.4	7.2	-	-	0.59	43.5	1.070

Plaza, Loamy sand	2.5	5.8	-	-	0.28	23	0.904
Northwood, Loam	1.2	7.0	-	-	0.76	26	0.914
Ephrata, Sand	3.0	6.4	-	-	0.12	35	0.916
Minto, Loam	0.35	6.7	-	-	0.86	26	0.900
Larned, Silty clay loam	3.2	7.5	-	-	0.5	48	0.915
Median					**0.55**	**30.6**	**0.916**
Geometric mean						**32.1**	
Arithmetic mean							**0.96**
pH dependence (yes or no)			**No**				

M11							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Gartenacker, silt loam	1.71	7.13	-	-	0.041[(a)]	2.4[(a)]	0.97
18 Acres, sandy clay loam	3.09	5.96	-	-	0.143[(a)]	4.7[(a)]	0.98
Marsillargues, silty clay loam	0.83	7.55	-	-	0	0	0.99
Geometric mean					**0.061[(b)]**	**2.4[(b)]**	
Arithmetic mean							**0.98**
pH dependence (yes or no)			Not applicable (small dataset)				

(a) Modified sorption parameters: Kf and Kfoc from *indirect* method divided by K_{fE}/K_f ratio as K_{fE}/K_f ratio > 1.3
(b) Arithmetic mean in this case, as geometric mean cannot be calculated if data set includes zero values; according to Habib (2012) the *weighted average geomean* = geomean(2.4;4.7) × 2/3 = 2.2 mL/g (also refer to EFSA, 2018; aged sorption opinion)

M52							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Gartenacker, silt loam	1.96	7.10	-	-	1.06	54.1	0.97
18 Acres, sandy clay loam	2.88	5.58	-	-	2.36	81.9	0.96
Marsillargues, silty clay loam	1.05	7.46	-	-	0.49[(a)]	55.2[(a)]	1.00
Geometric mean					**1.07**	**62.5**	
Arithmetic mean							**0.98**
pH dependence (yes or no)			Not applicable (small dataset)				

(a) Modified sorption parameters: Kf and Kfoc from *indirect* method divided by K_{fE}/K_f ratio as K_{fE}/K_f ratio > 1.3

M54							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Gartenacker, silt loam	1.96	7.10	-	-	0.267	13.6	0.93
18 Acres, sandy clay loam	2.88	5.58	-	-	0.201[(a)]	6.9[(a)]	1.03
Marsillargues, silty clay loam	1.05	7.46	-	-	0.310	29.5	1.00

Geometric mean	**0.255**	**14.1**	
Arithmetic mean			**0.99**
pH dependence (yes or no)	Not applicable (small dataset)		

(a) Modified sorption parameters: Kf and Kfoc from *indirect* method divided by K_{fE}/K_f ratio as K_{fE}/K_f ratio > 1.3

M55							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Gartenacker, silt loam	1.71	7.13	-	-	0.017[(a)]	1.0[(a)]	0.98
18 Acres, sandy clay loam	3.09	5.96	-	-	0.049[(a)]	1.6[(a)]	0.96
Marsillargues, silty clay loam	0.83	7.55	-	-	0.003[(a)]	0.3[(a)]	1.05
Geometric mean					**0.013**	**0.8**	
Arithmetic mean							**1.00**
pH dependence (yes or no)			Not applicable (small dataset)				

(a) Modified sorption parameters: Kf and Kfoc from *indirect* method divided by K_{fE}/K_f ratio as K_{fE}/K_f ratio > 1.3

M56							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Gartenacker, silt loam	2.01	7.01	-	-	0.189	9.4	1.15
18 Acres, sandy clay loam	2.46	6.01	-	-	0.149[(a)]	6.0[(a)]	0.97
Marsillargues, silty clay loam	0.83	7.55	-	-	nc	nc	1.29
Geometric mean						**6.0[(b)]**	
Arithmetic mean							**1.14**
pH dependence (yes or no)			Not applicable (small dataset)				

nc denotes not calculated (inconclusive results with respect to test item mass balance)
(a) Modified sorption parameters: Kf and Kfoc from *indirect* method divided by K_{fE}/K_f ratio as K_{fE}/K_f ratio > 1.3
(b) Worst case in this case, as only two valid results are available

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	For FOCUS gw modelling, values used – to obtian realistic default worst case PEC GW for metabolites M11, M52, M54, M55 and M56 (reported as MX). Modelling using FOCUS model(s), with appropriate FOCUSgw scenarios, according to FOCUS guidance. Model(s) used: FOCUS PELMO v3.3.2, FOCUS PEARL v3.3.3 Scenarios (list of names): Châteaudun, Hamburg, Jokioinen, Kremsmünster, Okehampton, Piacenza, Porto, Sevilla, Thiva Crop: winter cereals Pinoxaden: 0.34 d geomean (lab, normalisation to pF2, 20 °C with Q10 of 2.58; reliable DT50 field could not be established for pinoxaden therefore lab DT50 used) NOA 407854: 2.23 d geomean (field, normalisation to 20 °C with Q10 of 2.58). NOA 447204: 24.2 d geomean (field, normalisation to 20 °C with Q10 of 2.58). Lysimeter metabolites M11, M52, M54, M55 and M56 modelled as Met X using estimated conservative input parameters: Met Xa: high formation fraction (ff = 1), DT50 = 5 days Met Xb: low formation fraction (ff = 0.05), DT50 = 1000 days Met Xc: medium formation fraction (ff = 0.25), DT50 = 200 days K_{OC} (ml/g): parent, 323, $^1/_n$= 1 (median, n = 9) Metabolites: all above information required for each metabolite. NOA 407854: Kf = 0.18 mL/g, 1/n = 0.989 (median) NOA 447204: Koc (ml/g) = 31 (median, n = 8), 1/n = 0.92 (median) Met X: Koc (ml/g) = 0 (worst case assumption), 1/n = 1 (FOCUS default) Dates of application :

	Autumn application	Spring application
Châteaudun	15-Nov	15-Mar
Hamburg	20-Nov	15-Apr
Kremsmünster	25-Nov	15-Apr
Okehampton	05-Nov	15-Apr
	Spring application	
Jokoinen	15-Jun	
Piacenza	15-Mar	
Porto	15-Mar	
Sevilla	15-Mar	
Thiva	15-Mar	

Crop/Interception estimated:
winter cereals, 0 % autumn, 25 % spring

Application rate	Application rate:

N-EU: autumn 45 g as/ha, spring 60 g as/ha, interval 120 d S-EU: spring 60 g as/ha Time of application (month or season): autumn/spring (see above)

Revised ground water modelling with input parameters on basis of Confirmatory Data submitted

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	Model(s) used: FOCUS PEARL v4.4.4 Scenarios (list of names): All relevant ones Substance properties: see Table below
Application rate	Crop: winter cereals, spring cereals Application rate: 1 × 60 g/ha (annually, biennially, triennially) Crop interception: 0 % BBCH stage: 13 (spring application) Application timing:

Crop	Scenario	Application date
Winter cereals (spring application)	Châteaudun	31st January
	Hamburg	15th February
	Jokioinen	31st March
	Kremsmünster	15th February
	Okehampton	31st January
	Piacenza	15th February
	Porto	15th February
	Sevilla	15th January
	Thiva	15th January
Spring cereals	Châteaudun	13th March
	Hamburg	4th April
	Jokioinen	21st May
	Kremsmünster	4th April
	Okehampton	4th April
	Porto	13th March

Substance properties – lower tier assessment based on lab degradation data

Parameter	PXD	M2	M3	M11	M52	M54	M55	M56
Mol mass (g/mol)	400.5	316.4	332.4	362.4	360.3	362.4	376.4	360.4
Water solubility (mg/L)	200 (25 °C)	380000 (25 °C)	370 (25 °C)	1000 (25 °C)	1000 (25 °C)	1000 (25 °C)	1000 (25 °C)	1000 (25 °C)
Vapour pressure (Pa)	0 (25 °C)	0 (25 °C)	0 (25 °C)	0 (25 °C)	0 (25 °C)	0 (25 °C)	0 (25 °C)	0 (25 °C)
DegT50 (d) - lab	0.34	17.1	208 / 67.4	11.7	8.4	7.5	17.5	82.2
K_{foc} (L/kg)	299[a]	7.97[a]	32.1[a]	2.4	62.5	14.1	0.8	6.0
K_{fom} (L/kg)	173	4.63	18.6	1.4	36.3	8.2	0.5	3.5
1/n (-)	1.0[b]	0.99[b]	0.92[b]	0.98	0.98	0.99	1.0	1.14
Plant uptake factor (-)	0	0	0.784[c]	0	0	0	0	0

Formation fraction (-)	na	0.91 (from parent)	0.42[(d)] / 0.30 (from M2)	1.0 / 0.86[(e)] (from M3)	0.26 / 0.11[(e)] (from M2)	1.0 / 1.0[(e)] (from M3)	1.0 / 0.62[(e)] (from M3)	0.70 / 0.22[(e)] (from M3)

Values separated by an '/' refer to acidic and neutral/alkaline soil conditions, respectively
(a): Geomean; approach of Habib (2012) applied in case of M2 to address zeros in the data set
(b): Median; in line with previous assessments
(c): Brigg's equation (experimental log(K_{ow}) = 1.8)
(d): Manually adjusted to cover residues in acidic soils
(e): Manually adjusted to individually cover maximum unknowns in lab degradation studies (5.7 % AR in acidic soils and 2.4 % AR in neutral/alkaline soils)

Substance properties – higher tier assessment for M2 and M3 based on field degradation data for M2 and M3

Parameter	**PXD**	**M2**	**M3**
Mol mass (g/mol)	400.5	316.4	332.4
Water solubility (mg/L)	200 (25 °C)	380000 (25 °C)	370 (25 °C)
Vapour pressure (Pa)	0 (25 °C)	0 (25 °C)	0 (25 °C)
DegT50 (d) - field	0.34	2.23	49.4[(a)]
K_{foc} (L/kg)	299[(b)]	7.97[(b)]	32.1[(b)]
K_{fom} (L/kg)	173	4.63	18.6
1/n (-)	1.0[(c)]	0.99[(c)]	0.92[(c)]
Plant uptake factor (-)	0	0	0.784[(d)]
Formation fraction (-)	na	0.91 (from parent)	0.42[(e)] / 0.30 (from M2)

Values separated by an '/' refer to acidic and neutral/alkaline soil conditions, respectively
(a): Field *DegT50* under acidic conditions (considered to also cover neutral/alkaline soils)
(b): Geomean; approach of Habib (2012) applied in case of M2 to address zeros in the data set
(c): Median; in line with previous assessments
(d): Brigg's equation (experimental log(K_{ow}) = 1.8)
(e): Manually adjusted to cover residues in acidic soils

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1 m)

Annual application

Lower tier assessment (lab degradation data) – acidic soils

PEARL	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	**0.299**	**3.222**	**0.398**	0.030	**0.191**	**0.702**	**2.779**
		Hamburg	< 0.001	**1.009**	**3.002**	**0.632**	**0.113**	**0.233**	**1.083**	**1.923**
		Jokioinen	< 0.001	**0.915**	**2.951**	**1.209**	0.061	**0.299**	**2.213**	**3.960**
		Kremsmünster	< 0.001	**0.627**	**2.569**	**0.309**	0.083	**0.146**	**0.535**	**1.112**
		Okehampton	< 0.001	**1.022**	**2.396**	**0.274**	**0.140**	**0.140**	**0.448**	**0.721**
		Piacenza	< 0.001	**0.408**	**2.499**	**0.293**	0.065	**0.143**	**0.517**	**1.521**
		Porto	< 0.001	**0.405**	**2.133**	**0.339**	0.040	**0.164**	**0.537**	**1.017**
		Sevilla	< 0.001	0.002	**0.730**	**0.188**	< 0.001	0.074	**0.344**	**1.236**
		Thiva	< 0.001	0.087	**3.207**	**0.373**	0.009	**0.190**	**0.650**	**2.628**
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	**0.169**	**2.793**	**0.363**	0.016	**0.168**	**0.638**	**2.170**
		Hamburg	< 0.001	**1.135**	**3.163**	**0.720**	**0.105**	**0.256**	**1.279**	**2.386**
		Jokioinen	< 0.001	**0.975**	**2.981**	**1.010**	0.070	**0.268**	**1.879**	**2.869**
		Kremsmünster	< 0.001	**0.669**	**2.695**	**0.316**	0.087	**0.151**	**0.552**	**1.226**
		Okehampton	< 0.001	**0.665**	**2.302**	**0.297**	0.075	**0.147**	**0.493**	**0.862**
		Porto	< 0.001	**0.117**	**1.529**	**0.274**	0.010	**0.122**	**0.470**	**1.015**

Annual application

Lower tier assessment (lab degradation data) – neutral/alkaline soils

PEARL	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	**0.299**	**0.834**	**0.323**	0.012	**0.174**	**0.429**	**0.856**
		Hamburg	< 0.001	**1.009**	**1.048**	**0.630**	0.048	**0.268**	**0.838**	**0.798**
		Jokioinen	< 0.001	**0.915**	**0.787**	**1.068**	0.025	**0.276**	**1.490**	**1.459**
		Kremsmünster	< 0.001	**0.627**	**0.850**	**0.322**	0.035	**0.168**	**0.419**	**0.431**
		Okehampton	< 0.001	**1.022**	**1.023**	**0.336**	0.059	**0.190**	**0.394**	**0.343**
		Piacenza	< 0.001	**0.408**	**0.680**	**0.221**	0.027	**0.133**	**0.292**	**0.508**
		Porto	< 0.001	**0.405**	**0.621**	**0.319**	0.017	**0.166**	**0.377**	**0.405**
		Sevilla	< 0.001	0.002	0.037	0.077	< 0.001	0.026	**0.116**	**0.355**
		Thiva	< 0.001	0.087	**0.589**	**0.241**	0.004	**0.131**	**0.329**	**0.817**
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	**0.169**	**0.579**	**0.265**	0.007	**0.125**	**0.363**	**0.666**
		Hamburg	< 0.001	**1.135**	**1.066**	**0.769**	0.044	**0.292**	**1.016**	**1.023**
		Jokioinen	< 0.001	**0.975**	**0.862**	**0.973**	0.029	**0.279**	**1.373**	**1.177**
		Kremsmünster	< 0.001	**0.669**	**0.886**	**0.337**	0.036	**0.177**	**0.429**	**0.508**
		Okehampton	< 0.001	**0.665**	**0.876**	**0.348**	0.032	**0.187**	**0.415**	**0.394**
		Porto	< 0.001	**0.117**	**0.388**	**0.227**	0.004	**0.114**	**0.291**	**0.384**

Annual application

Higher tier assessment (field degradation data) – acidic soils

	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
PEARL	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	< 0.001	**0.294**	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.547**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.359**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.413**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	0.003	**0.529**	nc	nc	nc	nc	nc
		Piacenza	< 0.001	0.001	**0.317**	nc	nc	nc	nc	nc
		Porto	< 0.001	0.002	**0.265**	nc	nc	nc	nc	nc
		Sevilla	< 0.001	< 0.001	0.005	nc	nc	nc	nc	nc
		Thiva	< 0.001	< 0.001	**0.114**	nc	nc	nc	nc	nc
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	< 0.001	**0.178**	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.492**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.371**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.411**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	< 0.001	**0.419**	nc	nc	nc	nc	nc
		Porto	< 0.001	< 0.001	**0.151**	nc	nc	nc	nc	nc

Annual application

Higher tier assessment (field degradation data) – neutral/alkaline soils

	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
PEARL	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	< 0.001	**0.199**	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.381**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.246**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.287**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	0.003	**0.366**	nc	nc	nc	nc	nc
		Piacenza	< 0.001	0.001	**0.223**	nc	nc	nc	nc	nc
		Porto	< 0.001	0.002	**0.183**	nc	nc	nc	nc	nc
		Sevilla	< 0.001	< 0.001	0.003	nc	nc	nc	nc	nc
		Thiva	< 0.001	< 0.001	0.077	nc	nc	nc	nc	nc
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	< 0.001	**0.121**	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.339**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.251**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.283**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	< 0.001	**0.292**	nc	nc	nc	nc	nc
		Porto	< 0.001	< 0.001	**0.106**	nc	nc	nc	nc	nc

Biennial application

Lower tier assessment (lab degradation data) – acidic soils

PEARL	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	**0.157**	**1.574**	**0.207**	0.017	0.097	**0.369**	**1.491**
		Hamburg	< 0.001	**0.526**	**1.487**	**0.298**	0.059	**0.118**	**0.511**	**0.924**
		Jokioinen	< 0.001	**0.540**	**1.504**	**0.557**	0.032	**0.155**	**1.045**	**1.631**
		Kremsmünster	< 0.001	**0.368**	**1.304**	**0.162**	0.049	0.076	**0.278**	**0.532**
		Okehampton	< 0.001	**0.441**	**1.089**	**0.135**	0.062	0.065	**0.216**	**0.356**
		Piacenza	< 0.001	**0.220**	**1.232**	**0.138**	0.033	0.069	**0.231**	**0.719**
		Porto	< 0.001	**0.264**	**0.923**	**0.152**	0.022	0.072	**0.234**	**0.415**
		Sevilla	< 0.001	0.004	**0.637**	**0.117**	< 0.001	0.052	**0.198**	**0.678**
		Thiva	< 0.001	0.057	**1.637**	**0.198**	0.005	0.096	**0.349**	**1.567**
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	0.098	**1.413**	**0.190**	0.008	0.087	**0.336**	**1.191**
		Hamburg	< 0.001	**0.578**	**1.590**	**0.336**	0.057	**0.126**	**0.615**	**1.170**
		Jokioinen	< 0.001	**0.488**	**1.469**	**0.478**	0.032	**0.139**	**0.860**	**1.299**
		Kremsmünster	< 0.001	**0.359**	**1.404**	**0.170**	0.041	0.081	**0.293**	**0.585**
		Okehampton	< 0.001	**0.308**	**1.181**	**0.155**	0.039	0.074	**0.243**	**0.395**
		Porto	< 0.001	0.059	**0.805**	**0.137**	0.005	0.065	**0.212**	**0.380**

Biennial application

Lower tier assessment (lab degradation data) – neutral/alkaline soils

PEARL	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	**0.157**	**0.359**	**0.166**	0.007	0.085	**0.220**	**0.446**
		Hamburg	< 0.001	**0.526**	**0.512**	**0.312**	0.025	**0.130**	**0.381**	**0.395**
		Jokioinen	< 0.001	**0.540**	**0.401**	**0.528**	0.013	**0.140**	**0.749**	**0.651**
		Kremsmünster	< 0.001	**0.368**	**0.427**	**0.164**	0.021	0.083	**0.222**	**0.223**
		Okehampton	< 0.001	**0.441**	**0.472**	**0.157**	0.026	0.086	**0.183**	**0.162**
		Piacenza	< 0.001	**0.220**	**0.349**	**0.125**	0.014	0.068	**0.159**	**0.249**
		Porto	< 0.001	**0.264**	**0.308**	**0.132**	0.009	0.068	**0.160**	**0.173**
		Sevilla	< 0.001	0.004	0.045	0.060	< 0.001	0.024	0.077	**0.175**
		Thiva	< 0.001	0.057	**0.301**	**0.128**	0.002	0.067	**0.175**	**0.442**
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	0.098	**0.294**	**0.135**	0.003	0.067	**0.185**	**0.355**
		Hamburg	< 0.001	**0.578**	**0.512**	**0.360**	0.024	**0.143**	**0.496**	**0.511**
		Jokioinen	< 0.001	**0.488**	**0.398**	**0.481**	0.013	**0.147**	**0.639**	**0.526**
		Kremsmünster	< 0.001	**0.359**	**0.451**	**0.181**	0.017	0.091	**0.234**	**0.245**
		Okehampton	< 0.001	**0.308**	**0.441**	**0.168**	0.016	0.090	**0.205**	**0.180**
		Porto	< 0.001	0.059	**0.218**	**0.119**	0.002	0.064	**0.138**	**0.148**

Biennial application

Higher tier assessment (field degradation data) – acidic soils

	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
PEARL	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	< 0.001	**0.117**	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.274**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.167**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.205**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	0.001	**0.282**	nc	nc	nc	nc	nc
		Piacenza	< 0.001	< 0.001	**0.152**	nc	nc	nc	nc	nc
		Porto	< 0.001	0.001	**0.150**	nc	nc	nc	nc	nc
		Sevilla	< 0.001	< 0.001	0.008	nc	nc	nc	nc	nc
		Thiva	< 0.001	< 0.001	0.064	nc	nc	nc	nc	nc
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	< 0.001	0.083	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.245**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.167**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.201**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	< 0.001	**0.214**	nc	nc	nc	nc	nc
		Porto	< 0.001	< 0.001	0.083	nc	nc	nc	nc	nc

Biennial application

Higher tier assessment (field degradation data) – neutral/alkaline soils

	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
PEARL	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	< 0.001	0.080	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.189**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.115**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.142**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	0.001	**0.198**	nc	nc	nc	nc	nc
		Piacenza	< 0.001	< 0.001	**0.106**	nc	nc	nc	nc	nc
		Porto	< 0.001	0.001	**0.105**	nc	nc	nc	nc	nc
		Sevilla	< 0.001	< 0.001	0.005	nc	nc	nc	nc	nc
		Thiva	< 0.001	< 0.001	0.044	nc	nc	nc	nc	nc
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	< 0.001	0.055	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.169**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.114**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.139**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	< 0.001	**0.149**	nc	nc	nc	nc	nc
		Porto	< 0.001	< 0.001	0.058	nc	nc	nc	nc	nc

Triennial application

Lower tier assessment (lab degradation data) – acidic soils

	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
PEARL	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	**0.106**	**1.086**	**0.143**	0.011	0.068	**0.261**	**0.999**
		Hamburg	< 0.001	**0.414**	**0.947**	**0.180**	0.043	0.073	**0.297**	**0.527**
		Jokioinen	< 0.001	**0.338**	**1.061**	**0.333**	0.022	**0.105**	**0.587**	**0.976**
		Kremsmünster	< 0.001	**0.248**	**0.841**	**0.115**	0.036	0.053	**0.215**	**0.463**
		Okehampton	< 0.001	**0.308**	**0.750**	0.084	0.042	0.043	**0.134**	**0.221**
		Piacenza	< 0.001	**0.194**	**0.796**	0.096	0.028	0.049	**0.162**	**0.423**
		Porto	< 0.001	**0.194**	**0.612**	**0.102**	0.015	0.048	**0.167**	**0.330**
		Sevilla	< 0.001	0.001	**0.394**	0.072	< 0.001	0.031	**0.129**	**0.600**
		Thiva	< 0.001	0.044	**1.074**	**0.143**	0.005	0.067	**0.251**	**1.035**
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	0.067	**1.036**	**0.142**	0.006	0.066	**0.243**	**0.766**
		Hamburg	< 0.001	**0.355**	**0.967**	**0.204**	0.037	0.080	**0.345**	**0.673**
		Jokioinen	< 0.001	**0.382**	**1.041**	**0.308**	0.023	0.098	**0.553**	**0.892**
		Kremsmünster	< 0.001	**0.249**	**0.872**	**0.116**	0.032	0.053	**0.226**	**0.507**
		Okehampton	< 0.001	**0.196**	**0.747**	0.099	0.024	0.046	**0.160**	**0.266**
		Porto	< 0.001	0.036	**0.507**	0.088	0.004	0.041	**0.143**	**0.284**

Triennial application

Lower tier assessment (lab degradation data) – neutral/alkaline soils

PEARL	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	**0.106**	**0.256**	**0.124**	0.005	0.062	**0.160**	**0.277**
		Hamburg	< 0.001	**0.414**	**0.358**	**0.195**	0.018	0.090	**0.240**	**0.222**
		Jokioinen	< 0.001	**0.338**	**0.281**	**0.304**	0.009	**0.100**	**0.420**	**0.366**
		Kremsmünster	< 0.001	**0.248**	**0.290**	**0.119**	0.015	0.060	**0.156**	**0.189**
		Okehampton	< 0.001	**0.308**	**0.327**	**0.100**	0.017	0.060	**0.116**	**0.102**
		Piacenza	< 0.001	**0.194**	**0.253**	0.082	0.012	0.047	**0.100**	**0.155**
		Porto	< 0.001	**0.194**	**0.220**	0.092	0.006	0.050	**0.103**	**0.122**
		Sevilla	< 0.001	0.001	0.033	0.024	< 0.001	0.011	0.035	**0.137**
		Thiva	< 0.001	0.044	**0.202**	0.096	0.002	0.048	**0.131**	**0.312**
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	0.067	**0.213**	**0.102**	0.002	0.050	**0.133**	**0.234**
		Hamburg	< 0.001	**0.355**	**0.318**	**0.224**	0.015	0.092	**0.276**	**0.282**
		Jokioinen	< 0.001	**0.382**	**0.281**	**0.294**	0.010	**0.101**	**0.385**	**0.330**
		Kremsmünster	< 0.001	**0.249**	**0.316**	**0.126**	0.013	0.062	**0.167**	**0.206**
		Okehampton	< 0.001	**0.196**	**0.289**	**0.110**	0.010	0.060	**0.134**	**0.120**
		Porto	< 0.001	0.036	**0.142**	0.078	0.002	0.041	0.089	**0.105**

Triennial application

Higher tier assessment (field degradation data) – acidic soils

	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
PEARL	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	< 0.001	0.081	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.216**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.112**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.139**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	0.001	**0.186**	nc	nc	nc	nc	nc
		Piacenza	< 0.001	< 0.001	**0.117**	nc	nc	nc	nc	nc
		Porto	< 0.001	0.001	**0.104**	nc	nc	nc	nc	nc
		Sevilla	< 0.001	< 0.001	0.009	nc	nc	nc	nc	nc
		Thiva	< 0.001	< 0.001	0.039	nc	nc	nc	nc	nc
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	< 0.001	0.059	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.148**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	**0.121**	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	**0.139**	nc	nc	nc	nc	nc
		Okehampton	< 0.001	< 0.001	**0.148**	nc	nc	nc	nc	nc
		Porto	< 0.001	< 0.001	0.052	nc	nc	nc	nc	nc

Triennial application

Higher tier assessment (field degradation data) – neutral/alkaline soils

	Crop & rate (g as/ha)	Scenario	Parent (µg/L)	Metabolite (µg/L)						
				M2	M3	M11	M52	M54	M55	M56
PEARL	Winter cereals, 1 × 60 g/ha (spring application)	Châteaudun	< 0.001	< 0.001	0.055	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.149**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	0.076	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	0.096	nc	nc	nc	nc	nc
		Okehampton	< 0.001	0.001	**0.130**	nc	nc	nc	nc	nc
		Piacenza	< 0.001	< 0.001	0.082	nc	nc	nc	nc	nc
		Porto	< 0.001	0.001	0.072	nc	nc	nc	nc	nc
		Sevilla	< 0.001	< 0.001	0.006	nc	nc	nc	nc	nc
		Thiva	< 0.001	< 0.001	0.026	nc	nc	nc	nc	nc
	Spring cereals 1 × 60 g/ha	Châteaudun	< 0.001	< 0.001	0.040	nc	nc	nc	nc	nc
		Hamburg	< 0.001	< 0.001	**0.103**	nc	nc	nc	nc	nc
		Jokioinen	< 0.001	< 0.001	0.081	nc	nc	nc	nc	nc
		Kremsmünster	< 0.001	< 0.001	0.095	nc	nc	nc	nc	nc
		Okehampton	< 0.001	< 0.001	**0.103**	nc	nc	nc	nc	nc
		Porto	< 0.001	< 0.001	0.036	nc	nc	nc	nc	nc

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology)	Soil: pinoxaden (NOA 407855), NOA 407854 (M2), NOA 447204 (M3) Surface water: pinoxaden (NOA 407855), NOA 407854 (M2), NOA 447204 (M3) Sediment: pinoxaden (NOA 407855), NOA 407854 (M2), NOA 447204 (M3) Groundwater: pinoxaden (NOA 407855), NOA 407854 (M2), NOA 447204 (M3), SYN 504574 (M11)*, SYN 546105 (M52)*, SYN 546106 (M54)*, SYN 546107 (M55)*, SYN 546108 (M56)* Air: pinoxaden (NOA 407855)

* It is noted that the lysimeter metabolites M11, M52, M54, M55 and M56 were only observed above 0.1 µg/L in one lysimeter with autumn application followed by spring application (total annual application rate up to 115 g/ha), but not observed above the trigger in lysimeter studies with spring application (max. 60 g/ha) only (i.e., the revised GAP of this submission). Hence, these metabolites can be considered to be included in the definition of residue for groundwater as a precautionary approach.

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

Soil (indicate location and type of study)	No data submitted – none required
Surface water (indicate location and type of study)	No data submitted – none required
Ground water (indicate location and type of study)	**i) Pan-EU pinoxaden monitoring study** Number of monitoring sites: 70 (France 13, Germany 20, Italy 20, Lithuania 3 and United Kingdom 14) Type of monitoring: Targeted edge-of-field monitoring (newly drilled wells) Assessment area: One target field at each monitoring site Field size: 0.5 – 37.7 ha (median 3.5 ha) Number of sampling wells at each monitoring site: 1 (at 53 sites), 2 – 4 (at 17 sites) Sampling period: 2015 – Q1 2020 (2015 start: Q2 in UK; Q3 in DE, IT, LT; Q4 in FR) Sampling schedule: Quarterly (FR, IT, LT, UK), monthly or bimonthly (DE) Depth to groundwater: 1.1 – 9.4 m (median 2.8 m) Top soil organic carbon: 0.2 – 10.7 % (median 1.2 %) Soil pH ($CaCl_2$): 3.6 – 7.8 (median 6.1) Sand content: 17 – 98 % (median 50 %) Median annual temp.: 6.9 – 14.1 °C (median 10.7 °C) Median annual prec.: 575 – 1056 mm (median 692 mm) Site's mean annual application rate (2011 – 2019): 17 – 130 g/ha (median 45 g/ha); years with no application not accounted for Site's number of years with an application (2011 – 2019): 1 – 6 (median 3) LOQ = 0.025 µg/L (0.05 µg/L from 06/2015 – 01/2016) <u>% samples (out of 1931) with residues > LOQ / > 0.1 µg/L / max. concentration:</u> Pinoxaden: None / None / < LOQ (unreliable results, unstable during chilled storage) M2: 0.2 % / None / 0.064 µg/L M3: 3.9 % / 0.9 % / <u>0.361</u> µg/L M11: 0.6 % / 0.1 % / <u>0.108</u> µg/L M52: 1.8 % / 0.1 % / <u>0.162</u> µg/L M54: 0.3 % / None / 0.051 µg/L M55: 0.4 % / None / 0.068 µg/L (uncorrected) 0.6 % / None / 0.086 µg/L (storage DT50 = 18.2 d) 1.0 % / 0.1 % / <u>0.107</u> µg/L (storage DT50 = 9.2 d) M56: 3.8 % / None / 0.095 µg/L <u>% sites (out of 70) with residues > LOQ / > 0.1 µg/L:</u> M2: 2.9 % / None M3: 20.0 % / 2.9 % M11: 14.3 % / 1.4 % M52: 28.6 % / 2.9 % M54: 7.1 % / None M55: 8.6 % / None (uncorrected)

11.4 % / None (storage DT50 = 18.2 d)
14.3 % / 1.4 % (storage DT50 = 9.2 d)

M56: 14.3 % / None

<u>90th percentile of the site's maximum concentrations (2016 – 2019):</u>

M2: 0.013 µg/L
M3: 0.043 µg/L
M11: 0.035 µg/L
M52: 0.066 µg/L
M54: 0.014 µg/L
M55: 0.019 µg/L (uncorrected)
0.025 µg/L (storage DT50 = 18.2 d)
0.030 µg/L (storage DT50 = 9.2 days)
M56: 0.031 µg/L

ii) German national monitoring programme

Number of monitoring sites: 22

Type of monitoring: National groundwater monitoring (existing wells)

Assessment area: 39.3 ha (= 45° segment within 1 km to monitoring well)

Field size: n.a. (numerous fields in assessment area)

Number of sampling wells per monitoring site: 1

Sampling period: April 2014 – December 2019

Sampling schedule: Quarterly (2014 – 2015), monthly – bimonthly (2016), monthly (2017 onwards)

Depth to groundwater: 1.4 – 10.0 m (median 3.1 m), one spring pond

Top soil OC: 0.8 – 4.4 % (median 1.5 %)

Soil pH ($CaCl_2$): 4.0 – 7.7 (median 6.1)

Sand: 15 – 93 % (median 60 %)

Mean annual temperature: not stated

Mean annual precipitation: not stated

Annual application rate: 58.5 g/ha

% assessment area treated in individual years (2014 – 2018): 0 – 89 % (median 21 %) (location of treated area/fields varying from year to year)

LOQ: 0.05 µg/L

<u>% samples (out of 804) with residues > LOQ / > 0.1 µg/L / max. concentration:</u>

Pinoxaden: None / None / < LOD
M2: None / None / < LOQ
M3: None / None / < LOQ
M11: 0.7 % / None / 0.10 µg/L
M52: None / None / < LOQ
M54: None / None / < LOQ
M55: None / None / < LOQ
M56: None / None / < LOQ

<u>% sites (out of 22) with residues > LOQ / > 0.1 µg/L</u>

Pinoxaden None / None

M2: None / None
M3: None / None
M11: 19.2 % / None
M52: None / None
M54: None / None
M55: None / None
M56: None / None

iii) French national monitoring programme

Number of monitoring sites: 22

Type of monitoring: National groundwater monitoring (existing wells)

Assessment area: 87 – 314 ha (median 184 ha)
(max. 1-km circle around monitoring well)

Field size: n.a. (numerous fields in assessment area)

Number of sampling wells per monitoring site: 1

Sampling period: Q4 2015 – Q4 2019

Sampling schedule: Quarterly

Depth to groundwater: approx. 1.2 – 36.6 m (median 5.3 m)
(7 spring or possible spring sites)

Top soil OC: Not stated

Soil pH ($CaCl_2$): Not stated

Sand: Not stated

Mean annual temperature: Not stated

Median annual precipitation: Not stated

Annual application rate (2016 – 2019): 6 – 67 g/ha (median 47 g/ha)
(on basis of total annual mass applied divided by total hectare treated)

% assessment area treated in individual years (2016 – 2019): 0 – 62 % (median 6 %)
(location of treated area varying from year to year)

LOQ = 0.025 µg/L

<u>% samples (out of 300) with residues > LOQ / > 0.1 µg/L / max. concentration</u>

Pinoxaden None / None / < LOD
M2: 2.3 % / None / 0.037 µg/L
M3: None / None / < LOQ
M11: None / None / < LOQ
M52: None / None / < LOQ
M54: None / None / < LOQ
M55: None / None / < LOQ
M56: None / None / < LOQ

<u>% sites (out of 22) with residues > LOQ / > 0.1 µg/L</u>

Pinoxaden None / None
M2: 18.2 % / None
M3: None / None
M11: None / None
M52: None / None
M54: None / None
M55: None / None

	M56: None / None **iv) Public groundwater monitoring** Estonia: 85 sites, 2017 – 2018, pinoxaden < LOQ (i.e., 0.0048 µg/L), metabolites not analysed Finland: 632 samples, 2011 – 2018, pinoxaden < LOQ (i.e., 0.01 µg/L), metabolites not analysed France: 10,800 samples, 2012 – 2018, pinoxaden < LOQ (i.e., 0.01 – 1 µg/L), metabolites not analysed Netherlands: 160 samples, 2014 – 2015, pinoxaden < LOQ (i.e., 0.01 µg/L), metabolites not analysed
Air (indicate location and type of study)	No data submitted – none required

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

Compartment	
soil	Pinoxaden
water	Pinoxaden, M2
sediment	pinoxaden