CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance fenpicoxamid (XDE-777)

European Food Safety Authority (EFSA),
Maria Arena, Domenica Auteri, Stefania Barmaz, Giulia Bellisai, Alba Brancato, Daniela Brocca, Laszlo Bura, Harry Byers, Arianna Chiusolo, Daniele Court Marques, Federica Crivellente, Chloe De Lentdecker, Marcella De Maglie, Mark Egsmose, Zoltan Erdos, Gabriella Fait, Lucien Ferreira, Marina Goumenou, Luna Greco, Alessio Ippolito, Frederique Istace, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Christopher Lythgo, Jose Oriol Magrans, Paula Medina, Ileana Miron, Tunde Molnar, Alexandre Nougadere, Laura Padovani, Juan Manuel Parra Morte, Ragnor Pedersen, Hermine Reich, Angela Sacchi, Miguel Santos, Rositsa Serafimova, Rachel Sharp, Alois Stanek, Franz Streissl, Juergen Sturma, Csaba Szentes, Jose Tarazona, Andrea Terron, Anne Theobald, Benedicte Vagenende, Alessia Verani and Laura Villamar-Bouza

Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State, the United Kingdom, for the pesticide active substance fenpicoxamid (XDE-777) and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Regulation (EC) No 1107/2009 of the European Parliament and of the Council. The conclusions were reached on the basis of the evaluation of the representative use of fenpicoxamid (XDE-777) as a fungicide on cereals (winter and spring wheat, durum wheat, rye and triticale). MRLs were assessed in rye and wheat (including triticale and spelt). An MRL application for the import tolerance on bananas was also assessed. The reliable endpoints, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: fenpicoxamid (XDE-777), peer review, risk assessment, pesticide, fungicide, maximum residue level

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Correspondence: pesticides.peerreview@efsa.europa.eu

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Summary

Fenpicoxamid (XDE-777) is a new active substance for which, in accordance with Article 7 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council (hereinafter referred to as 'the Regulation'), the rapporteur Member State (RMS), the United Kingdom, received an application from Dow AgroSciences GmbH on 26 January 2015 for approval. In accordance with Article 8(1)(g) of the Regulation, Dow AgroSciences GmbH submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 13 January 2015.

The RMS provided its initial evaluation of the dossier on fenpicoxamid (XDE-777) in the draft assessment report (DAR), which was received by the European Food Safety Authority (EFSA) on 13 October 2016. The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 27 October 2016 by dispatching the DAR for consultation to the Member States and the applicant, Dow AgroSciences GmbH.

Following consideration of the comments received on the DAR, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour, and ecotoxicology.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether fenpicoxamid (XDE-777) can be expected to meet the approval criteria provided for in Article 4 of the Regulation taking into consideration recital (10) of the Regulation and give a reasoned opinion concerning MRL applications, as referred to in Article 10(1) of Regulation (EC) No 396/2005. Furthermore, this conclusion also addresses the assessment required from EFSA under Article 12 of Regulation (EC) No 396/2005, provided the active substance will be approved under Regulation (EC) No 1107/2009 without restrictions affecting the residue assessment.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative use of fenpicoxamid (XDE-777) as a fungicide in cereals (winter and spring wheat, durum wheat, rye and triticale), spring application only, as proposed by the applicant. MRLs were assessed in rye and wheat (including triticale and spelt). Full details of the representative uses and the proposed MRLs can be found in Appendix A of this report.

Data were submitted to conclude that the proposed representative uses of fenpicoxamid result in a sufficient fungicidal efficacy against the target organisms.

A data gap was identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites in the mammalian toxicology area. For fate and behaviour and ecotoxicology areas, a data gap was identified for a search of the scientific peer-reviewed open literature for one metabolite (X12433979).

There were not any data gaps identified in the area of identity, physical and chemical properties and analytical methods.

In the mammalian toxicology area, data gaps were identified in relation to possible phototoxicity within ultraviolet B (UVB) wavelength, the need for genotoxicity and repeated dose toxicity data relevant to consumer exposure for the metabolites X12314005, X12019520, X12264475 and X12335723, the need for data in order to address the toxicological relevance of the impurities present in the technical specification and the lack of mechanistic data related to the observed thyroid effects in order to address possible endocrine disruption of XDE-777. This last data gap leads also to an issue that cannot be finalised. A critical area of concern is identified as the technical specification proposed is not covered by the batches used in the key toxicological studies. A formal data gap was set for the evaluation of the inhalation study.

In the residue area, two data gaps were identified in relation to the peer review of the representative uses, for processing trials and the level of residues fenpicoxamid in bee products. The consumer risk assessment could not be finalised with regard of processed commodities.

As for MRL application, the data were sufficient to derive a MRL on the use in bananas.

For fate and behaviour, a data gap was identified for information on the effect of water treatment processes on the nature of both the active substance and its identified metabolites potentially present in surface water and ground, when surface water or groundwater is abstracted for drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses. Furthermore, further field dissipation studies are required for metabolite

X696476 (data gap). For metabolite X12433979, a data gap was identified for predicted environmental concentration (PEC) in surface water and sediment.

In the area of ecotoxicology, data gaps were identified for further information to address the risk to aquatic organisms for XDE-777 (critical area of concern) and for various sediment and surface water pertinent metabolites. In the absence of an exposure assessment, the risk to aquatic organisms could not be performed for metabolite X12433979 (issue that could not be finalised). In addition, data gaps were identified for a risk assessment and for additional toxicity studies on honeybees. A critical area of concern is identified as the technical specifications proposed are not covered by the batches used in the ecotoxicological studies.

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Background

Regulation (EC) No 1107/2009 of the European Parliament and of the Council[1] (hereinafter referred to as 'the Regulation') lays down, inter alia, the detailed rules as regards the procedure and conditions for approval of active substances. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States and the applicant(s) for comments on the initial evaluation in the draft assessment report (DAR), provided by the rapporteur Member State (RMS), and the organisation of an expert consultation, where appropriate.

In accordance with Article 12 of the Regulation, EFSA is required to adopt a conclusion on whether an active substance can be expected to meet the approval criteria provided for in Article 4 of the Regulation (also taking into consideration recital (10) of the Regulation) within 120 days from the end of the period provided for the submission of written comments, subject to an extension of 30 days where an expert consultation is necessary, and a further extension of up to 150 days where additional information is required to be submitted by the applicant(s) in accordance with Article 12(3).

Fenpicoxamid (XDE-777) is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, the United Kingdom (hereinafter referred to as the 'RMS'), received an application from Dow AgroSciences GmbH on 2 December 2014 for approval of the active substance fenpicoxamid (XDE-777). In accordance with Article 8(1)(g) of the Regulation, Dow AgroSciences GmbH submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[2]. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 13 January 2015.

The RMS provided its initial evaluation of the dossier on fenpicoxamid (XDE-777) in the DAR, which was received by EFSA on 13 October 2016 (United Kingdom, 2016). The co-RMS France was in charge of the identity, physical and chemical properties, analytical methods and residues sections. The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 27 October 2016 by dispatching the DAR for consultation of the Member States and the applicant, Dow AgroSciences GmbH, for consultation and comments. EFSA also provided comments. In addition, EFSA conducted a public consultation on the DAR. The comments received were collated by EFSA and forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 12(3) of the Regulation were considered in a telephone conference between EFSA, the RMS and the co-RMS (France) on 1 March 2017. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour, and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation where this took place, were reported in the final column of the evaluation table.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether fenpicoxamid (XDE-777) can be expected to meet the approval criteria provided for in Article 4 of the Regulation, taking into consideration recital (10) of the Regulation, and give a reasoned opinion concerning MRL applications as referred to in Article 10(1) of Regulation (EC) No 396/2005. A final

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

[2] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

consultation on the conclusions arising from the peer review of the risk assessment and on the proposed MRLs took place with Member States via a written procedure in November 2017.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative use of fenpicoxamid (XDE-777) as a fungicide in cereals (winter and spring wheat, durum wheat, rye and triticale), spring application only, as proposed by the applicant. MRLs were assessed in rye and wheat (including triticale and spelt). A MRL application for the import tolerance on bananas was also addressed. Furthermore, this conclusion also addresses the assessment required from EFSA under Article 12 of Regulation (EC) No 396/2005, provided the active substance will be approved under Regulation (EC) No 1107/2009 without restrictions affecting the residue assessment. In the event of a non-approval of the active substance or an approval with restrictions that have an impact on the residue assessment, the MRL proposals from this conclusion might no longer be relevant and a new assessment under Article 12 of Regulation (EC) No 396/2005 will be required. A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2017), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views where applicable, can be found:

- the comments received on the DAR;
- the reporting table (1 March 2017);
- the evaluation table (12 December 2017);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the DAR including its revisions (United Kingdom, 2017) and the peer review report, both documents are considered as background documents to this conclusion.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Fenpicoxamid (XDE-777) is the provisionally approved ISO common name for (3*S*,6*S*,7*R*,8*R*)-8-benzyl-3-{3-[(isobutyryloxy)methoxy]-4-methoxypyridine-2-carboxamido}-6-methyl-4,9-dioxo-1,5-dioxonan-7-yl isobutyrate (IUPAC).

The representative formulated product for the evaluation was 'GF-2925', a suspension concentrate (SC) containing 130 g/L fenpicoxamid.

The representative uses evaluated were spray applications in spring for the control of *Septoria tritici* leaf blotch in cereals (winter wheat, spring wheat, durum wheat, rye and triticale) in Europe. Full details of the good agricultural practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the representative uses of fenpicoxamid proposed at EU level result in a sufficient fungicidal efficacy against the target organism, following the guidance document SANCO/10054/2013-rev. 3 (European Commission, 2013).

A search of the scientific peer-reviewed open literature on the residue relevant metabolites, dealing with side effects on health, the environment and non-target species and on one metabolite (X12433979) in fate and behaviour and ecotoxicology areas and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

Conclusions of the evaluation

1. Identity, physical/chemical/technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The proposed specification for fenpicoxamid is based on batch data from pilot scale production. The minimum purity of the active substance as manufactured is 750 g/kg. It should be noted that once the industrial scale production has stabilised, the specification and the levels of some impurities might need to be reconsidered. No FAO specification exists for fenpicoxamid.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of fenpicoxamid or the representative formulation. The main data regarding the identity of fenpicoxamid and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation.

Fenpicoxamid residues and also its metabolite X642188 can be monitored in food and feed of plant origin by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with limit of quantifications (LOQs) of 0.01 mg/kg in all plant commodity groups for each analyte. Monitoring residues of fenpicoxamid and metabolite X642188 in milk, meat, liver, fat and poultry egg can be performed using LC–MS/MS with LOQs of 0.01 mg/kg all matrices for both compounds. The residue definition for monitoring in soil and water was defined as fenpicoxamid and its metabolite X642188. Appropriate LC–MS/MS methods exist for monitoring fenpicoxamid and metabolite X642188 in soil and water with LOQs of 0.05 mg/kg and LOQs of 0.05 μg/L, respectively, for both analytes. Fenpicoxamid residues in air can be determined by LC–MS/MS with a LOQ of 1.39 $\mu g/m^3$.

Determination of residues of fenpicoxamid in urine and blood can be done by LC–MS/MS with a LOQ of 0.05 mg/L.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and Guidance on Dermal Absorption (EFSA PPR Panel, 2012).

The toxicological profile of the active substance XDE-777 and its metabolites was discussed at the Pesticides Peer Review Experts' Meeting 162 (session 1).

A number of impurities in the technical specification was reported for XDE-777. The technical specification (based on batch data from pilot scale production) is not supported by the toxicological assessment as a number of impurities either were not present in batches used for key studies or they were not present at sufficient amounts; this was identified as a critical area of concern by EFSA, the RMS did not agree considering that the final production specification is not yet available. The relevance of the impurities reported cannot be assessed due to lack of adequate information regarding their toxicological profile (data gap).

XDE-777 absorption is rapid but not extensive (2–42%). The highest absorption was observed in rabbits (42%) without difference between both sexes, while a difference exists in the mice absorption between males (12%) and females (25%). In the high dose in rats, a considerable lower percentage of absorption was noticed indicating probably saturation. XDE-777 is not extensively distributed and significant amounts were found only in the gastrointestinal tract. Excretion is fast and mainly through faeces. In rats, biliary excretion was also observed. The absorbed XDE-777 in the rat is extensively metabolised via hydrolysis and O-dealkylation. Unchanged parent is observed practically only in faeces. Comparative *in vitro* interspecies metabolism study utilising rat, mouse and human liver microsomes did not reveal human specific metabolites.

Low acute toxicity was observed when XDE-777 was administered by the oral, dermal or inhalation routes. No skin or eye irritation, neither potential for skin sensitisation were attributed to the active substance. XDE-777 did not show phototoxic potential in the OECD 3T3 NRU-PT test. However, the OECD 3T3 NRU-PT test might not be appropriate for UVB absorbers as XDE-777 (data gap).

In the 90-day rat study, no adverse effects were observed leading to a no-observed adverse effect level (NOAEL) of 732 mg/kg body weight (bw) per day (highest dose tested). In the 90-day study in mice, the NOAEL was 39.6 mg/kg bw per day due to increased liver toxicity. In the 90-day study in dogs, adverse effects were not observed leading to NOAEL of 939 mg/kg bw per day (highest tested dose). In contrary, in the 1-year dog study, increased liver toxicity was observed and the NOAEL set at 84 mg/kg bw per day. The genotoxic potential of XDE-777 was fully tested. Although positive results were given by the *in vitro* chromosomal aberration (CA) assay in rat lymphocytes the follow-up *in vivo* micronucleus (MN) test was negative supporting that overall XDE-777 is unlikely to be genotoxic. Thyroid effects were observed in all treatment groups of the 2-year rat study and consequently only a low-observed adverse effect level (LOAEL) at the low dose of 101 mg/kg bw per day can be set. As discussed in the experts' meeting, these effects cannot be attributed definitively to the presence of iodine in the test material and they may be related to endocrine disruption. No carcinogenic potential was observed in this study. For the 18-month study in mice, the NOAEL was set at 5.27 mg/kg bw per day based on the observed liver toxicity. Some increases in the liver adenomas and carcinomas incidences were observed but as being inside the range of the historical control values they were not considered as treatment related or biologically relevant.

In the multigeneration study provided in rat, adverse effects were not observed and the NOAELs for offspring, reproductive and parental toxicity were set at 1,000 mg/kg bw per day (highest dose tested). For development toxicity, two studies were provided, one in rats and one in rabbits. Adverse effects were not observed in rats and the NOAELs for maternal and developmental toxicity were set at 1,036 mg/kg bw per day (highest dose tested). In rabbits, a decrease of the maternal body weight was observed and the maternal NOAEL was set at 177 mg/kg bw per day. Adverse developmental effects were not observed in rabbits and the respective NOAEL was set at 495 mg/kg bw per day (highest dose tested). The neurotoxicity of XDE-777 was studied as part of the 90-day rat study. No related adverse effects were observed and the NOAEL for neurotoxicity was 732 mg/kg bw per day.

XDE-777 has no harmonised classification in accordance with the provisions of Regulation (EC) No 1272/2008[3] and on the basis of the current evaluation there is no proposal. As it is not classified or proposed to be classified as toxic for carcinogenicity and reproduction category 2, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting (ED) properties are not met. However, adverse effects in the thyroid were already observed from the low dose in the 2-year rat study as discussed above and considering the absence of mechanistic data on the mode of action, no clear conclusion can be drawn on the ED properties of XDE-777 and further data are needed (data gap). The issue could not be finalised.

The acceptable daily intake (ADI) is set at 0.05 mg/kg bw per day based on the NOAEL of 5.27 mg/kg bw per day from the 18-month mice study and an uncertainty factor (UF) of 100. The acceptable operator exposure level (AOEL) is set also at 0.05 mg/kg bw per day but based on the NOAEL of 39.6 mg/kg bw per day from the 90-day study in mice, applying an UF of 100 and a correction for the limited oral absorption (12%) in mice. An acute reference dose (ARfD) is set at 1.8 mg/kg bw due to the maternal toxicity observed in the rabbit developmental study (NOAEL of 177 mg/kg bw per day) and applying an UF of 100. The RMS disagreed expressing the view that an ARfD is not needed based on the lack of significant acute effects. Finally, an acute acceptable operator exposure level (AAOEL) is set at 0.2 mg/kg bw (as the ARfD but with a correction for the mice oral absorption of 12%). An inhalation study for the formulation was submitted by the Applicant but not evaluated by the RMS, therefore a formal data gap was set for RMS to evaluate the inhalation study.

The non-dietary exposure (i.e. operator, worker, bystander and resident) was estimated considering dermal absorption values derived from an *in vitro* dermal absorption study on human skin, i.e. 0.2% for the concentrated formulation, 3% for low dilution (1.3 g/L) and 6% for high dilution (0.4 g/L) of the product. In all the cases, operator's, worker's, resident's and bystander's exposure was well below the AOEL.

The metabolites X12314005, X12019520, X12326349, X12264475 and X12335723 are provisionally included in the residue definition for risk assessment in processed commodities (see Section 3) and their toxicological profiles were discussed in the experts meeting PPR 162. No ground water metabolites were identified. X12326349 is a rat metabolite present in urine almost up to 10% and considering the limited absorption and metabolism of the parent, it can be considered as covered by

[3] 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. 1–1355.

the toxicological profile of the parent. For the metabolite X12314005, based on data provided from two quantitative structure–activity relationship (QSAR) models, it can be considered that it is not of concern for genotoxicity. For the metabolites X12019520, X12335723 and X12264475, some positive QSAR alerts were noticed. One of them is for CA and it is the same as for the XDE-777 which is proved to be clastogenic *in vitro* but not *in vivo*. However, this alert cannot be disregarded for the three metabolites as they have considerably smaller size than the parent and different absorption can be assumed. Overall, for X12019520, X12335723 and X12264475, a concern for genotoxicity cannot be excluded and further data are needed (data gap). In addition, data regarding the repeated-dose toxicity, relevant to consumer exposure of the metabolites X12314005, X12019520, X12264475, and X12335723 are not available and a conclusion cannot be drawn (data gap pending on the final conclusion on the residue definition for risk assessment in processed commodities in the residue area, Section 3).

3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of the residue chemistry studies (OECD, 2009), the OECD publication on the MRL calculations (OECD, 2011) the European Commission guideline document on the MRL setting (European Commission, 2011) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Fenpicoxamid was discussed at the Pesticides Peer Review Experts' meeting 164 (September 2017) on residues.

The metabolism was investigated following foliar application in wheat (representative use), tomatoes and cabbage with both labelled phenyl (PH) and pyridine (PY) fenpicoxamid. The parent compound was the major component in all investigated crops, accounting for 38% total radioactive residues (TRRs) (PH labels) in grain, up to 95% in tomatoes fruits and up to 96% of TRRs in cabbage. The metabolite X642188 was found in small amounts, up to 0.08 mg/kg in straw (feeds items) and 0.015 mg/kg in cabbage. In addition, X12314005 metabolite occurs up to 13% TRR in cabbage. Results from field trials on wheat analysed for the parent and X642188 confirmed the metabolic pattern. Based on the metabolism studies, the proposed residue definition for enforcement and risk assessment was parent fenpicoxamid, this residue definition cover all crop groups. The experts discussed also the inclusion of metabolites X642188 and X12314005 in the risk assessment residue definition. X12314005 was considered currently not relevant since there is no use on leafy crops while X642188 is precursor of the parent and the occurrence ratio compared to the parent was very low.

Under hydrolysis condition investigated with (PH)-14C-fenpicoxamid and (PY)-14C-fenpicoxamid, the parent compound degraded under pasteurisation in X12314005 (10% applied radioactivity (AR)) and X12335723 (15% AR), under baking/brewing/boiling, X12019520 (12% AR), X12314005 (47.5% AR) and X12335723 (76.5% AR) while under sterilisation degraded completely in X12019520 (97% AR), X12335723 (65% AR) and X12264475 (17% AR). Therefore, the residue definition for risk assessment in processed commodities was provisionally proposed as parent, X12019520, X12314005, X12335723, X12264475; pending upon the outcome on the new wheat processing residue trials (see data gap on processing wheat trials). Whether quantifiable residues will be found in the processing trials (> 0.01 mg/kg) the toxicity profile of these compounds have to be investigated. For monitoring, for the commodities processed under baking/brewing/boiling, fenpicoxamid is still a good marker to be monitored, while for the sterilisation X12019520 would be more appropriate.

Livestock metabolism studies were investigated for 5 days at dosing level of 21.3 mg/kg bw per day for lactating goats and 7 consecutive days by using [^{14}C-PY] or [^{14}C-PH] labels at max dose of 10.7 mg/kg bw per day in laying hens. Most of the radioactivity was excreted via faeces and urine both, in poultry and in ruminants. In ruminants, the parent compound was not detected in liver and kidney, whilst the metabolite X12326349 occurred at significant proportions in liver (from 10.4% to 13.20% TRR) and in kidney (from 16.8% to 32.7% TRR) for both labellings. In addition, 13495S-3S metabolite (isomer of X696872) was also observed at 11% TRR in kidney (PH labelling only) but in low absolute level (0.004 mg/kg).The feeding study confirmed the metabolic pattern observed in the metabolism studies, where the parent was never detected while X12326349 was detected at the 1N dosing level in liver and kidney. The toxicity of X12326349 is covered by toxicological properties of the parent compound; therefore, the residue definition for risk assessment was derived as X12326349 expressed as parent. The same residue definition was proposed for monitoring. Validated analytical method to monitor X12326349 is available.

In poultry, the parent compound was hardly detected in fat only (5% TRR). The predominant compounds were identified as X12264475 in eggs (14% TRR), X129300 in fat (14% TRR), X11963422 in liver (11.6% TRR), in fat (up to 28.4% TRR) and eggs (32.2% TRR) and X696872 in fat (up to 17% TRR). However, since metabolite X11963422 co-eluted with other compound, the exact amount was not possible to be determined. Therefore, the meeting could not conclude on the relevant compound to be included in the residue definition due to analytical uncertainties regarding the resolution of the major fraction in liver, fat and eggs. In addition, the residue level in the metabolism study conducted at approximately 5N dosing rate was very low; thus, no residue definitions were considered necessary for the representative use. Fish metabolism studies are not necessary since the estimated dietary intake does not exceed 0.1 mg/kg dry matter (DM).

Although wheat, rye and triticale's are considered low attractive to bees for pollen/nectar, their collection cannot be excluded without data. Therefore, the determination of fenpicoxamid residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from wheat, rye and triticale's at blossom have to be provided (data gap).

3.1. Representative use residues

As it regards the representative use in cereals (wheat, rye, triticale), sufficient GAP-compliant residue trials are available for northern Europe (NEU) and southern Europe (SEU) uses. The trials were analysed for residues of fenpicoxamid and X642188 and they are covered by the storage stability and validated analytical method.

To assess the magnitude of fenpicoxamid residues and all degradation products in processed wheat, the available studies were considered not sufficiently representative for the critical situation. Therefore, wheat processing residue trials analysed for parent and the relevant metabolites (X12019520, X12314005, X12335723, X12264475) in all processed commodities that undergo in a heating step, representative of baking conditions (bread) conducted with sufficiently high residue levels in grain is required (data gap).

Since the dietary intakes in ruminant was significant, a lactating cattle feeding study was conducted with fenpicoxamid at three different dose levels. Residues in animal commodities were estimated based on this study and they were used in the consumer risk assessment and for deriving the MRL proposals. No feeding studies were submitted in laying hens, however no residue are expected from the representative use considering the overdosed metabolism study in poultry (approx. 5N rate).

A consumer risk assessment using the EFSA Pesticide Residues Intake model (PRIMo) rev.2, was conducted for the representative use in cereals (wheat, rye, and triticale) and animal matrices. The chronic and acute dietary intakes were all below the ADI and ARfD for all considered European consumer groups, total theoretical maximum daily intake (TMDI) at max 11.9% ADI (DK child) and international estimated short-term intake (IESTI) max 0.5% ARfD, wheat (UK child). The consumer risk assessment should be regard as provisional pending the outcome on processed commodities (see data gap for processed commodities).

Regarding the determination of fenpicoxamid residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from wheat, barley, oats, rye and triticale's at blossom no data were provided (data gap).

3.2. Maximum residue levels

A MRL application for the import tolerance on bananas, for which there is a proof of authorisation (GAP) and MRL setting in the exporting country, was assessed. The trials analysed for XDE-777 and X642188 in unbagged bananas were all compliant with the proposed GAP. These trials covered by storage stability studies and validated analytical method, were sufficient to derive a MRL of 0.15 mg/kg.

The results from peeled banana analysed for XDE-777 residues showing non-quantifiable residues occurs above the LOQ, demonstrates that no further investigation is needed for processed bananas.

The consumer risk assessment related to the intended use was calculated, using the EFSA PRIMo rev.2, for banana and the representative use on wheat, barley, oats, rye and triticale. The total TMDI accounted for 12.3% ADI (DK child) while the IESTI accounted less than 0.1% ARfD (UK infant).

4. Environmental fate and behaviour

XDE-777 was discussed at the Pesticides Peer Review meeting 163 in September 2017.

Only spring application to both winter and spring cereals is supported in the GAP table. Therefore, autumn applications are not included in the present assessment.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, XDE-777 exhibited very low to low persistence, forming the major (> 10% AR) metabolites X696872 (max. 16% AR), X763024 (max. 5.2% AR), X12313581 (max. 10.1% AR), which exhibited low to moderate persistence, metabolites X12264475 (max. 35.4% AR) and X11963422 (max. 10.7% AR), which exhibited very low to low persistence, and metabolite X696476 (max. 43.4% AR), for which no DT_{50} values were derived. Mineralisation of the phenyl and pyridine rings ^{14}C radiolabel to carbon dioxide accounted for 66% AR after 120 days. The formation of unextractable residues (not extracted by acetonitrile/water) accounted for 60.5% AR for the pyridine ring ^{14}C radiolabel and for 25.5% AR for phenyl radiolabel after 120 days. In anaerobic soil incubations, XDE-777 transformation was similar to that under aerobic conditions, forming the same major (> 10% AR) metabolites. Anaerobic conditions were not considered to be of major importance for the representative uses.

In soil photolysis studies, new metabolites were formed at > 10% AR X12314005 (max. 5.4% AR), which exhibited very low persistence and metabolites X12019520 (max. 9.8% AR) and X12255349 (max. 6.9% AR), which exhibited low persistence. The contribution of photolytic transformation processes on soil surfaces to the dissipation of XDE-777 from the soil environment is regarded as minor.

XDE-777 exhibited low mobility to immobility. Metabolite X642188 exhibited low mobility to immobility, metabolite X696476 exhibited slight mobility to immobility, and metabolite X12255349 medium soil mobility to immobility. Metabolites X763024 and X12313581 exhibited medium to low soil mobility, metabolite X696872 exhibited medium to slight soil mobility. Metabolite X12264475 exhibited high to low mobility, metabolite X12314005 exhibited high to medium soil mobility. Metabolites X11963422 and X12019520 exhibited very high to medium mobility. It was concluded that the adsorption of XDE-777 and its metabolites was not pH dependent.

In reliable field soil dissipation studies carried out at two sites in France, one in Germany, one in the UK and one in Spain (spray application to the soil surface on bare soil plots in spring), XDE-777 exhibited low to moderate persistence. Sample analyses were carried out also for major (> 10% AR) metabolites X642188, which exhibited low to medium persistence, X12264475, which exhibited moderate to medium persistence, X696476, which exhibited high to very high persistence, and X12313581, which exhibited medium persistence. For metabolite X696476, degradation endpoints were available only for two fields, therefore a data gap was set for further field dissipation studies (see Section 7). Field study DT_{50} values were accepted as being reasonable estimates of degradation and were normalised to FOCUS reference conditions (20°C and pF2 soil moisture) using the time step normalisation procedure in accordance with FOCUS (2006) kinetics guidance.

In laboratory incubations in dark aerobic natural sediment water systems, XDE-777 exhibited very low to low persistence, forming the major metabolites X642188 (max. 8.9% AR in water and 10.6% AR in sediment, exhibiting low persistence based on the available data), X12335723 (max. 45.9% AR in water, exhibiting low persistence), X11963422 (max. 40.2% AR in water and 7.7% AR in sediment, exhibiting moderate persistence), X12314005 (max. 31.8% AR in water and 3.3% AR in sediment, exhibiting very low persistence), X12264475 (max. 25.8% AR in water and 46.9% AR in sediment, exhibiting moderate persistence), X12313581 (max. 9.3% AR in sediment, exhibiting very high persistence), X696476 (max. 67.1% AR in sediment, exhibiting very high persistence). The unextractable sediment fraction for both the phenyl and pyridine ring ^{14}C radiolabel accounted for 15.8–18% AR at study end (106 days). Mineralisation of these radiolabels accounted for 59.3–65.9% AR at the end of the study. The rate of decline of XDE-777 in a laboratory sterile aqueous photolysis experiment was similar to that occurred in the aerobic sediment water incubations. Irradiation of phenyl- and pyridine-labelled XDE-777 in sterile natural water resulted in formation of the major photodegradation products (> 10% AR) X12019520 (max. 69.3% AR), X12314005 (max. 61.6% AR), X12433979 (max. 16.2% AR), MW 312 (X12446477) (max. 12.5% AR) and X12335723 (max. 77.0% AR).

The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites X696872, X12264475, X763024, X12313581, X696476, X11963422, X12314005, X12019520, X12335723 and X12446477 using the FOCUS (2001) step 1 and step 2 approach (version 2.1 of the Steps 1–2 in FOCUS calculator). For metabolite X12433979, no PEC in surface water and sediment were available; therefore, a data gap was set (see Section 7). For the active substance XDE-777 and metabolites

X642188 and X12255349, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available. The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 57–91% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% erosion runoff by 95%) being implemented for the run-off scenarios. However, risk managers and others may wish to note that while run-off mitigation is included in the step 4 calculations available, the FOCUS (2007) report acknowledges that for substances with K_{Foc} < 2,000 mL/g (i.e. X12255349), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (2009) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3 for the active substance XDE-777 and metabolites X642188, X696872, X12264475, X763024, X12313581, X696476, X11963422, X12314005, X12019520 and X12255349. The potential for groundwater exposure from the representative uses by XDE-777 above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

The applicant did not provide appropriate information to address the effect of water treatments processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013).

Some aspects of the risk assessment of XDE-777 were discussed at the Pesticide Peer Review meeting 165.

The applicant submitted further information to address the compliance of the batches used in the ecotoxicological studies with the technical specifications. It is however noted that the additional information from the applicant was not fully evaluated by the RMS (data gap and critical area of concern). The RMS disagreed with this assessment.

A low acute and long-term risk to **birds** and **mammals** for XDE-777 was concluded for all the representative uses and exposure routes. A low risk via dietary exposure to XDE-777 plant metabolites was concluded for all the representative uses for both birds and mammals. The secondary poisoning assessment was triggered for XDE-777 and its surface water and soil metabolites X642188 and X12255349. It is noted that due to the short half-life in water of metabolite X642188, the exposure to fish-eating birds was considered unlikely; therefore, a low risk was concluded. In the case of XDE-777 and metabolite X12255349, a low risk was concluded too. A low risk to earthworm-eating birds and mammals was concluded for both metabolites for all the representative uses.

Valid acute and chronic endpoints on **aquatic organisms** were available. A detailed assessment of the validity criteria was not provided for the studies on algae, therefore data gap was formally identified. However, it is noted that the validity criteria according to the latest version of the OECD 201 are reported as being met and that the risk assessment is not driven by the algae. At tier 1 level, a high acute risk to fish and aquatic invertebrates was concluded for all representative uses of XDE-777 while a low chronic risk to fish (when mitigation measures are considered) and algae was concluded. A valid chronic study on aquatic invertebrates was not available; however, at the Pesticide Peer Review meeting 165 considering the difficulties to test the active substance and the availability of higher tier study, further test was not considered necessary by the experts. It is however noted that from the available information it cannot be excluded that the active substance is not more chronically toxic to aquatic organisms when formulated (data gap). The species sensitivity distribution (SSD) proposed by the applicant to refine the acute risk assessment for fish was discussed at the Pesticide Peer Review meeting 165. Considering that this additional refinement was not reported in details in the RAR and due to concerns raised during the meeting, the experts deemed this refinement questionable. The acute risk to fish was therefore refined by using the geomean approach. By using this refinement, a high risk was still concluded for 4/9 FOCUS scenarios (data gap). The risk assessment for aquatic

invertebrates was further refined by using the ETO-RAC derived from an available mesocosm study and agreed upon by the experts at the Pesticide Peer Review meeting 165. By using this refinement, a low risk to aquatic invertebrates was concluded for the FOCUS scenarios D4, D5, R1 and R4 while a high risk was concluded for the remaining scenarios (D1, D2, D3, D6 and R3) (data gap).

The risk assessment for the pertinent surface water metabolites was performed considering the available experimental data and the estimated endpoints (ECOSAR predictions). Where experimental data were lacking and the estimated endpoints were not sufficiently reliable, a screening assessment was performed by EFSA. A high risk to aquatic organisms could not be excluded for metabolite X642188, X12019520 and X12446477 (data gap) while for the remaining metabolites (X12255349, X696872, X12264475, X763024, X12313581, X696476, X11963422, X12314005, X12019520, X12335723) a low risk was concluded. In the absence of an exposure assessment, the risk to aquatic organisms could not be performed for metabolite X12433979 (data gap).

Further information is needed to address the risk of the pertinent sediment metabolites to sediment dwellers (data gap). The sediment dwellers risk assessment for the parent was considered covered by the available mesocosm study.

In the case of honey**bees**, acute (oral and contact) toxicity data were available for the active substance and the formulation. A chronic toxicity study and a semi-field study on the effects on brood development were available. In the semi-field study, some effects were observed. However, both the chronic and the brood development study were performed with a formulation different from the representative formulation and with a lower content of active substance. In addition, in the study with larvae repellency was noted, therefore, their use in the risk assessment is considered questionable (data gap). It is noted that the RMS disagree with the data gap for the chronic toxicity study. It is further noted that a standard toxicity study addressing the effects on bee larvae was not available (data gap). A risk assessment in line with EFSA (2013) was not performed; therefore, a data gap has been identified. No assessment was available for sublethal effects, e.g. effects on hypopharyngeal gland (data gap). A suitable assessment for accumulative effects was not available. Information regarding metabolites occurring in pollen and nectar was not available (data gap). No data were available for **bumblebees** and **solitary bees**.

A low risk to **non-target arthropods** was concluded for all the representative uses of XDE-777.

A low risk to **earthworms, soil macroorganisms** and **soil microorganisms** was concluded for XDE-777 and its pertinent soil metabolites. It is noted that a high risk to *Hypoaspis aculeifer* for the formulated product 'GF-2925' was concluded this issue should be further addressed at Member State level.

A low risk was concluded for **non-target terrestrial plants** and **biological methods of sewage treatment**.

The ecotoxicological data were not sufficient to address the potential endocrine activity of XDE-777 in non-target organisms. Pending on the outcome of the data gap in Section 2, further data may be necessary to address the potential endocrine disrupting properties of XDE-777 for non-target organisms. As reported in Section 2, adverse effects in thyroid already from the low dose were observed in the available 2-year rat study, pending on the mechanisms at the basis of these effects further consideration for wild mammals might be needed.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
XDE-777	Very low to low persistence biphasic kinetics DT_{50} 0.8–1.9 days (DT_{90} 8.3–33.1 days, 20°C MWHC 57.6–80.3) European field dissipation studies low to moderate persistence single first-order and biphasic kinetics DT_{50} 3.1–14.7 days	Low risk
X642188	European field dissipation studies low to medium persistence single first-order DT_{50} 5.8–67.2 days	Low risk
X696872	Low to moderate persistence biphasic kinetics DT_{50} 5.5–18.9 days (DT_{90} 24.3–197 days, 20°C MWHC 57.6–80.3)	Low risk
X12264475	Very low to low persistence biphasic kinetics DT_{50} 0.6–1.9 days (DT_{90} 4.4–12.4 days, 20°C MWHC 57.6–80.3) European field dissipation studies moderate to medium persistence single first-order DT_{50} 18.0–98.1 days	Low risk
X763024	Low to moderate persistence single first order and biphasic kinetics DT_{50} 5.6–21.6 days (DT_{90} 52.1–144 days, 20°C MWHC 57.6–80.3)	Low risk
X12313581	Low to moderate persistence biphasic kinetics DT_{50} 8.9–23.7 days (DT_{90} 42.2–111 days, 20°C MWHC 57.6–80.3) European field dissipation studies medium persistence single first-order DT_{50} 92.2 days	Low risk
X696476	No valid European field dissipation studies high to very high persistence single first-order DT_{50} 246–5,260 days	Low risk
X11963422	Very low to low persistence single first order and biphasic kinetics DT_{50} 0.12–4.9 days (DT_{90} 1.5–16.5 days, 20°C MWHC 57.6–80.3)	Low risk
X12314005	Very low persistence biphasic kinetics DT_{50} 0.004–0.1 days (DT_{90} 0.07–0.63 days, 20°C 50% MWHC)	Low risk
X12019520	Low persistence single first-order DT_{50} 1.8–4.9 days (DT_{90} 5.9–21.0 days, 20°C 50% MWHC)	Low risk
X12255349	Low persistence single first-order DT_{50} 1.3–4.4 days (DT_{90} 7.5–16.9 days, 20°C 50% MWHC)	Low risk

DT_{50}: period required for 50% dissipation; DT90: period required for 90% dissipation; MWHC: maximum water-holding capacity.

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
XDE-777	Low mobility to immobile K_{Foc} 936–63,394 mL/g	No	Yes	Yes
X642188	Low mobility to immobile K_{Foc} 1,626–33,614 mL/g	No	Yes	No data – No data required
X696872	Medium to slight mobility K_{Foc} 266–2,869 mL/g	No	No data	No (covered by the parent)

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
X12264475	High to low mobility K_{Foc} 138–737 mL/g	No	No data	QSAR gave alerts – No data required
X763024	Medium to low mobility K_{Foc} 159–885 mL/g	No	No data	No data – No data required
X12313581	Medium to low mobility K_{Foc} 360–1,775 mL/g	No	No data	No data – No data required
X696476	Slight mobility to immobile K_{Foc} 3,884–26,044 mL/g	No	No data	No data – No data required
X11963422	Very high to medium mobility K_{Foc} 29.3–218 mL/g	No	No data	QSAR gave no alerts – No data required
X12314005	High to medium mobility K_{Foc} 58–452 mL/g	No	No data	QSAR gave no alerts – No data required
X12019520	Very high to medium mobility K_{Foc} 32–301 mL/g	No	No data	QSAR gave alerts – No data required
X12255349	Medium mobility to immobile K_{Foc} 168–19,725 mL/g	No	No data	No (covered by the parent)

K_{Foc}: Freundlich organic carbon adsorption coefficient; QSAR: quantitative structure–activity relationship.
(a): At least one FOCUS scenario or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
XDE-777	High risk to surface water organisms, low risk to sediment dwellers
X642188 (soil, water and sediment)	Data gap (surface water and sediment)
X696872 (soil)	Low risk to surface water organisms
X12264475 (soil, water and sediment)	Low risk to surface water organisms, data gap for sediment dwellers
X763024 (soil)	Low risk to surface water organisms
X12313581 (soil, water and sediment)	Low risk to surface water organisms, data gap for sediment dwellers
X696476 (soil, water and sediment)	Low risk to surface water organisms, data gap for sediment dwellers
X11963422 (soil, water and sediment)	Low risk to surface water organisms, data gap for sediment dwellers
X12314005 (soil, water and sediment)	Low risk to surface water organisms, data gap for sediment dwellers
X12019520 (soil, water and sediment)	High risk to surface water organisms, data gap for sediment dwellers

Compound (name and/or code)	Ecotoxicology
X12255349 (soil)	Low risk to surface water organisms
X12335723 (water and sediment)	Low risk to surface water organisms, data gap for sediment dwellers
X12446477 (MW 312) (aqueous photolysis)	High risk to surface water organisms
X12433979 (aqueous photolysis)	Data gap

Table 4: Air

Compound (name and/or code)	Toxicology
XDE-777	Rat LC_{50} inhalation > 0.53 mg/L air per 4 h (nose only) (highest attainable respirable concentration)

LC_{50}: lethal concentration, median.

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of the Regulation concerning information on potentially harmful effects).

7.1. Data gaps identified for the representative uses evaluated

- A search of the scientific peer-reviewed open literature on the residue relevant metabolites, dealing with side effects on health, the environment and non-target species and on one metabolite (X12433979) in fate and behaviour and ecotoxicology areas and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011; relevant for all representative uses evaluated; submission date proposed by the applicant unknown; see Sections 2, 4 and 5).
- Data for the phototoxicity evaluation in the area of UVB wavelength – it is noted that no validated test method is currently available to satisfy this data gap (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; study submitted by the applicant: unknown; see Section 2).
- Acute toxicity study by inhalation performed with the representative formulation (relevant for all representative uses evaluated; study submitted by the applicant, but not evaluated in the DAR; see Section 2).
- Genotoxicity data for the metabolites X12019520, X12264475, and X12335723 and, pending on the conclusion on the residue definition for processed commodities in the residue area, repeated-dose toxicity relevant for performing a consumer risk assessment for X12314005, X12019520, X12264475, and X12335723 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Data to address the toxicological relevance of the impurities present in the technical specification (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Mechanistic data related to the observed thyroid effects in order to address possible endocrine disruption (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Wheat processing residue trials for all processed commodities that undergoes in a heating step, representative of baking conditions (bread) conducted with sufficiently high residue levels in grain to allow determination of the magnitude of relevant identified metabolites X12019520, X12314005, X12335723, X12264475 (relevant for representative uses in wheat; submission date proposed by the applicant; see Section 3).
- Potential residue levels in pollen and bee products (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Additional field dissipation studies for metabolite X696476 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Information on the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface and groundwater, when surface water or groundwater are abstracted for drinking water, were not sufficient in order to assess the consumer risk from the consumption of drinking water (relevant for all representative uses evaluated, submission date proposed by the applicant: unknown; see Section 4).
- PEC in surface water and sediment and a risk assessment for aquatic organisms for metabolite X12433979 (relevant for all representative uses evaluated, submission date proposed by the applicant: unknown; see Sections 4 and 5).
- A detailed assessment of the validity criteria for the studies on algae (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

- Further information to address the toxicity of the active substance when formulated with particular refer to aquatic invertebrates (chronic toxicity) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address to risk to aquatic organisms, in particular fish and aquatic invertebrates for XDE-777 and metabolites X642188, X12019520 and X12446477 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to sediment dwellers for the metabolites X642188, X12264475, X12313581, X696476, X11963422, X12314005, X12019520 and X12335723 (relevant for all representative uses evaluated; submission date proposed by the applicant unknown; see Section 5).
- Further information to address the chronic effects (larvae and adult) and the sublethal effects e.g. effects on hypopharyngeal gland to honeybee (relevant for all representative uses evaluated; submission date proposed by the applicant unknown; see Section 5).
- A risk assessment for honeybees for XDE-777 and its metabolites in line with EFSA (2013) (relevant for all representative uses evaluated; submission date proposed by the applicant unknown; see Section 5).
- A detailed assessment of the analysis of the compliance of the batches used in the ecotoxicological studies with the technical specification provided by the applicant (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

8. Particular conditions proposed to be taken into account to manage

Measures (up to 40 m buffer zones; corresponding to $\leq$ 95% drift reduction) are needed to mitigate the risk to aquatic organisms for scenarios D4, D5, R1 and R4. The risk could not be mitigated for the remaining scenarios.

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of the Regulation and as set out in Commission Regulation (EU) No 546/2011[4] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of the Regulation.

1) The interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met for XDE-777. However, considering the effects observed in the available studies, the endocrine disrupting potential of XDE-777 cannot be ruled out and further clarification is needed using mechanistic data (see Sections 2 and 5).
2) The consumer risk assessment could not be finalised with regard of processed commodities considering the provisional residue definition for risk assessment and insufficient data on the magnitude of hydrolysis metabolites in processed commodities (see Section 3).
3) The consumer risk assessment from the consumption of water could not be finalised, whilst satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).
4) The risk assessment for aquatic organisms for metabolite X12433979 could not be finalised (see Section 4 and 5).

[4] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of the Regulation and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at the higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of the Regulation.

5) The technical specification proposed is not covered by the batches used in the key (eco)toxicological studies (see Sections 2 and 5).
6) A high risk to aquatic organisms (invertebrates) was concluded for XDE-777 (see Section 5).

9.3. Overview of the concerns identified for each representative use considered

All columns are grey, as the technical material specification proposed was not comparable to the material used in the testing that was used to derive the (eco)toxicological reference values (Table 5).

Table 5: Overview of concerns

Representative use		Cereals (NEU, CEU, SEU)
Operator risk	Risk identified	
	Assessment not finalised	
Worker risk	Risk identified	
	Assessment not finalised	
Resident/bystander risk	Risk identified	
	Assessment not finalised	
Consumer risk	Risk identified	
	Assessment not finalised	X[2,3]
Risk to wild non-target terrestrial vertebrates	Risk identified	
	Assessment not finalised	
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	
	Assessment not finalised	
Risk to aquatic organisms	Risk identified	X[6]
	Assessment not finalised	X[4]
Groundwater exposure to active substance	Legal parametric value breached	
	Assessment not finalised	
Groundwater exposure to metabolites	Legal parametric value breached	
	Parametric value of 10 µg/L[(a)] breached	
	Assessment not finalised	

NEU: northern Europe; CEU: central Europe; SEU: southern Europe.
Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.
(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).

References

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Abbreviations

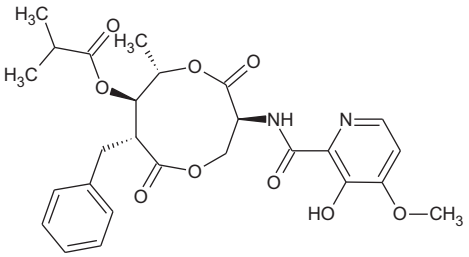
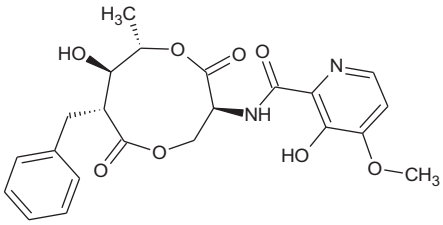
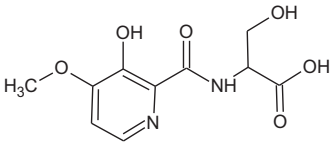
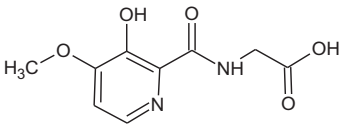
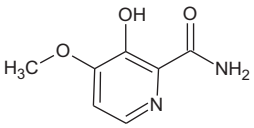
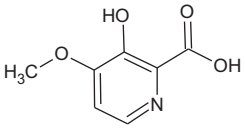
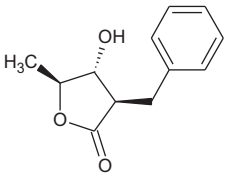
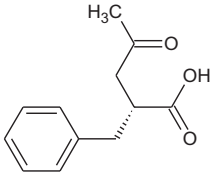
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
CA	chromosomal Aberration
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
ED	endocrine disrupting
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
M/L	mixing and loading
MN	micronucleus
MRL	maximum residue level
MWHC	maximum water-holding capacity
NEU	northern Europe
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
QSAR	quantitative structure–activity relationship
RMS	rapporteur Member State
SC	suspension concentrate

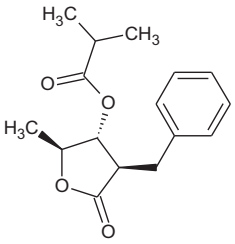
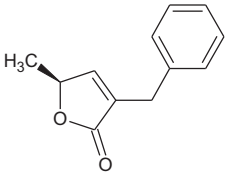
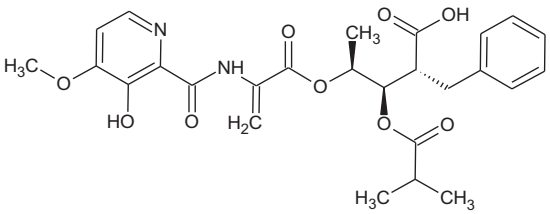
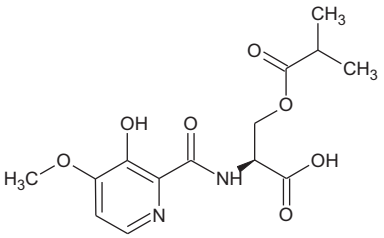
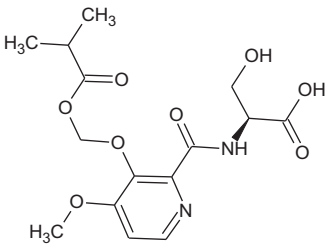
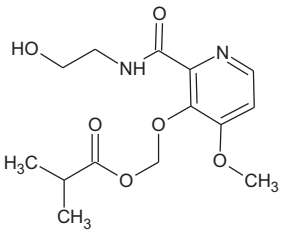
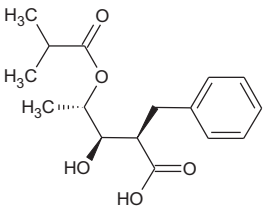
SEU	southern Europe
SMILES	simplified molecular-input line-entry system
SSD	species sensitivity distribution
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
WHO	World Health Organization

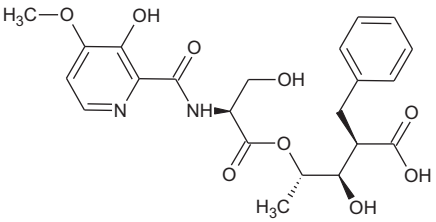
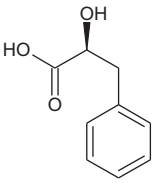
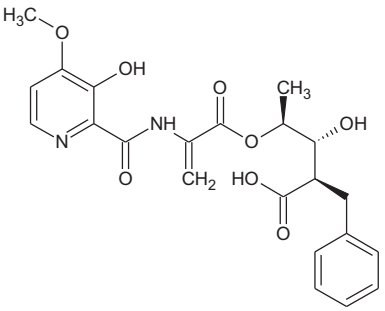
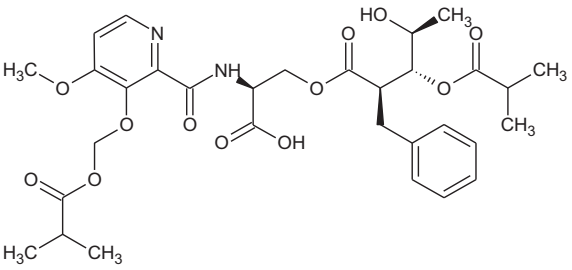
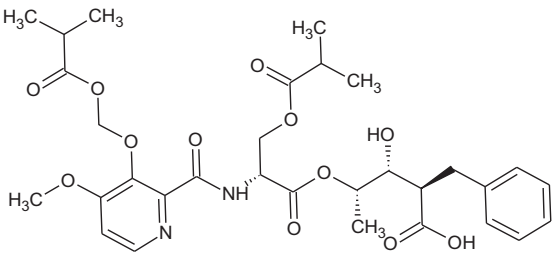
Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5146

Appendix B – Used compound codes

Code/trivial name[(a)]	Chemical name/SMILES notation	Structural formula
X642188	(3*S*,6*S*,7*R*,8*R*)-8-benzyl-3-[(3-hydroxy-4-methoxypyridine-2-carboxamido]-6-methyl-4,9-dioxo-1,5-dioxonan-7-yl isobutyrate Oc1c(OC)ccnc1C(=O)N[C@H]3COC(=O)[C@H](Cc2ccccc2)[C@@H](OC(=O)C(C)C)[C@H](C)OC3=O	
X696872	*N*-[(3*S*,7*R*,8*R*,9*S*)-7-benzyl-8-hydroxy-9-methyl-2,6-dioxo-1,5-dioxonan-3-yl]-3-hydroxy-4-methoxypyridine-2-carboxamide Oc1c(OC)ccnc1C(=O)N[C@H]3COC(=O)[C@H](Cc2ccccc2)[C@@H](O)[C@H](C)OC3=O	
X12264475	*N*-(3-hydroxy-4-methoxypyridine-2-carbonyl)-DL-serine Oc1c(ccnc1C(=O)NC(CO)C(=O)O)OC	
X763024	*N*-(3-hydroxy-4-methoxypyridine-2-carbonyl)glycine Oc1c(ccnc1C(=O)NCC(=O)O)OC	
X12313581	3-hydroxy-4-methoxypyridine-2-carboxamide Oc1c(ccnc1C(=O)N)OC	
X696476	3-hydroxy-4-methoxypyridine-2-carboxylic acid Oc1c(ccnc1C(O)=O)OC	
X11963422	(3*R*,4*R*,5*S*)-3-benzyl-4-hydroxy-5-methyldihydrofuran-2(3*H*)-one O[C@@H]2[C@@H](Cc1ccccc1)C(=O)O[C@H]2C	
MW=206.2 (open ring isomer of X11963422)	(2*R*)-2-benzyl-4-oxopentanoic acid O=C(O)[C@@H](CC(C)=O)Cc1ccccc1	

Code/trivial name[a]	Chemical name/SMILES notation	Structural formula
X12314005	(2*S*,3*R*,4*R*)-4-benzyl-2-methyl-5-oxotetrahydrofuran-3-yl 2-methylpropanoate O=C(O[C@@H]2[C@@H](Cc1ccccc1)C(=O)O[C@H]2C)C(C)C	
X12019520	(5*S*)-3-benzyl-5-methylfuran-2(5*H*)-one C[C@H]2C=C(Cc1ccccc1)C(=O)O2	
X12255349	2-benzyl-2,5-dideoxy-4-*O*-{2-[(3-hydroxy-4-methoxypyridine-2-carbonyl)amino]acryloyl}-3-*O*-(2-methylpropanoyl)-L-arabinonic acid Oc2c(ccnc2C(=O)NC(=C)C(=O)O[C@@H](C)[C@H](OC(=O)C(C)C)[C@@H](Cc1ccccc1)C(=O)O)OC	
X12386481	*N*-(3-hydroxy-4-methoxypyridine-2-carbonyl)-*O*-(2-methylpropanoyl)-L-serine Oc1c(ccnc1C(=O)N[C@@H](COC(=O)C(C)C)C(=O)O)OC	
X12335723	*N*-(4-methoxy-3-{[(2-methylpropanoyl)oxy]methoxy}pyridine-2-carbonyl)-L-serine O=C(N[C@@H](CO)C(=O)O)c1nccc(OC)c1OCOC(=O)C(C)C	
X12446477 (MW 312)	({2-[(2-hydroxyethyl)carbamoyl]-4-methoxypyridin-3-yl}oxy)methyl 2-methylpropanoate O=C(NCCO)c1nccc(OC)c1OCOC(=O)C(C)C	
X12433979	2-benzyl-2,5-dideoxy-4-*O*-(2-methylpropanoyl)-L-arabinonic acid CC(C)C(=O)O[C@@H](C)[C@H](O)[C@@H](Cc1ccccc1)C(=O)O	

Code/trivial name[(a)]	Chemical name/SMILES notation	Structural formula
X12326349	2-benzyl-2,5-dideoxy-4-*O*-[*N*-(3-hydroxy-4-methoxypyridine-2-carbonyl)-L-seryl]-L-arabinonic acid Oc2c(ccnc2C(=O)N[C@@H](CO)C(=O)O[C@@H](C)[C@H](O)[C@@H](Cc1ccccc1)C(=O)O)OC	
X129300 (MW=166.17)	(2*S*)-2-hydroxy-3-phenylpropanoic acid O[C@@H](Cc1ccccc1)C(=O)O	
13495S-3S metabolite (isomer of X696872)	2-benzyl-2,5-dideoxy-4-*O*-{2-[(3-hydroxy-4-methoxypyridine-2-carbonyl)amino]acryloyl}-L-arabinonic acid Oc2c(ccnc2C(=O)NC(=C)C(=O)O[C@@H](C)[C@H](O)[C@@H](Cc1ccccc1)C(=O)O)OC	
MW 632	(2*S*)-3-({(2*R*,3*R*,4*S*)-2-benzyl-4-hydroxy-3-[(2-methylpropanoyl)oxy]pentanoyl}oxy)-2-[(4-methoxy-3-{[(2-methylpropanoyl)oxy]methoxy}pyridine-2-carbonyl)amino]propanoic acid O=C(N[C@@H](COC(=O)[C@H](Cc1ccccc1)[C@@H](OC(=O)C(C)C)[C@H](C)O)C(=O)O)c2nccc(OC)c2OCOC(=O)C(C)C 2-benzyl-2,5-dideoxy-4-*O*-[*N*-(4-methoxy-3-{[(2-methylpropanoyl)oxy]methoxy}pyridine-2-carbonyl)-*O*-(2-methylpropanoyl)-D-seryl]-L-arabinonic acid O=C(N[C@H](COC(=O)C(C)C)C(=O)O[C@@H](C)[C@H](O)[C@@H](Cc1ccccc1)C(=O)O)c2nccc(OC)c2OCOC(=O)C(C)C	 or 

SMILES: simplified molecular-input line-entry system.
(a): The metabolite name in bold is the name used in the conclusion.