Peer review of the pesticide risk assessment of the active substance florpyrauxifen (variant assessed florpyrauxifen-benzyl)

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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, Italy, for the pesticide active substance florpyrauxifen-benzyl 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 florpyrauxifen-benzyl as an herbicide on rice. The reliable endpoints, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

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Keywords: florpyrauxifen, florpyrauxifen-benzyl, peer review, risk assessment, pesticide, herbicide

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Summary

Florpyrauxifen-benzyl 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), Italy, received an application from Dow AgroSciences on 24 March 2016 for approval. 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 17 June 2016.

The RMS provided its initial evaluation of the dossier on florpyrauxifen-benzyl in the draft assessment report (DAR), which was received by the European Food Safety Authority (EFSA) on 28 April 2017. The peer review was initiated on 5 July 2017 by dispatching the DAR for consultation to the Member States and the applicant, Dow AgroSciences.

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 and residues.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether the florpyrauxifen variant assessed, florpyrauxifen-benzyl, can be expected to meet the approval criteria provided for in Article 4 of the Regulation taking into consideration recital (10) of the Regulation. 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 florpyrauxifen-benzyl as a herbicide on rice, as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the uses of florpyrauxifen-benzyl according to the representative uses proposed result in a sufficient herbicidal efficacy against target weeds.

Data gaps were not identified in the section on identity, physical-chemical properties and analytical methods.

Regarding the mammalian toxicology area, a data gap was identified to address a potential endocrine-mediated mode of action in relation to mammary gland tumours observed in male rats. The assessment of the endocrine-disrupting potential of florpyrauxifen benzyl could not be finalised.

In the residue area, two data gaps were identified, one related to the magnitude of residues in pollen and bee products and the other for fish metabolism studies. With regard to the consumer risk assessment, although provisional pending the final decision on the residue definition for plants, a significant consumer intake is not expected and the consumer risk is expected to be low as the theoretical maximum daily intake (TMDI) calculated is less than 0.01% of the acceptable daily intake (ADI).

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at the European Union (EU) level for the representative uses, though a data gap was identified because values for the substance properties used to calculate predicted environmental concentration (PEC) surface water for benzyl alcohol (X195023) and benzoic acid (X194873) were supported by information from secondary literature or primary literature that was not included in the dossier and therefore these PEC values are uncertain. While a potential for groundwater exposure above the parametric drinking water limit of 0.1 µg/L by metabolite X11966341 was indicated, sufficient toxicological information was provided to indicate that X11966341 would not be considered a relevant groundwater metabolite for the situation assessed where the calculated groundwater concentrations were < 0.75 µg/L and quantifiable residues of X11966341 in human food matrices are not expected.

In the ecotoxicology area, a low risk was concluded for all non-target groups, but, mitigation measures are needed to demonstrate a low risk to aquatic and terrestrial non-target plants.
Table of contents

Abstract................................................................................................................................................... 1
Summary................................................................................................................................................. 3
Background ............................................................................................................................................. 5
The active substance and the formulated product....................................................................................... 6
Conclusions of the evaluation.................................................................................................................... 6
1. Identity, physical/chemical/technical properties and methods of analysis ............................................... 6
2. Mammalian toxicity............................................................................................................................ 7
3. Residues........................................................................................................................................... 9
4. Environmental fate and behaviour ...................................................................................................... 10
5. Ecotoxicology.................................................................................................................................... 11
6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)......................................................................... 13
7. Data gaps......................................................................................................................................... 15
7.1. Data gaps identified for the representative uses evaluated ............................................................. 15
8. Particular conditions proposed to be taken into account to manage the risk(s) identified .................... 15
9. Concerns .......................................................................................................................................... 15
9.1. Issues that could not be finalised .................................................................................................. 15
9.2. Critical areas of concern .............................................................................................................. 16
9.3. Overview of the concerns identified for each representative use considered .................................. 16
References ............................................................................................................................................... 17
Abbreviations ........................................................................................................................................... 18
Appendix A – List of end points for the active substance and the representative formulation ................. 19
Appendix B – Used compound codes .................................................................................................. 20
Background

Regulation (EC) No 1107/2009 of the European Parliament and of the Council\(^1\) (hereinafter referred to as ‘the Regulation’) lays down, \textit{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 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 in accordance with Article 12(3).

The florpyrauxifen variant assessed florpyrauxifen-benzyl is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, Italy (hereinafter referred to as the ‘RMS’), received an application from Dow AgroSciences on 24 March 2016 for approval of the active substance florpyrauxifen-benzyl. 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 28 April 2017.

The RMS provided its initial evaluation of the dossier on florpyrauxifen-benzyl in the DAR, which was received by EFSA on 28 April 2017 (Italy, 2017). The peer review was initiated on 5 July 2017 by dispatching the DAR for consultation of the Member States and the applicant, Dow AgroSciences, 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 and the RMS on 17 October 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 and residues.

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 at least one variant of florpyrauxifen can be expected to meet the approval criteria provided for in Article 4 of the Regulation, (noting that the dossier only contained information aimed to satisfy the requirements for the single variant florpyrauxifen-benzyl), taking into consideration recital (10) of the Regulation. A final consultation on the conclusions arising from the peer review of the risk assessment place with Member States via a written procedure in June 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 florpyrauxifen-benzyl as an herbicide on rice as proposed by the applicant. 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, from this conclusion might no longer be relevant and a new assessment under Article 12 of Regulation (EC)

\(^1\) 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.
No 396/2005 will be required. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2018), 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 (17 October 2017);
- the evaluation table (27 June 2018);
- 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 (Italy, 2018) 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

Florpyrauxifen-benzyl is the modified ISO common name for benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (IUPAC). This substance is a derivative of florpyrauxifen, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid (IUPAC).

The representative formulated product for the evaluation was 'GF-3206', an emulsifiable concentrate (EC) containing 25 g/L florpyrauxifen-benzyl.

The representative uses evaluated were foliar spray applications in rice to control a range of annual weeds. 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 uses of florpyrauxifen-benzyl according to the representative uses proposed result in a sufficient herbicidal efficacy against the target weeds following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

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), SANCO/825/00-rev. 8.1 (European Commission, 2010).

Florpyrauxifen-benzyl is produced as a technical material with a minimum purity of 920 g/kg. The proposed specification is based on batch data from pilot plant production. Toluene was considered to be a relevant impurity with the maximum amount of 3 g/kg. An FAO specification is not available.

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 florpyrauxifen-benzyl or the representative formulation. The main data regarding the identity of florpyrauxifen-benzyl and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the determination of the active substance and toluene in the technical material and in the representative formulation.

Florpyrauxifen-benzyl residues in food and feed of plant origin can be determined by high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) methods and also by the quick, easy, cheap, effective and safe (QuEChERS) multiresidue method using HPLC-MS/MS with limit of quantifications (LOQs) of 0.01 mg/kg in all commodity groups. Adequate HPLC-MS/MS methods and the QuEChERS multiresidue method are available for the determination of the florpyrauxifen-benzyl residues in food and feed of animal origin with LOQs of 0.01 mg/kg in all matrices.
The residue definition for monitoring in soil was defined as florypyrauxifen-benzyl and its metabolite florypyrauxifen (X11438848). Appropriate HPLC–MS/MS method exists for monitoring the compounds of the residue definition with LOQs of 6.5 ng/kg for florypyrauxifen-benzyl and 12 ng/kg for florypyrauxifen. Florpyrauxifen-benzyl and florypyrauxifen can be monitored in surface water and ground water by the HPLC–MS/MS method with LOQs of 0.0025 and 0.05 μg/L, respectively.

Florypyrauxifen-benzyl residues in air can be determined by HPLC–MS/MS with a LOQ of 150 μg/m³.

HPLC–MS/MS methods exist for the determination of florypyrauxifen-benzyl and its metabolite florypyrauxifen in body fluids and tissues with LOQs of 0.05 mg/L and 0.01 mg/kg, respectively.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003a), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on Dermal Absorption (EFSA PPR Panel, 2012) and Guidance on the Application of the TTC assessment (including data from open literature, detailed QSAR analysis and TTC assessment) was provided. Toluene is a relevant impurity due to its harmonised classification as suspected of damaging the unborn child. The analytical methods used in the toxicological studies were appropriately validated, except for three studies that were not considered critical since they were not used to set the toxicological reference values (28-day dermal toxicity in rat and developmental toxicity studies in rabbit).

Florpyrauxifen-benzyl was moderately well absorbed with higher absorption at lower doses (36–42% at single or multiple doses of 10 mg/kg body weight [bw]) compared to higher doses (8–9% at a single dose of 300 mg/kg bw) in rats. Excretion occurs primarily via faeces, and urine to a lesser extent, in a biphasic manner, being rapid during the first 2 h after administration; the majority of radioactivity was eliminated within 24 h. The oral absorption relevant for the derivation of the acceptable operator exposure level (AOEL) was set at 25% based on the percentage of administered dose as parent and main metabolite florypyrauxifen (X11438848) recovered in the urine in the 2-year study in rats (at 50 mg/kg bw per day dose level). Florpyrauxifen-benzyl is well metabolised, primarily to a single metabolite, florypyrauxifen (X11438848), therefore, the residue definition for body fluids (plasma and urine) should include the parent and this metabolite (X11438848) for the purpose of human biomonitoring. No unique human metabolites were formed in an in vitro interspecies comparative metabolism study showing consistent metabolic profile across species.

Florpyrauxifen-benzyl showed low acute toxicity via oral and dermal routes (LD₅₀ > 5,000 mg/kg bw) and it exhibited low acute toxicity via inhalation (LC₅₀ > 5.23 mg/L air per 4 h). In the eye irritation study in New Zealand White Rabbits, minimal irritation was observed; there were no corneal effects at any time in any animal. There was no evidence of skin irritation potential. Florpyrauxifen-benzyl demonstrated a weak dermal sensitisation potential (classification as Skin Sens.1B – H317 ‘May cause an allergic skin reaction’ is proposed⁴). Although not required, a phototoxicity study was provided showing negative results.

In short-term dietary studies, the kidneys were the target organs in rats based on renal medullary tubular mineralisation observed in the 90-day study and increase in urinary pH observed in the 28-day study; the RMS did not agree with the conclusion reached by the majority of the experts, considering the kidney findings as non-treatment-related. Reduced body weight gain and ovary weights were observed in the 90-day mouse study with a no observed adverse effect level (NOAEL) of 100 mg/kg bw per day.⁵ Therefore, the relevant short-term NOAEL is 100 mg/kg bw per day from the 90-day study in mice.

Florpyrauxifen-benzyl is unlikely to be genotoxic, since all in vivo and in vitro studies were negative.

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2 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/ECC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.
3 See evaluation table Section 2, data requirement 2.5.
4 It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.
5 Refer to evaluation table Section 2, EFSA response to data requirement 2.1.
The relevant long term NOAEL is 50 mg/kg bw per day from the 2-year study in rats based on an increased incidence of mammary gland tumours observed in males. The RMS did not agree with the conclusion reached by the majority of the experts, considering the mammary gland tumours as non-treatment-related. All experts agreed not to propose classification regarding carcinogenicity, the majority of experts considering that the study presented short-comings, such as lack of investigations leading to a weaker statistical power, uncertainties linked to the study design and the top dose not reaching the maximum tolerated dose.6

Regarding the reproduction, fertility and developmental parameters, no adverse effects were observed either in rats or in rabbits. It was however noted that the highest dose tested in the two-generation reproductive toxicity study should have been higher as the highest dose tested did not attain the limit dose (of 1,000 mg/kg bw per day) and did not exhibit any signs of toxicity. The RMS considered the dose sufficiently high considering that saturation of absorption is seen in toxicokinetic studies at 300 mg/kg bw per day dose level. Regarding the developmental dietary rabbit toxicity study, it was noted that the gavage route is the preferred route of exposure for this kind of study in order to determine a more reliable acute reference dose (ARfD) but overall the majority of the experts considered the study as acceptable.

There was no evidence of neurotoxic effects (based on a functional observational battery included in the 90-day rat toxicity study). Concerning immunotoxicity, florpyrauxifen-benzyl did not exhibit evidence of immunotoxicity at any dose level as it did not result in a treatment-related effect on the primary immune response to sheep red blood cells (SRBC) in male and female rats.

Florpyrauxifen-benzyl is not classified or proposed to be classified as carcinogenic or toxic for reproduction category 2, on this basis, 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. No evidence of endocrine or reproductive toxicity were seen in the whole toxicity data package except for reduced ovary weights in the 90-day mice study and mammary gland tumours in males in the 2-year rat study. A data gap was set to clarify a potential endocrine-mediated mode of action with a minimum of in vitro studies (e.g. oestrogen receptor binding and transduction assay). It is noted that the RMS did not agree with this data gap since it considered the mammary gland tumours as non-treatment-related.

Toxicity studies were provided on the groundwater and plant residue metabolite X11966341; the metabolite is unlikely to be genotoxic, however a potential for aneugenicity was not investigated and its general toxicity profile (in comparison with the parent compound) would be needed to conclude on its toxicological relevance in groundwater were it to be predicted to occur above 0.75 µg/L or should it be expected to be present in plants as a significant residue (neither of which is expected from the representative use assessed, see Sections 3 and 4). The metabolite X11438848 was found to be a major rat metabolite; therefore, the reference values of the parent apply to this metabolite. Regarding metabolite X12300837, despite limitations and out of domain predictions of the QSAR analysis, the metabolite is considered unlikely to be genotoxic, while no conclusion on the genotoxicity profile of metabolite X12131932 could be reached as the QSAR prediction were considered not sufficiently reliable. Taking into consideration the representative use in rice, there is no need for additional toxicological data on any of the metabolites considered.

The acceptable daily intake (ADI) of florpyrauxifen-benzyl is 0.5 mg/kg bw per day based on the 2-year study in the rat (NOAEL of 50 mg/kg bw per day) applying an uncertainty factor (UF) of 100. The AOEL is 0.13 mg/kg bw per day based on the same 2-year study in rats considering an oral absorption of 25% and applying an uncertainty factor (UF) of 100. An ARfD or acute acceptable operator exposure level (AAOEL) were not considered necessary and were not allocated to florpyrauxifen-benzyl.

Based on human skin in vitro dermal absorption study, dermal absorption values for the representative formulation GF-3206 are 0.45% for the concentrate and 11% for the aqueous dilution. To obtain a level of exposure below the AOEL, no personal protective equipment (PPE) is required for operators according to the EFSA calculator (EFSA, 2014). The estimated bystander and residential exposure levels were below the AOEL according to the EFSA calculator and German model.

Regarding the worker, exposure scenarios are not relevant since re-entry is not considered necessary shortly after spraying in paddy fields. However, a conservative assessment predicted low exposure compared to the AOEL for workers wearing adequate clothing (normal workwear) when re-entering crops treated with the representative formulation.

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6 Refer to the Report on the Pesticides Peer Review Meeting 175, experts’ consultation 2.4.
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 maximum residue level (MRL) calculations (OECD, 2011) the European Commission guideline document on the MRL setting (European Commission, 2011).

Florpyrauxifen-benzyl was discussed at the Pesticide Peer Review Experts’ Meeting 176 in April 2018. Metabolism of florpyrauxifen-benzyl was investigated in rice following three scenarios, water injection plant ‘W scenario’ (6.5N), foliar-flooded ‘F scenario’ (2N rate) and dry-seeded foliar application (2N rate) by using $^{14}$C-radiolabelled phenyl, pyridine and benzyl.

The metabolic pathway indicates the cleavage of the molecule between phenyl and pyridine ring yielding X11438848 and X11966341. These compounds and the parent represented the majority of total radioactive residues (TRRs) in all plant fractions accounting together up to 58% of TRRs in immature rice, 60% TRRs in straw and 46% of TRRs in rice hulls. In rice grain, TRRs were low in all three scenarios (up to 0.061 mg/kg) in ‘W scenario’, 0.032 mg/kg ‘F scenario’ and 0.015 mg/kg and ‘D scenario’. Most of the radioactivity remained incorporated in the starch (up to 44% of TRRs) and further identification of metabolites was not possible. Although ‘F’ and ‘D’ scenarios are the most representative for agricultural practices in Europe, all three scenarios were considered for the proposal of the residue definitions since the metabolic picture is similar. From the confined rotational metabolism studies investigated in wheat straw and hay at the target application rate of 4N, the same metabolic pattern was observed as in primary crops, therefore the same residue definitions are applicable. Two rotational field trials conducted with 60 g a.s/ha on leafy, roots, cereals and oilseed crop, covering all plant-back intervals (PBIs) were also submitted. Samples were analysed for the parent, X11438848, X11966341 and detectable residues were not found.

Based on the available metabolism studies in primary and rotational crops, the proposed residue definition for monitoring was florpyrauxifen-benzyl, while for risk assessment was florpyrauxifen-benzyl, X11438848, X11966341 expressed as florpyrauxifen-benzyl limited to cereals only. The expression of risk assessment residue definitions is provisional defined, assuming that X11966341 is covered by the parent toxicity.

Although four out of eight submitted trials were conducted with the last application at growth stages significantly beyond (up to BBCH 69) the latest growth stage indicated in the representative GAP (BBCH 45), they were considered applicable since the level of residue in grain was below LOQ and the level of residues in straw does not impact the livestock dietary burden. The residues were covered by the storage stability, validated analytical method and the MRL of 0.02* mg/kg can be proposed in rice.

Storage stability data demonstrate florpyrauxifen-benzyl residues and its metabolites X11438848, X11966341 in rice grain, straw, hulls, bran, flour are stable for 12 months while in high water, high acid, high starch and high protein commodities for 6 months. In animal commodities, stability of residues was demonstrated for a limited period (see Appendix A).

Regarding the hydrolysis studies, the nature of residues was investigated and it was proven that florpyrauxifen-benzyl is stable under pasteurisation, baking/brewing/boiling condition and it degraded to X11438848 (47% applied radioactivity [AR]) and benzyl alcohol (X195023) 53.5% AR) under sterilisation conditions. Since benzyl alcohol is not a pesticide specific compound and also not of toxicological concern compared to the parent, it was not included the risk assessment residue definition for processed commodities. Thus, the same residue definition as for plant is applicable.

Livestock metabolism studies were investigated in poultry and ruminants for 14 days, respectively, at the dose rate of approximately 11 mg/kg bw. No absorption of the residues occurred, up to 97% of TRRs was eliminated via excretion, and therefore, the total residue level in all animal matrices was very low. X11438848 and X11966341 were the major compounds in ruminants liver and kidney representing up to 45% of TRRs. Considering the low TRRs, the residue definition for monitoring was proposed by default as florpyrauxifen-benzyl while for the risk assessment is set as florpyrauxifen-benzyl, X11966341, X11438848, expressed as florpyrauxifen-benzyl (provisional).

Ruminants feeding studies at four dosing level with animal tissues analysed according to the proposed residue definition for risk assessment were available. Detectable residues of X11966341, X11438848 were found only in the kidney and liver at the first dosing level (approximately 480N), thus no MRL proposals in animal matrices are considered necessary.

A provisional consumer risk assessment has been conducted by using EFSA PRIMo rev.2. and the proposed risk assessment residue definition florpyrauxifen-benzyl, X11438848, X11966341 expressed...
as florypyrauxifen-benzyl. No concerns regarding chronic intake for consumers associated to florypyrauxifen-benzyl is expected since the TMDI accounted for less than 0.01% of the ADI. Acute exposure calculation was not necessary since the compound is not acutely toxic.

Although the consumer risk assessment is provisional since the relative toxicity of X11966341 compared with the parent is not known, no concerns regarding consumer intake is expected due to the low residue level in rice grain, livestock and ground water (see Section 4).

Nevertheless, this assumption is valid only for the current GAP assessed under peer review.

For additional uses (MRL application), the consumer risk assessment has to be revisited by addressing the toxicological profile of the X11966341 and consequently the finalisation of the risk assessment residue definition for plant and animal commodities.

The data requirement for the determination of the residue levels in pollen and bee products for human consumption resulting from residues taken up by honeybees at blossom from rice was not addressed (data gap), the RMS did not support this data gap.

Regarding fish, it should be noted, that the use of the bioconcentration study to support the metabolism study following dietary exposure is not appropriate (data gap).

4. Environmental fate and behaviour

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. Route and rate of degradation of florypyrauxifen-benzyl under aerobic conditions has been investigated in four reliable laboratory experiments in agricultural soils (50% maximum water holder capacity [MWHC]) and in two soils under aerobic flooded conditions. In the studies under flooded conditions, florypyrauxifen-benzyl exhibited moderate persistence. Degradation was slower in two of the soils incubated at 50% MWHC than in the two soil investigations available under flooded conditions; in the other two soils incubated at 50% MWHC the rate of degradation was comparable to the flooded condition incubations.

Metabolites needing further consideration including for potential groundwater contamination were: florypyrauxifen (X11438848, max. 33% AR flooded; 62% 50% MWHC), X12300837 (max. 16% AR flooded) and X11966341 (max. 64% AR flooded; 8% 50% MWHC). At 50% MWHC, the metabolite X12483137 was formed (max. 11% AR). Under aerobic flooded conditions, these metabolites exhibited: low, moderate to medium and medium to very high persistence, respectively. At 50% MWHC, metabolite X12483137 exhibited high to very high persistence. Under flooded conditions mineralisation to CO₂ accounted for 0.3–0.4% AR for the pyridine ring, 2.8–3.6% AR for the phenyl ring but 35–65% AR for the benzyl ring ¹⁴C radiolabels all at the end of the studies (after 122 days). Under these conditions, non-extractable residues accounted for 14–59% AR at study end. In rice paddy field, dissipation studies carried out at two sites in Italy and one in Spain, dissipation rates of florypyrauxifen-benzyl and florypyrauxifen (X11438848) were either comparable to or faster than estimated from the flooded soil laboratory incubations. Florypyrauxifen-benzyl and X12300837 were immobile or exhibited low mobility in soil. Florypyrauxifen (X11438848) and X11966341 exhibited very high to medium mobility.

Degradation and dissipation of florypyrauxifen-benzyl in the aquatic environment was investigated in two water sediment systems. Florypyrauxifen-benzyl exhibits low persistence in both systems forming the transformation products: florypyrauxifen (X11438848, max. 45%, being primarily in the water exhibiting low persistence); X12300837 (max. 23%, being proportionally more in the sediment exhibiting low to moderate persistence); X11966341 (max. 78%, being proportionally more in the water exhibiting moderate to high persistence) and benzoic acid (X194973, max. 21%, being primarily in the water exhibiting low persistence). Mineralisation to CO₂ accounted for 1–4% AR for the pyridine ring, 3–10% AR for the phenyl ring but 67–76% AR for the benzyl ring ¹⁴C radiolabels, all at the end of the studies (after 105 days). Under these conditions, non-extractable residues accounted for 6–42% AR at study end. Under the conditions of sterile laboratory aqueous photolysis studies, florypyrauxifen-benzyl formed the major transformation products X12131932 (max. 28–31% AR); X12393505 (max. 8–10% AR) and benzyl alcohol (X195023, max. 52–82% AR).

MEDRICE (European Commission, 2003b) guidance was used to calculate predicted environmental concentrations (PEC) in surface water and sediment for florypyrauxifen-benzyl, florypyrauxifen (X11438848), X12300837, X11966341, benzyl alcohol (X195023), benzoic acid (X194973) and in just surface water for X12131932 and X12393505 (photolysis transformation products). Note that some substance property information relied on to justify the values used as input to calculate these PEC for benzyl alcohol (X195023) and benzoic acid (X194973), came from secondary literature or primary literature data not included in the dossier and are therefore uncertain. PEC via spray drift alone (to a
1 m deep receiving water body) relevant for the product aquatic risk assessment where PEC were calculated as florpyrauxifen-benzyl equivalents, which incorporated spray drift reduction due to a 10-m no spray buffer combined with 75% drift reduction nozzles were also calculated and used for the aquatic risk assessment. These PEC were used together with endpoints from effects studies where the product had been dosed (see Section 5). This mitigation equated to 92% drift reduction so respects the ceiling on spray drift mitigation of a maximum of 95% mitigation as discussed in EFSA (2013) aquatic risk assessment guidance.

Groundwater exposure of florpyrauxifen-benzyl, florpyrauxifen (X11438848), X12300837 and X11966341 has been assessed using the MEDRICE guidance document (European Commission, 2003b). Calculations were completed considering a maximum annual total dose. Florpyrauxifen-benzyl, florpyrauxifen (X11438848) and X12300837 did not exceed the limit of 0.1 µg/L in the two MEDRICE scenarios. Concentrations of metabolite X11966341 were calculated to be 0.22 and 0.41 µg/L in the MEDRICE clayey and sandy scenarios, respectively. Sufficient information was provided on X11966341 to conclude that it was not toxicologically relevant regarding groundwater for this situation assessed, where the calculated groundwater concentrations were < 0.75 µg/L (see Section 2) and quantifiable residues of X11966341 in human food matrices are not expected (see Section 3).

In relation to the effect of water treatments processes on the nature of the residues present in surface water and groundwater, when surface water or groundwater are extracted for drinking water; satisfactory information was provided that indicated, nitroso compounds are not expected to be formed from florpyrauxifen-benzyl or its metabolites via ozonation or chloramination. Though the potential formation of other chlorinated products was not explicitly addressed by the information submitted, as the compounds being assessed already include chlorine and fluoride in their structure, further chlorination might be considered unlikely.

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).

The acute and chronic dietary risk assessment to birds and mammals was indicated as low for the representative use. Also, the risk from secondary poisoning and via consumption of contaminated water was indicated as low.

Several toxicity studies were available for aquatic organisms with the active substance, the metabolites and the representative formulation. The aquatic plant _Myriophyllum spicatum_ is the most sensitive organism; therefore, the lowest Tier 1 RAC was derived based on the toxicity endpoints from this species. The routes of exposure considered were via spray drift and via outflow from the paddy. The acute Tier 1 risk assessment indicated a low risk from the parent and the metabolites. The chronic Tier 1 risk was demonstrated as low for florpyrauxifen-benzyl when mitigation measures such as spray drift buffer zone of 10 m combined with 75% drift reduction nozzles were applied. The chronic Tier 1 risk assessment for the metabolite florpyrauxifen (X11438848) (exposure via outflow from paddy) was indicated as high; however, the risk was indicated as low with the Tier 2 outflow exposure assessment. The risk for the metabolite benzyl alcohol was indicated as low by applying mitigation measures (e.g. 50% drift reduction nozzles). The risk for the other metabolites was low.

The risk assessment to bees was based on the guidance document on terrestrial ecotoxicology European Commission (2002a) and the guidance document for bees EFSA (2013). The acute oral and contact risk was assessed as low (based on the screening step when using the EFSA guidance document (EFSA, 2013). Data on chronic toxicity on adult and larvae were not provided. On the basis of the available information, the chronic risk was considered likely to be low for representative use. An acute screening assessment from consumption of contaminated paddy water and from guttation water was available and a low risk was indicated. The risk assessment for the metabolites in pollen and nectar was concluded as low.

No data on sublethal effects (e.g. hypopharyngeal glands (HPG) study) was provided. Non information on accumulative toxicity was submitted. No data on bumblebees and solitary bees were provided.

The risk assessment for non-target arthropods was considered as low based on standard and extended laboratory test on _Typhlodromus pyri_, _Aphidius rhopalosiphi_ and _Chrysoperla carnea_.

The risk to soil macro- and microorganisms, organisms in sewage treatment plant was assessed as low.
The risk to **non-target terrestrial plants** was demonstrated as low only when mitigation measures comparable to no-spray buffer zone up to 10 m in combination with 50% of drift reduction nozzle were applied. The risk to metabolites was considered as low based on the lower toxicity compared to the active substance.

In relation to the endocrine properties of florpyrauxfen-benzyl, following the data gap identified in Section 2, further information may be needed to draw a firm conclusion for non-target organisms.
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 |
|-----------------------------|-------------|---------------|
| Florpyrauxifen-benzyl | Moderate persistence; Single first-order and biphasic kinetics DT\(_{50}\) 8–10 days (DT\(_{90}\) 34–104 days, 20°C flooded soil) | Low risk |
| Florpyrauxifen (X11438848) | Low persistence; Single first-order DT\(_{50}\) 7–10 days (20°C flooded soil) | Low risk |
| X12300837 | Moderate to medium persistence; Single first-order DT\(_{50}\) 17–61 days (20°C flooded soil) | Low risk |
| X11966341 | Medium to very high persistence; Single first-order DT\(_{50}\) 66–610 days (20°C flooded soil) | Low risk |
| X12483137 (only in not flooded soil) | High to very high persistence; Single first-order DT\(_{50}\) 146–478 days (20°C 50% MWHC) | Low risk |

DT\(_{50}\): period required for 50% dissipation; DT\(_{90}\): period required for 90% dissipation; MWHC: maximum water-holding capacity.

**Table 2: Groundwater**

| Compound (name and/or code) | Mobility in soil | > 0.1 \(\mu\)g/L at 1 m depth for the representative uses\(^{(a)}\) | Pesticidal activity | Toxicological relevance |
|-----------------------------|------------------|---------------------------------|-------------------|------------------------|
| Florpyrauxifen-benzyl | Low mobility to immobile \(K_{\text{Foc}}\) 15,305–33,500 mL/g | No | Yes | Yes |
| Florpyrauxifen (X11438848) | Very high to medium mobility \(K_{\text{Foc}}\) 30–195 mL/g | No | Assessment not triggered | No, up to stage 3 of step 3; Unlikely to be genotoxic (based on parent data package); reference values of the parent apply to the metabolite |
| X12300837 | Low mobility to immobile \(K_{\text{Foc}}\) 779–17,050 mL/g | No | Assessment not triggered | No, up to stage 3 of step 3; Unlikely to be genotoxic according to QSAR predictions |
| X11966341 | Very high to medium mobility \(K_{\text{Foc}}\) 15–226 mL/g | Yes 0.22 and 0.41 \(\mu\)g/L | No | No, up to stage 3 of step 3; Unlikely to be genotoxic based on complete *in vitro* data package |

\(K_{\text{Foc}}\): 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  |
|-----------------------------|----------------|
| Florpyrauxifen-benzyl        | Low risk       |
| Florpyrauxifen (X11438848)  | Low risk       |
| X12300837                    | Low risk       |
| X11966341                    | Low risk       |
| X12131932 (water only)      | Low risk       |
| X12393505 (water only)      | Low risk       |
| Benzyl alcohol (X195023, water only) | Low risk |
| Benzoic acid (X194973, water only) | Low risk |

### Table 4: Air

| Compound (name and/or code) | Toxicology                                                                 |
|-----------------------------|-----------------------------------------------------------------------------|
| Florpyrauxifen-benzyl        | Rat LC$_{50}$ inhalation $> 5.23$ mg/L air per 4 h (nose only) (no classification required) |

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**

- ED potential has to be addressed with regards to the occurrence of mammary gland tumours observed in males in the 2-year rat study, the underlying mode of action needs to be investigated with at least *in vitro* studies (e.g. oestrogen receptor binding and transduction assay) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- Data on residue levels in pollen and bee products for human consumption resulting from residues taken up by honeybees at blossom from rice have to be provided (relevant for all representative uses evaluated; submission date proposed by the applicant unknown; see Section 3)
- Fish metabolism study is required since the florpyrauxifen-benzyl is fat soluble (\(P_{ow} > 5.5\)) and rice is feed item for fish (relevant for all representative uses evaluated; submission date proposed by the applicant unknown; see Section 3)
- Studies cited as justifying the substance properties used in PEC\(_{sw}\) calculations for metabolites X195023 (benzyl alcohol) and X194873 (benzoic acid) as cited in the evaluation table, or comparable published literature were not available in the applicants dossier. While PEC\(_{sw}\) were appropriately calculated for these two metabolites, the fact that the secondary literature or primary literature not included in the dossier was used to justify the calculations makes them uncertain (relevant for all representative uses evaluated; submission date proposed by the applicant unknown; see Section 4).

8. **Particular conditions proposed to be taken into account to manage the risk(s) identified**

- Mitigation measures are needed to demonstrate a low risk to aquatic and terrestrial non-target plants (see Section 5).

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\(^7\) 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) Florpyrauxifen benzyl is not classified or proposed to be classified as carcinogenic or toxic for reproduction category 2, on this basis, 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 ED properties are not met. No evidence of endocrine or reproductive toxicity were seen in the whole toxicology data package except for reduced ovary weights in the 90-day mice study and mammary gland tumours in males in the 2-year rat study; in addition, it was questioned whether the two-generation reproductive toxicity study was performed with sufficiently high doses allowing to identify a reproductive toxicity hazard.

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\(^7\) 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.
Therefore an endocrine-mediated mode of action could not be ruled out and the endocrine disrupting potential of the active substance could not be finalised (see Section 2).

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 a higher tier level could not be finalised due to lack of information, and if the assessment performed at a 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.

2) None proposed for the representative uses.

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

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then ‘risk identified’ is not indicated in Table 5.)

Table 5: Overview of concerns

| Representative use                                      | Rice                                      |
|--------------------------------------------------------|-------------------------------------------|
| 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                  |
| 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                           |
|                                                        | Assessment not finalised                  |
| Groundwater exposure to active substance                | Legal parametric value breached           |
|                                                        | Assessment not finalised                  |
| Groundwater exposure to metabolites                     | Parametric value of 10 µg/L breached(a)   |
|                                                        | Assessment not finalised                  |

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.
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### Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AAOEL        | Acute acceptable operator exposure level |
| ADI          | Acceptable daily intake |
| AOEL         | Acceptable operator exposure level |
| AR           | Applied radioactivity |
| ARfD         | Acute reference dose |
| bw           | Body weight |
| DAR          | Draft assessment report |
| DT<sub>50</sub> | Period required for 50% dissipation (define method of estimation) |
| DT<sub>90</sub> | Period required for 90% dissipation (define method of estimation) |
| EC           | Emulsifiable concentrate |
| ECHA         | European Chemicals Agency |
| 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 |
| HPG          | Hypopharyngeal glands |
| HPLC-MS/MS   | High performance liquid chromatography with tandem mass spectrometry |
| HQ<sub>contact</sub> | Hazard quotient for contact exposure |
| ISO          | International Organization for Standardization |
| IUPAC        | International Union of Pure and Applied Chemistry |
| K<sub>Foc</sub> | Freundlich organic carbon adsorption coefficient |
| LC<sub>50</sub> | Lethal concentration, median |
| LD<sub>50</sub> | Lethal dose, median; dosis letalis media |
| LOQ          | Limit of quantification |
| MRL          | Maximum residue level |
| MWHC         | Maximum water-holding capacity |
| NOAEL        | No observed adverse effect level |
| OECD         | Organisation for Economic Co-operation and Development |
| PEC          | Predicted environmental concentration |
| PEC<sub>air</sub> | Predicted environmental concentration in air |
| PEC<sub>gw</sub> | Predicted environmental concentration in groundwater |
| PEC<sub>sed</sub> | Predicted environmental concentration in sediment |
| PEC<sub>soil</sub> | Predicted environmental concentration in soil |
| PEC<sub>sw</sub> | Predicted environmental concentration in surface water |
| P<sub>ow</sub> | Partition coefficient between n-octanol and water |
| PPE          | Personal protective equipment |
| QSAR         | Quantitative structure-activity relationship |
| QuEChERS     | Quick, easy, cheap, effective and safe method |
| REACH        | Registration, Evaluation, Authorisation of Chemicals Regulation |
| RMS          | Rapporteur Member State |
| SMILES       | Simplified molecular-input line-entry system |
| SRBC         | Sheep red blood cells |
| TMDI         | Theoretical maximum daily intake |
| TRR          | Total radioactive residue |
| UF           | Uncertainty factor |
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.2018.5378
### Appendix B – Used compound codes

| Code/trivial name(a) | IUPAC name/SMILES notation/InChIKey(h) | Structural formula(c) |
|----------------------|-----------------------------------------|-----------------------|
| florpypaufen-benzyl (XDE-848 BE) | benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate | ![Structural formula](image) |
| | Clc1cc(c2nc(C(=O)Oc3cccc3)c(Cl)c(N)c2F)c(F)c1OC | ![Structure](image) |
| florpypaufen (X11438848) | 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid | ![Structural formula](image) |
| | Clc1c(N)c(F)c(nc1cC(=O)O)c1ccc(Cl)c(O)cc1F | ![Structure](image) |
| X12300837 | benzy 4-amino-3-chloro-6-(4-chloro-3-hydroxy-2-nitrophenyl)-5-fluoropyridine-2-carboxylate | ![Structural formula](image) |
| | O-N(=O)c1cO(cCl)c1ccc1nc(C(=O)Oc2cccc2)c(Cl)c(N)c1F | ![Structure](image) |
| X11966341 | 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxyphenyl)-5-fluoropyridine-2-carboxylic acid | ![Structural formula](image) |
| | Clc1c(N)c(F)c(nc1cC(=O)O)c1ccc(Cl)c(O)cc1F | ![Structure](image) |
| X12483137 | 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-hydroxy-6-nitrophenyl)-5-fluoropyridine-2-carboxylic acid | ![Structural formula](image) |
| | Clc1c(N)c(F)c(nc1cC(=O)O)c1c(F)c(O)c(Cl)c1N(=O)=O | ![Structure](image) |
| X12131932 | benzyl 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate | ![Structural formula](image) |
| | O-C(OC1cccc1c1cc(N)c(F)c(n1)c1ccc(Cl)c(O)cc1F | ![Structure](image) |
| X12393505 | 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid | ![Structural formula](image) |
| | O-C(O)c1cc(N)c(F)c(n1)c1ccc(Cl)c(O)cc1F | ![Structure](image) |
| Code/trivial name<sup>(a)</sup> | IUPAC name/SMILES notation/<br>**InChiKey**<sup>(b)</sup> | Structural formula<sup>(c)</sup> |
|-------------------------------|-------------------------------------------------|---------------------------------|
| benzyl alcohol (X195023)      | phenylmethanol (hydroxymethyl)benzene<br>OCc1ccccc1<br>WVDGDGGMODSV-UHFFFAOYSA-N | ![Structural formula](image) |
| benzoic acid (X194973)        | benzoic acid<br>O=\(\text{C}(\text{O})\)c1ccccc1<br>WPYMKLBDIGXBTP-UHFFFAOYSA-N | ![Structural formula](image) |
| conjugate X12431091           | 4-amino-6-(4-chloro-2-fluoro-3-\(\beta\)-glycosyloxy)phenyl)-5-fluoropyridine-2-carboxylic acid<br>O=\(\text{C}(\text{O})\)c1cc(N)c(F)c(n1)c1ccc(C)c(O[C@@H]2O[C@@H](O)[C@@H](O)[C@@H]2O)c1F<br>XMNPHGKZHQTJ-GGAJMDGNSA-N | ![Structural formula](image) |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system.

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2017.2.1 ACD/Labs 2017 Release (File version N40E41, Build 96719, 6 September 2017).
(c): ACD/ChemSketch 2017.2.1 ACD/Labs 2017 Release (File version C40H41, Build 99535, 14 February 2018).