CONCLUSION ON PESTICIDES PEER REVIEW

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# Peer review of the pesticide risk assessment of the active substance oxathiapiprolin

## European Food Safety Authority (EFSA)

## 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 Ireland for the pesticide active substance oxathiapiprolin and the assessment of applications for maximum residue levels 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 uses of oxathiapiprolin as a fungicide on grapes, potatoes, tomatoes and aubergines. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed.



**Keywords:** oxathiapiprolin, peer review, risk assessment, pesticide, fungicide, maximum residue level

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## Summary

Oxathiapiprolin 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 (hereafter referred to as 'the Regulation'), the rapporteur Member State (RMS), Ireland, received an application from DuPont de Nemours (Deutschland) GmbH on 14 November 2013 for approval. In accordance with Article 8(1)(g) of the Regulation, DuPont de Nemours (Deutschland) 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 15 January 2014.

The RMS provided its initial evaluation of the dossier on oxathiapiprolin in the draft assessment report (DAR), which was received by the European Food Safety Authority (EFSA) on 12 February 2015. The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 15 March 2015 by dispatching the DAR for consultation to the Member States and the applicant, DuPont de Nemours (Deutschland) 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 and environmental fate and behaviour.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether oxathiapiprolin 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 uses of oxathiapiprolin as a fungicide on grapes, potatoes, tomatoes and aubergines, as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

Sufficient evidence of the efficacy of the representative formulation was provided.

A data gap was identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites.

Data gaps were identified for a shelf life study of the representative formulation and also for a physical and chemical compatibility study, as the formulation is recommended for use in tank mixes.

In the field of mammalian toxicology, two data gaps were identified: one for further assessment of the toxicological relevance of the impurities in the technical specification, and one for *in vitro* metabolism data. No area of concern was identified for the representative uses.

The data were sufficient to propose the plant and animal residue definitions as oxathiapiprolin for monitoring and risk assessment. No consumer intake concern was identified for any of the European diets incorporated in the EFSA Pesticide Residues Intake Model (PRIMo). A data gap was identified for the submission of residue trials on wine grape, conducted in compliance with the proposed agricultural practices (GAP). MRLs have been proposed for non-representative uses on cucumber, courgettes and melons.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at the European Union level for representative uses. The potential for groundwater exposure above the parametric drinking water limit of 0.1 μg/L for the metabolite IN-E8S72 was indicated to be high for all of the representative uses. As the consumer risk assessment from drinking water indicated a low risk, IN-E8S72 can be considered non-relevant in the context of the representative uses assessed.

In the area of ecotoxicology, no data gaps or areas of concerns were identified for the representative uses.

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## Background

Regulation (EC) No 1107/2009 of the European Parliament and of the Council[1] (hereafter 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).

Oxathiapiprolin is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, Ireland (hereafter referred to as the 'RMS'), received an application from DuPont de Nemours (Deutschland) GmbH on 14 November 2013 for approval of the active substance oxathiapiprolin. In accordance with Article 8(1)(g) of the Regulation, DuPont de Nemours (Deutschland) 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 15 January 2014.

The RMS provided its initial evaluation of the dossier on oxathiapiprolin in the DAR, which was received by EFSA on 12 February 2015 (Ireland, 2015). The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 15 March 2015 by dispatching the DAR for consultation of the Member States and the applicant, DuPont de Nemours (Deutschland) GmbH. 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 15 July 2015. 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 EFSA should conduct an expert consultation in the areas of mammalian toxicology and environmental fate and behaviour.

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 oxathiapiprolin can be expected to meet the approval criteria provided for in Article 4 of the Regulation, taking into consideration recital (10) of the Regulation. A final 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 May 2016.

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 uses of oxathiapiprolin as a fungicide on grapes, potatoes, tomatoes and aubergines, as proposed by the

[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.

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, 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 is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2016), 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 (15 July 2015);
- the evaluation table (20 May 2016);
- the report(s) 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 (Ireland, 2016) 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

Oxathiapiprolin is the ISO common name 1-(4-{4-[(5*RS*)-5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}-1-piperidyl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone (IUPAC).

The representative formulated product for the evaluation was 'Oxathiapiprolin 100 g/L OD', an oil dispersion (OD) containing 100 g/L oxathiapiprolin.

The representative uses evaluated were applications by spraying against *Plasmopara viticola* in table and wine grapes and against *Phythophthora infestans* in potatoes, tomatoes and aubergines. 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 oxathiapiprolin according to the representative uses proposed at the EU level result in a sufficient fungicidal efficacy against the target organisms, following the guidance document SANCO/10054/2013-rev. 3 (European Commission, 2013).

## 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/10597/2003-rev. 10.1 (European Commission, 2012), SANCO/825/00-rev. 8.1 (European Commission, 2010).

The minimum purity of the active substance as manufactured is 950 g/kg. No FAO specification exists.

The technical material is a racemic mixture. The proposed specification is based on batch data from pilot scale production. It should be noted that the five-batch analysis from full-scale production will need to be reconsidered. 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 oxathiapiprolin or the representative formulation; however, data gaps were identified for a shelf life study of the representative formulation and also for a physical and chemical compatibility study of the formulation, as there were recommendations for use in tank mixes. The main data regarding the identity of oxathiapiprolin and its physical and chemical properties are given in Appendix A.

Adequate analytical methods are available for the determination of oxathiapiprolin in the technical material and in the representative formulation.

Oxathiapiprolin residues can be monitored in food and feed of plant origin by the multi-residue method DFG S19 using LC-MS/MS in dry, high water content and acidic matrices with limits of quantification (LOQs) of 0.01 mg/kg, or by a single HPLC-MS/MS method with LOQs of 0.01 mg/kg for all plant commodity groups. Residues of oxathiapiprolin in food of animal origin can be monitored with the multi-residue method DFG S19 using LC-MS/MS in meat, fat, liver, milk and eggs with LOQs of 0.01 mg/kg or by a single HPLC-MS/MS method with LOQs of 0.01 mg/kg for all animal matrices.

Residues of oxathiapiprolin in soil, water and air can be monitored by LC-MS/MS with LOQs of 1 μg/kg, 0.1 μg/L and 0.05 μg/$m^3$, respectively.

No analytical method is required for the determination of oxathiapiprolin in body fluids and tissues as oxathiapiprolin is not classified as toxic or very toxic.

## 2. Mammalian toxicity

The toxicological profile of the active substance oxathiapiprolin was discussed at the Pesticides Peer Review Experts' Meeting 137 (January 2016).

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), Guidance on Dermal Absorption (EFSA PPR Panel, 2012) and Guidance on the assessment of exposure of operators, workers, residents and bystanders (EFSA, 2014a).

On the basis of the available revised assessment, the levels of impurities proposed in the technical specification can be considered acceptable from a toxicological point of view. Two impurities (methanol and acetate) are considered toxicologically relevant based on their toxicity profile, but the proposed levels are not of concern. The toxicological relevance of the other impurities cannot be concluded on the basis of the available data.

In toxicokinetic studies, a low oral absorption rate was demonstrated for oxathiapiprolin (30%, based on bile-cannulated animals). After expert consultation, it was noted that no data were provided for *in vitro* metabolism data (addressing potentially unique human metabolites) (data gap). Oxathiapiprolin was shown to be of low acute toxicity after oral, dermal or inhalative exposure, not irritant to skin and eyes and not sensitising. A phototoxicity study showed negative results. In short-term dietary studies, the findings were limited to changes in organ weights, clinical chemistry parameters and liver cytochrome P450 isoenzymes. The relevant no observed adverse effect levels (NOAELs) are 1,096 mg/kg body weight (bw) per day for rats (the highest dose tested), 1,058 mg/kg bw per day for mice (the highest dose tested) and 13.6 mg/kg bw per day for dogs, based on increased relative liver weight in the 1-year study. In a battery of *in vitro* genotoxicity tests with and without metabolic activation, and in a micronucleus test *in vivo*, no genotoxic potential was detected for oxathiapiprolin. In long-term toxicity studies with mice and rats, no carcinogenic potential was observed. In mice, polyps of the female reproductive tract and the histiocytic sarcoma at the high dose were considered not adverse, taking into account the historical control data and the magnitude of the increase compared to the concurrent control group. In rats, neoplastic and non-neoplastic findings were within the historical control range. The relevant long-term NOAELs are the high doses tested (i.e. 735 mg/kg bw per day for rats and 948 mg/kg bw per day for mice). In the multigeneration rat study, the parental and reproductive NOAEL is 1,013 mg/kg bw per day (high dose tested) whereas the offspring NOAEL is 86.37 mg/kg bw per day based on an effect of delayed preputial separation. The degree of the effect was not considered sufficient to trigger a classification proposal for reproductive toxicity. In the developmental toxicity studies, no adverse effects were observed in both species, with a common maternal and developmental NOAEL at 1,000 mg/kg bw per day for rats and rabbits. In accordance with the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 (criteria of approval), in the absence of (proposed) classification for health effects, oxathiapiprolin may be considered as not having endocrine-disrupting properties. On the basis of the available data and current knowledge (OECD Conceptual Framework, as analysed in the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA Scientific Committee, 2013)), it can also be concluded that oxathiapiprolin is unlikely to be an endocrine disruptor in mammals.

No potential for neurotoxicity or immunotoxicity was detected in the available studies.

With regard to plant metabolites, no genotoxic potential (*in vitro* or *in vivo*) was demonstrated for IN-E8S72. Based on a 28-day rat study, an acceptable daily intake (ADI) of 1.157 mg/kg bw per day is derived, applying an increased uncertainty factor of 1,000 to cover for the extrapolation of sub-acute to long-term toxicity and for the lack of a complete toxicity data package. The derivation of an acute

reference dose (ARfD) was considered not needed on the basis of the available toxicological data. As groundwater metabolite, IN-E8S72 was concluded not toxicologically relevant according to the guidance (European Commission, 2003). For the metabolite IN-SXS67, no genotoxic potential was shown in the available studies. In the absence of repeat dose studies, the experts considered that the data were insufficient for the derivation of specific reference values for IN-SXS67. EFSA notes that this metabolite is the glucoside form of IN-E8S72, and therefore the toxicological data can be read across for both compounds.

For oxathiapiprolin, the ADI is 0.14 mg/kg bw per day based on the 1-year dog study and applying an uncertainty factor of 100; whereas the ARfD is not considered necessary. The acceptable operator exposure level (AOEL) is 0.04 mg/kg bw per day, with a correction for a 30% oral absorption and the application of an uncertainty factor of 100. For dermal absorption estimates, the use of the triple pack approach resulted in a value of 0.8% for the concentrate and 1% for the dilution. With the use of the EFSA calculator (EFSA, 2014a), the revised exposure estimates for operators, workers, bystanders and residents are below the systemic AOEL, without the use of personal protective equipment. Considering that the toxicity studies were performed with the racemic mixture, a conservative assessment assuming that the toxicity is attributed to only one isomer would not trigger a concern as the exposure estimates for the mixture are well below the AOEL value.

# 3. Residues

## 3.1. Representative use residues

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

The metabolism of oxathiapiprolin in primary crops was investigated in the fruit (grape), leaf (lettuce) and tuber (potato) crop groups using $^{14}$C-labelling on the pyrazole or thiazole moiety and following three foliar applications at the dose rate of 70 g/ha per treatment. Having regard to the low radioactive levels at harvest (0.005–0.012 mg/kg), identification of the residues was not attempted in potato tubers. In grape, lettuce and potato leaves, oxathiapiprolin was observed as the major component of the radioactive residues, accounting mostly for 25–85% TRR. In contrast, in grape grains at harvest, 2 months after the third application and considering pyrazole labelling, oxathiapiprolin accounted for 9.9% TRR only (0.03 mg/kg) and the main components were identified as metabolites IN-E8S72 and IN-WR791, representing 14.4% and 18.6% TRR (0.06 mg/kg), respectively. Many additional low-level metabolites were identified in primary crops, all representing less than 7% of the TRR. In primary crops, the metabolism proceeds by hydroxylation of the molecule at the phenyl ring leading to the metabolites IN-Q7H09 and IN-RDG40, the cleavage of the bond between the piperidine and pyrazole rings to form the thiazole-containing metabolites (IN-Q9L80 and IN-QPS10) or the pyrazole metabolites (IN-E8S72, IN-KJ552, IN-R7B20 and IN-WR791). Further conjugation leads to additional glucoside-conjugated metabolites (IN-SXS67). An additional minor pathway is the hydroxylation on the isoxazoline ring followed by the loss of a water molecule, resulting in the formation of metabolite IN-Q7D41. In rotational crops, the metabolism was found to be different and exclusively composed of the metabolites containing the pyrazole moiety (especially metabolite IN-E8S72 and its glucose-conjugated IN-SXS67) accounting for more than 50% of the TRR. Oxathiapiprolin, metabolites denoting the structure of the parent compound and metabolites containing the thiazole moiety were almost never detected. The metabolic profile in rotational crops is mostly the result of a preferential uptake from soil of the metabolites containing the pyrazole moiety. Chiral analysis of samples indicated that the enantiomeric ratio (ca 1:1) remained unchanged in plants. Based on these studies and considering that the pyrazole metabolite IN-E8S72 was concluded by the Pesticides Peer Review Experts' Meeting 137 on toxicology of lower toxicity than oxathiapiprolin (see Section 2), metabolite IN-E8S72 and its conjugate IN-SXS67 were not included in the plant residue definitions that were proposed as oxathiapiprolin for monitoring and risk assessment.

Sufficient numbers of residue trials were provided to derive MRLs on table grapes, potato, tomato, aubergine, cucurbits, lettuce and vine leaves. Additional trials conducted according to the proposed GAP were requested to derive a MRL for wine grapes (data gap). Numerous field rotational crop studies were submitted to confirm that residues of pyrazole metabolites (IN-SXS67 and IN-E8S72) are not expected to be detected in significant levels in rotational crops when the active

substance is applied at a maximum seasonal application rate of 90 g/ha. Residue data are supported by storage stability studies where oxathiapiprolin and its metabolites IN-Q7H09, IN-RDG40, IN-E8S72, IN-R7B20, IN-RZD74, IN-SXS67 and IN-WR791 were concluded to be stable for at least 18 months in high water, high oil, high starch, high protein and high acid content matrices. The active substance was shown to be stable under standard hydrolysis conditions. Processing studies were provided and processing factors were calculated for grape, tomato and potato processed commodities. These processing factors are recommended for inclusion in Annex VI of Regulation (EC) No 396/2005.

Livestock metabolism studies conducted on lactating goat over seven consecutive days and on poultry over 14 days at a dose rate of ca. 14 and 17 mg/kg bw were submitted. Most of the radioactivity was excreted and less than 1% of the administered dose was recovered in animal matrices. Most of the radioactive residues were identified as oxathiapiprolin and the hydroxy metabolites IN-RDG40 and IN-Q7H09. The residue definition for products of animal origin was proposed as oxathiapiprolin for monitoring and risk assessment. Having regard to the supported uses, the setting of MRLs for product of animal origin was concluded to be unnecessary.

The consumer risk assessment was conducted with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo). A long-term consumer intake concern was not identified for any of the European diets incorporated in the PRIMo model. The highest chronic intake was calculated to be 0.2% of the ADI (DE, Child). An acute consumer exposure assessment was not performed, as the setting of an ARfD was concluded to be unnecessary for oxathiapiprolin.

A risk assessment related to the consumer exposure to the metabolite IN-E8S72, expected to be present in groundwater above 0.75 μg/L (see Section 4), indicated that intakes represented only 0.15% of its ADI.

### 3.2. Maximum residue levels

An MRL application to set additional MRL was included in the DAR. Sufficient residue trials conducted according to the EU GAPs were submitted to derive MRL proposals for oxathiapiprolin in cucumber, courgette, melon, lettuce, tomato and aubergine.

## 4. Environmental fate and behaviour

Oxathiapiprolin was discussed at the Pesticides Peer Review Experts' Meeting 140 in January 2016.

Information in the dossier was sufficient to conclude that during transformation in the environmental matrices soil, water and sediment, the isomer ratio of oxathiapiprolin did not change (i.e. it remained a racemic mixture). Satisfactory information was not provided to address the environmental behaviour of each individual enantiomer of metabolites which contain chiral carbon atoms (IN RAB06, IN-RDT31 and IN-QPS10 in soil and IN RSE01, IN-RYJ52 and IN-S2K66 in aerobic water sediment). However, it is considered that the margin of safety on the risk assessments for the representative uses is large enough that the uncertainty on the relative toxicity and contributions to the total residue levels of the isomers of these metabolites does not change the conclusion of low aquatic risk and low risk for soil organisms. 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, oxathiapiprolin exhibited moderate to high persistence, forming the major (> 10% applied radioactivity (AR)) metabolite **IN-RAB06** (max 13.5% AR), which exhibited low to high persistence. Metabolites **IN-RDT31** (which exhibited moderate to very high persistence), **IN-QPS10** (which exhibited low to high persistence) and **IN-E8S72** (which exhibited high to very high persistence) were present at levels that trigger a groundwater exposure assessment. A potential pH dependency of laboratory degradation rates was observed for metabolite IN-QPS10, with slower degradation in acidic soils. Mineralisation of the thiazole and pyrazole ring $^{14}C$ radiolabel to carbon dioxide accounted for up to 12% AR after 120 days. The formation of unextractable residues for these radiolabels accounted for ca. 38% AR after 120 days, whereas for the isoxazoline ring $^{14}C$ radiolabel accounted for ca. 8% AR. Degradation of oxathiapiprolin by photolysis in soil proceeds along the same multiple minor pathways as in the dark. Photolysis does not appear to contribute significantly to the degradation of oxathiapiprolin under field conditions as demonstrated in the Florida, USA, field study, which was conducted in two adjacent plots (one covered with soil and one uncovered) and showed similar rates of degradation. Oxathiapiprolin can be considered to exhibit slight mobility or to be immobile in soil. Metabolite IN-QPS10 can be

considered to exhibit low mobility or to be immobile in soil. Metabolite IN-E8S72 exhibited very high mobility; metabolite IN-RAB06 exhibited medium to low mobility; and metabolite IN-RDT31 exhibited low to slight mobility in soil. It was concluded that the adsorption of oxathiapiprolin and these four metabolites was not pH dependent. In satisfactory field dissipation studies carried out at 10 sites (four in Europe, four in USA and two in Canada; spray application on bare soil plots), oxathiapiprolin exhibited low to high persistence. Field study $DT_{50}$ values were also estimated for metabolite IN-RDT31, which exhibited high persistence. For the other metabolites no reliable fits could be obtained to derive persistence end points, but modelling data (normalised day length, formed from parent) are available for IN-E8S72 and IN-RAB06.

Oxathiapiprolin was degraded in irradiated sterile pH 7 buffer solutions and in natural water at 25°C under simulated sunlight (xenon arc light, continuous irradiation). The photolysis half-life of oxathiapiprolin in sterile pH 7 buffer was 15.4 days under continuous irradiation. In pH 7 buffer, one major degradation product (**IN-P3X26**) was formed up to 14% AR. In laboratory incubations in dark aerobic natural sediment water systems, oxathiapiprolin exhibited moderate persistence, forming the major (> 10% AR) metabolites **IN-RYJ52** (a mixture of two isomers, max. 7.9% AR in water and 14.7% in sediment, exhibiting moderate to medium persistence) and **IN-Q7D41** (max. 1.5% AR in water and 10.5% in sediment, exhibiting very high persistence). Metabolites IN-RAB06, **IN-S2K66** and **IN-RSE01** were also formed (max. ca. 9.5% AR, 7.0% AR and 10.4% AR in both water and sediment, respectively). The unextractable sediment fraction was a limited sink, accounting for 7.3–16.6% AR at study end (99 days). Mineralisation of these radiolabels accounted for only 0.2–7.2% AR at the end of the study. The necessary surface water and sediment exposure assessments (predicted environmental concentration (PEC) calculations) were appropriately carried out for oxathiapiprolin and its metabolites IN-RDT31, IN-RAB06, IN-QPS10, IN-E8S72, IN-S2K66, IN-RSE01, IN-RYJ52, IN-Q7D41 and IN-P3X26 using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 2.1 of steps 1 and 2 in FOCUS calculator). Following Pesticides Peer Review Experts' Meeting 140, revised $PEC_{sw}$ and $PEC_{sed}$ modelling using a value of 10 mL/g for aquatic metabolites IN-S2K66, IN-RSE01, IN-RYJ52 and IN-Q7D41 and a default value of 10,000 mL/g for aquatic photodegradate IN P3X26 were provided.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2009) scenarios and the models PELMO 5.5.3 and PEARL 4.4.4[3] for the active substance oxathiapiprolin and metabolites IN-RDT31, IN-RAB06, IN-QPS10 and IN-E8S72 that reached levels triggering assessment. The potential for groundwater exposure from the representative uses by oxathiapiprolin and metabolites IN-RDT31, IN-RAB06 and IN-QPS10 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. For the metabolite IN-E8S72, all the FOCUS groundwater scenario simulations gave an 80th percentile annual average recharge concentration moving below 1 m above the parametric drinking water limit of 0.1 μg/L (max $PEC_{gw}$ for IN-E8S72 is 7.5 μg/L, predicted with PEARL model in Thiva scenario from early application of oxathiapiprolin to grapes). The available mammalian toxicology data are sufficient to set an ADI for IN-E8S72 (see Section 2). So because a consumer risk assessment from drinking water indicated a low risk, IN-E8S72 can be considered non-relevant in the context of the representative uses assessed (see Section 3).

The applicant provided appropriate information to address the effect of water treatment 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. The conclusion of this consideration was that neither oxathiapiprolin nor any of its degradation products that trigger assessment (IN-E8S72, IN-RDT31 IN-RAB06 IN-QPS10 or IN-P3X26) would be expected to undergo any substantial transformation due to processes such as chlorination or ozonation at the disinfection stage of usual water treatment processes.

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

## 5. Ecotoxicology

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

[3] Simulations correctly used the Q10 of 2.58 in accordance with EFSA (2008) and a Walker equation coefficient of 0.7.

On the basis of the available data on oxathiapiprolin, a low acute and long-term dietary risk to birds and mammals was concluded for all representative uses.

The log $P_{ow}$ of oxathiapiprolin and its pertinent metabolites IN-RDT31 (soil), IN-S2K66 (water), IN-Q7D41 (water) is > 3, and therefore a risk assessment for birds and mammals from secondary poisoning was triggered. Using the available bioconcentration factors (BCF) in fish and FOCUS step 2 values, a low risk to fish-eating birds and mammals was concluded, both for the parent and its metabolites. For the pertinent metabolite IN-Q7D41, the BCF in fish (533 L/kg) was estimated using a method (trout hepatocyte screen assay) which has not been properly investigated and validated for its use for regulatory purpose. However, considering the high margin of safety in the toxicity exposure ratio (TER) calculations for secondary poisoning in birds and mammals, no further data are considered needed. The first tier risk assessment for earthworm-eating birds and mammals indicated a low risk for both the parent and its pertinent soil metabolite.

For aquatic organisms, a low risk was concluded for oxathiapiprolin and all the pertinent metabolites based on FOCUS step 1 and 2 values for all representative uses.

On the basis of the available risk assessments, a low risk was concluded for honeybees, non-target arthropods, non-target terrestrial plants and organisms involved in sewage treatment processes.

A set of laboratory studies on earthworms, soil mites, collembolan and on soil microorganisms was available for oxathiapiprolin and its pertinent soil metabolites. Based on the results of these studies, the risk to earthworms and non-target soil macro- and microorganisms was assessed as low for all representative uses.

With regard to the endocrine disruption potential, as discussed in Section 2, it is unlikely that oxathiapiprolin is an endocrine disruptor in mammals; however, no firm conclusion can be drawn regarding fish and birds.

## 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 |
|---|---|---|
| Oxathiapiprolin | Moderate to high persistence<br>SFO and biphasic kinetics $DT_{50}$ 18.2–134.8 days ($DT_{90}$ 197.2–1,224 days, 20°C 50% MWHC soil moisture)<br>Low to high persistence<br>Field dissipation studies SFO and biphasic kinetics $DT_{50}$ 3.9–205.3 days ($DT_{90}$ 75.8–682 days) | The risk to soil organisms was assessed as low |
| IN-E8S72 | High to very high persistence<br>SFO $DT_{50}$ 216.2–477.4 days (20°C 50% MWHC soil moisture) | The risk to soil organisms was assessed as low |
| IN-QPS10 | Low to high persistence<br>Biphasic kinetics $DT_{50}$ 3–310.2 days ($DT_{90}$ 171.3–2,266.6 days, 20°C 50% MWHC soil moisture) | The risk to soil organisms was assessed as low |
| IN-RAB06 | Low to high persistence<br>SFO and biphasic kinetics $DT_{50}$ 3.5–170.2 days ($DT_{90}$ 58.6–565.2 days, 20°C 50% MWHC soil moisture) | The risk to soil organisms was assessed as low |
| IN-RDT31 | Moderate to very high persistence<br>Biphasic kinetics $DT_{50}$ 46.3–736.4 days ($DT_{90}$ 222.7–3,652 days, 20°C 50% MWHC soil moisture)<br>High persistence<br>Field dissipation studies SFO $DT_{50}$ 134.5–190 days | The risk to soil organisms was assessed as low |

SFO: single first-order; $DT_{50}$: 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 µg/L at 1 m depth for representative uses[a] | Pesticidal activity | Toxicological relevance | Ecotoxicology |
|---|---|---|---|---|---|
| Oxathiapiprolin | Slight mobility to immobile $K_{Foc}$ 4,350–45,586 mL/g | No | Yes | Yes | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-E8S72 | Very high mobility $K_{Foc}$ 4.9–11.0 mL/g | Yes 9/9 FOCUS scenarios > 0.75 µg/L (max $PEC_{gw}$ 7.5 µg/L in Thiva scenario with PEARL model for early application to grapes) | No | No ADI 1.2 mg/kg bw per day ARfD not necessary Consumer intake 0.15% of the ADI | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-QPS10 | Low mobility to immobile $K_{Foc}$ 1,790–14,368 mL/g | No | Assessment not triggered | Minor metabolite in dog | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-RAB06 | Medium to low mobility $K_{Foc}$ 381–665 mL/g | No | Assessment not triggered | Minor metabolite in rat | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-RDT31 | Low to slight mobility $K_{Foc}$ 630–2,521 mL/g | No | Assessment not triggered | Minor metabolite in rat Not genotoxic *in vitro* | Low risk to aquatic organisms was indicated in the surface water assessment |

$K_{Foc}$: Freundlich organic carbon adsorption coefficient; FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use; $PEC_{gw}$: predicted environmental concentration in groundwater; ADI: acceptable daily intake; ARfD: acute reference dose.
(a): At least one FOCUS scenario or relevant lysimeter.

**Table 3:** Surface water and sediment

| Compound (name and/or code) | Ecotoxicology |
|---|---|
| Oxathiapiprolin | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-RDT31 | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-RAB06 | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-QPS10 | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-E8S72 | Low risk to aquatic organisms was indicated in the surface water assessment |
| IN-S2K66 (sediment) | Low risk to aquatic and sediment organisms was indicated in the surface water assessment |
| IN-RSE01 (sediment) | Low risk to aquatic and sediment organisms was indicated in the surface water assessment |
| IN-RYJ52 (sediment) | Low risk to aquatic and sediment organisms was indicated in the surface water assessment |
| IN-Q7D41 (sediment) | Low risk to aquatic and sediment organisms was indicated in the surface water assessment |
| IN-P3X26 (aqueous photolysis) | Low risk to aquatic organisms was indicated in the surface water assessment |

**Table 4:** Air

| Compound (name and/or code) | Toxicology |
|---|---|
| Oxathiapiprolin | Rat $LC_{50} \geq 5.0$ mg/L (4 h, nose-only) |

$LC_{50}$: 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).

- Shelf life study of the representative formulation (relevant to all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Physical and chemical compatibility study of the formulation used in tank mixes (relevant to all representative uses evaluated; submission date proposed by the applicant unknown; see Section 1).
- Further assessment of the toxicological relevance of the impurities has to be provided (relevant to all representative uses evaluated; submission date proposed by the applicant unknown; see Section 2).
- *In vitro* metabolism data, addressing the identification of potentially unique human metabolites (relevant to all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Supervised residue trials conducted according to the GAP proposed for wine grapes are required (relevant to the representative use on wine grape; submission date proposed by the applicant unknown; see Section 3).
- Soil degradation rates for metabolites IN-RAB06 and IN-RDT31 derived in line with the recommendations of the FOCUS kinetics guidance (i.e. considering the values from the triazole and the pyrazole radiolabels as replicates). Data gap not relevant to finalise the risk assessment (relevant to all representative uses evaluated; submission date proposed by the applicant unknown; see evaluation table contained in EFSA (2016), open points 4.8 and 4.15).
- A transparent RMS evaluation of the possibility of combining $DegT_{50}$ values from laboratory studies with $DegT_{50}$ values obtained from field studies for metabolite IN-RAB06 according to the recommendations of the EFSA Guidance Document on $DegT_{50}$ (EFSA (2014b)) is not available. Data gap not essential to finalise the risk assessment (relevant to all representative uses evaluated; see evaluation table contained in EFSA (2016), data requirement 4.4).

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

No particular conditions are proposed for the representative uses evaluated.

# 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.

- None identified for the representative uses assessed.

[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 a 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.

- None identified for the representative uses assessed.

## 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 | | Grape | Potato | Field tomato, aubergine |
|---|---|---|---|---|
| **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** | Legal parametric value breached[(a)] | | | |
| | Parametric value of 10 µg/L[(b)] breached | | | |
| | Assessment not finalised | | | |

(a): Based on classification made in the context of this evaluation procedure under Regulation (EC) No 1107/2009. It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).

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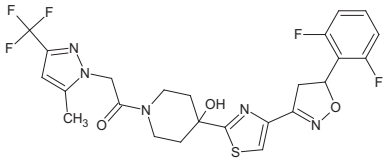
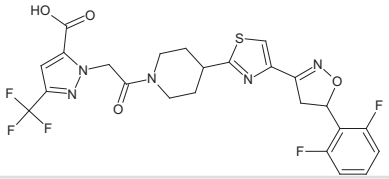
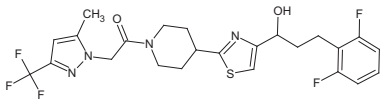
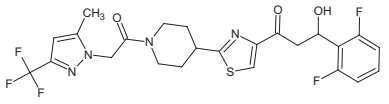
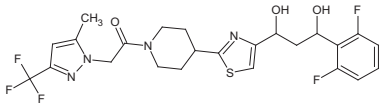
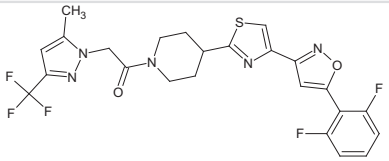
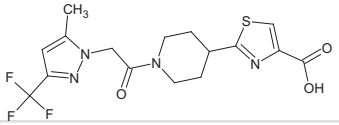
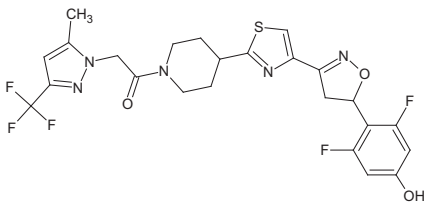
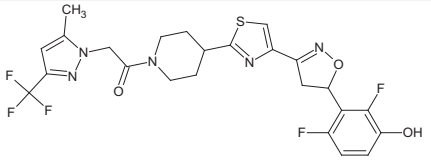
## Abbreviations

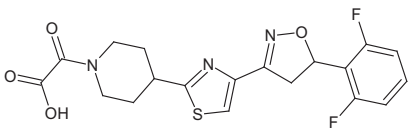
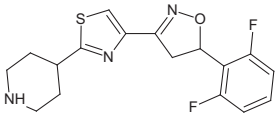
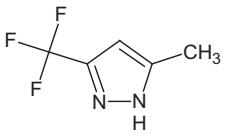
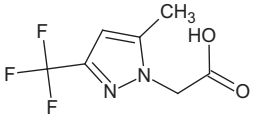
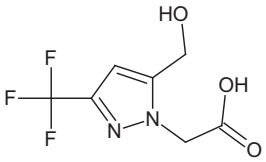
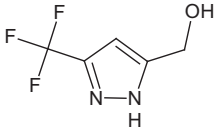
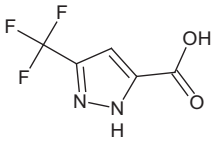
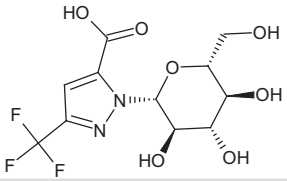
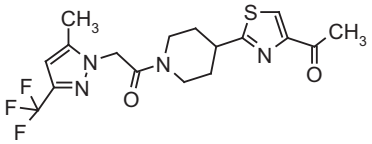
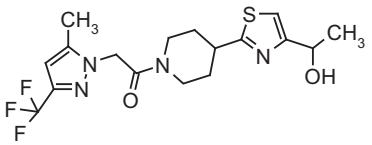
| | |
|---|---|
| ADI | acceptable daily intake |
| AOEL | acceptable operator exposure level |
| AR | applied radioactivity |
| ARfD | acute reference dose |
| BCF | bioconcentration factor |
| bw | body weight |
| DAR | draft assessment report |
| DFG | Deutsche Forschungsgemeinschaft method |
| $DT_{50}$ | period required for 50% dissipation (define method of estimation) |
| $DT_{90}$ | period required for 90% dissipation (define method of estimation) |
| EC | European Commission |
| 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 |
| HPLC | high-pressure liquid chromatography or high performance liquid chromatography |
| HPLC-MS | high performance liquid chromatography–mass spectrometry |
| HPLC-MS/MS | high performance liquid chromatography with tandem mass spectrometry |
| ISO | International Organization for Standardization |
| IUPAC | International Union of Pure and Applied Chemistry |
| JMPR | Joint Meeting of 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 | liquid chromatography |
| $LC_{50}$ | lethal concentration, median |
| LC-MS | liquid chromatography–mass spectrometry |
| LC-MS/MS | liquid chromatography with tandem mass spectrometry |
| LOQ | limit of quantification (determination) |
| MRL | maximum residue level |
| MS | mass spectrometry |
| MWHC | maximum water-holding capacity |
| NOAEL | no observed adverse effect level |
| OD | oil dispersion |
| OECD | Organisation for Economic Co-operation and Development |
| PEC | predicted environmental concentration |
| $PEC_{gw}$ | predicted environmental concentration in groundwater |
| $PEC_{sed}$ | predicted environmental concentration in sediment |
| $PEC_{sw}$ | predicted environmental concentration in surface water |
| $P_{ow}$ | partition coefficient between *n*-octanol and water |
| PRIMo | Pesticide Residues Intake Model |
| SFO | single first-order |
| SMILES | simplified molecular-input line-entry system |
| TER | toxicity exposure ratio |
| TRR | total radioactive residue |
| 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): http://dx.doi.org/10.2903/j.efsa.2016.4504

# Appendix B – Used compound codes

| Code/ trivial name[a] | Chemical name/SMILES notation | Structural formula |
|---|---|---|
| **IN-RDT31** | 1-(4-{4-[(5*RS*)-5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}-4-hydroxypiperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(O)(CC2)c3nc(cs3)C=4CC(ON=4)c5c(F)cccc5F |  |
| **IN-RAB06** | 1-[2-(4-{4-[(5*RS*)-5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-oxoethyl]-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid<br>O=C(O)c5cc(nn5CC(=O)N1CCC(CC1)c2nc(cs2)C=3CC(ON=3)c4c(F)cccc4F)C(F)(F)F |  |
| **IN-S2K66** | 1-(4-{4-[(1*RS*)-3-(2,6-difluorophenyl)-1-hydroxypropyl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(CC2)c3nc(cs3)C(O)CCc4c(F)cccc4F |  |
| **IN-RSE01** | (3*RS*)-3-(2,6-difluorophenyl)-3-hydroxy-1-[2-(1-{[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl}piperidin-4-yl)-1,3-thiazol-4-yl]propan-1-one<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(CC2)c3nc(cs3)C(=O)CC(O)c4c(F)cccc4F |  |
| **IN-RYJ52** | 1-(4-{4-[(1*RS*,3*RS*)-3-(2,6-difluorophenyl)-1,3-dihydroxypropyl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(CC2)c3nc(cs3)C(O)CC(O)c4c(F)cccc4F |  |
| **IN-Q7D41** | 1-(4-{4-[5-(2,6-difluorophenyl)-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(CC2)c3nc(cs3)c4cc(on4)c5c(F)cccc5F |  |
| **IN-P3X26** | 2-(1-{[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetyl}piperidin-4-yl)-1,3-thiazole-4-carboxylic acid<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(CC2)c3nc(cs3)C(=O)O |  |
| **IN-Q7H09** | 1-(4-{4-[(5*RS*)-5-(2,6-difluoro-4-hydroxyphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(CC2)c3nc(cs3)C=4CC(ON=4)c5c(F)cc(O)cc5F |  |
| **IN-RDG40** | 1-(4-{4-[(5*RS*)-5-(2,6-difluoro-3-hydroxyphenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)-2-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethanone<br>FC(F)(F)c1cc(C)n(n1)CC(=O)N2CCC(CC2)c3nc(cs3)C=4CC(ON=4)c5c(F)ccc(O)c5F |  |

| Code/ trivial name[(a)] | Chemical name/SMILES notation | Structural formula |
|---|---|---|
| **IN-Q9L80** | (4-{4-[(5*RS*)-5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidin-1-yl)(oxo)acetic acid<br>O=C(O)C(=O)N1CCC(CC1)c2nc(cs2)C=3CC(ON=3)c4c(F)cccc4F |  |
| **IN-QPS10** | 4-{4-[(5*RS*)-5-(2,6-difluorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-1,3-thiazol-2-yl}piperidine<br>Fc1cccc(F)c1C2CC(=NO2)c3csc(n3)C4CCNCC4 |  |
| **IN-KJ552** | 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole<br>FC(F)(F)c1cc(C)nn1 |  |
| **IN-WR791** | [5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetic acid<br>OC(=O)Cn1nc(cc1C)C(F)(F)F |  |
| **IN-R7B20** | [5-(hydroxymethyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl] acetic acid<br>OC(=O)Cn1nc(cc1CO)C(F)(F)F |  |
| **IN-RZD74** | [3-(trifluoromethyl)-1*H*-pyrazol-5-yl]methanol<br>FC(F)(F)c1cc(CO)nn1 |  |
| **IN-E8S72** | 3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid<br>FC(F)(F)c1cc(nn1)C(O)=O |  |
| **IN SXS67** | 1-β-D-glucopyranosyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid<br>O=C(O)c2cc(nn2[C@@H]1O[C@H](CO)[C@@H](O)[C@H](O)[C@H]1O)C(F)(F)F |  |
| **IN-QFD61** | 1-[4-(4-Acetyl-2-thiazolyl)-1-piperindyl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone |  |
| **IN-S2K67** | 1-[4-[4-(1-Hydroxyethyl)-2-thiazolyl)-1-piperindyl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]ethanone |  |

(a): The metabolite name in bold is the name used in the conclusion.