CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance metrafenone

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Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State Latvia and co-rapporteur Member State Slovakia for the pesticide active substance metrafenone are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The conclusions were reached on the basis of the evaluation of the representative uses of metrafenone as a fungicide on wheat, rye, triticale, oats, barley and grapes (field use). 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. Concerns are reported where identified.

Keywords: metrafenone, peer review, risk assessment, pesticide, fungicide

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Summary

Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659, lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Metrafenone is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), Latvia, and co-rapporteur Member State (co-RMS), Slovakia, received an application from BASF SE for the renewal of approval of the active substance metrafenone. In addition, an application for maximum residue levels (MRLs) was submitted, as referred to in Article 7 of Regulation (EC) No 396/2005, for barley and oat (the same uses as the representative uses) with a higher MRL proposal than the existing MRLs.

An initial evaluation of the dossier on metrafenone was provided by the RMS in the renewal assessment report (RAR) and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 13 of Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The following conclusions are derived.

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

The assessment of the data package revealed no issues that could not be finalised or that need to be included as critical areas of concern with respect to the **identity, physical, chemical and technical properties** of metrafenone or formulation for the representative uses.

In the area of **mammalian toxicology**, a data gap was identified to further address the phototoxicity and photomutagenicity potential of metrafenone, leading to an issue that could not be finalised. Critical areas of concern were not identified.

In the area of **residues**, the consumer risk assessment should be regarded as provisional only in view of the data gaps identified. As regards the MRL application on barley and oat, no proposal could be made due to the insufficient residue data.

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at the European Union (EU) level.

In the area of **ecotoxicology,** a high acute and chronic risk to aquatic invertebrates at FOCUS surface water Step 3 was indicated in FOCUS scenario D2 (out of nine scenarios) for the use in winter cereals (spring applications) at 2 $\times$ 150 g a.s./ha. Critical areas of concern were not identified.

With regard to the assessment of the **endocrine disruption (ED) potential** of metrafenone **for humans,** based on the available information and according to the ECHA/EFSA guidance (2018), the ED criteria according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, are not met for the EAS- and T-modalities. Regarding **non-target organisms**, based on the available evidence the ED criteria are not met for the EAS-modalities for wild mammals and non-mammalian species. For the T-modality, the available study shows equivocal results, and therefore a conclusion whether the ED criteria according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 are met, could not be drawn.

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Background

Commission Implementing Regulation (EU) No 844/2012[1], as amended by Commission Implementing Regulation (EU) No 2018/1659[2], (hereinafter referred to as 'the Regulation'), lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009[3]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3). Furthermore, in accordance with Article 13(3a), where the information available in the dossier is not sufficient to conclude the assessment on whether the approval criteria for endocrine disruption are met, additional information can be requested to be submitted in a period of minimum 3 months, not exceeding 30 months, depending on the type of information requested.

In accordance with Article 1 of the Regulation, the RMS Latvia and co-RMS Slovakia received an application from BASF SE for the renewal of approval of the active substance metrafenone. In addition, an application for maximum residue levels (MRLs) was submitted, as referred to in Article 7 of Regulation (EC) No 396/2005[4], for barley and oat (the same uses as the representative uses) with a higher MRL proposal than the existing MRLs. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Slovakia), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on metrafenone in the RAR, which was received by EFSA on 30 October 2018 (Latvia, 2018).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, BASF SE, for consultation and comments on 7 February 2019. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 10 April 2019. At the same time, the collated comments were 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's 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 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 21 May 2019. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

In addition, following a consultation with Member States in the Pesticides Peer Review Experts' Meetings PREV 18 and 21 (November 2019), it was considered necessary to apply an additional clock stop of 28 months in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2] Commission Implementing Regulation (EU) No 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605.

[3] 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.

[4] 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.

able to conclude whether the approval criteria for endocrine disruption in line with the scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605[5], are met.

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 and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in March 2023.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the formulations for representative uses, evaluated on the basis of the representative uses of metrafenone as a fungicide on wheat, rye, triticale, oats, barley and grapes (field use), as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review, if any, are presented in the conclusion. A list of the relevant end points for the active substance and the formulation is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for metrafenone according to Annex II of Regulation (EC) No 1107/2009 are summarised in Appendix A.

A key supporting document to this conclusion is the peer review report (EFSA, 2023), 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 RAR;
- the reporting table (17 May 2019 and 2 October 2022[6]);
- the evaluation table (31 March 2023);
- 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 RAR, including its revisions (Latvia, 2023), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the 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 formulations for representative uses

Metrafenone is the ISO common name for 3′-bromo-2,3,4,6′-tetramethoxy-2′,6-dimethylbenzophenone (IUPAC).

The formulations for representative uses for the evaluation were 'BAS 560 00 F', and 'BAS 560 02 F', both suspension concentrates (SCs) containing 300 and 500 g/L metrafenone, respectively.

The representative uses evaluated were spray applications for the control of fungal diseases in winter and spring cereals and for the control of *Erysiphe necator* in wine and table grapes in the EU. Full details of the GAPs can be found in the list of end points in Appendix B.

Data were submitted to conclude that the representative uses of metrafenone proposed at EU level result in a sufficient fungicidal efficacy against the target organisms, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

[5] Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, p. 33–36.

[6] Reporting Table following consultation on the revised RAR on the assessment of the endocrine disrupting properties made available after the clock stop applied in accordance with Commission Regulation (EU) No 2018/1659.

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: European Commission (2000a,b, 2010).

The proposed specification for metrafenone is based on batch data from industrial scale production. The minimum purity of the active substance as manufactured is 980 g/kg. A starting material may be considered as a relevant impurity with maximum content of 0.01 g/kg (see Section 2). A data gap was identified for five-batch data for the content of the relevant impurity in the technical material (see Section 10). It is proposed to update the reference specification as the original specification based on pilot scale is no longer representative of the industrial scale production. The batches used in the (eco) toxicological assessment support the proposed updated reference specification (see Sections 2 and 5). No FAO specification exists for metrafenone.

The main data regarding the identity of metrafenone and its physical and chemical properties are given in Appendix B. A data gap for information on the content of the relevant impurity before and after storage of the formulations for representative uses was identified (see Section 10).

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical material and in the formulations for representative uses. Data gaps for analytical methods for determination of the relevant impurity in the technical material and in the formulations for representative uses were identified (see Section 10).

Metrafenone residues in food and feed of plant origin can be monitored by the quick, easy, cheap, effective and safe multi-residue method (QuEChERS) using high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) with limit of quantification (LOQ) of 0.01 mg/kg in all plant commodity groups. It is noted that the residue definition for monitoring on fruits is provisional (see Section 3). Metrafenone residues in food of animal origin can be determined by QuEChERs using HPLC–MS/MS with LOQ of 0.01 mg/kg in all animal matrices. The efficiency of the extraction procedures used was not verified; however, it is not required since residues equal or above the LOQ, as a result of the representative uses, are not expected. Appropriate HPLC–MS/MS methods exist for monitoring metrafenone in the environmental matrices with LOQs of 0.005 mg/kg in soil, 0.05 μg/L in water and 0.03 mg/m^3 in the air, respectively.

Determination of residues of metrafenone in body fluids can be done by HPLC–MS/MS with a LOQ of 0.05 mg/L. Metrafenone residues in body tissues can be determined by using the monitoring method for residues in food of animal origin. Pending on the final decision on the residue definition for monitoring (see Section 2), an analytical method might be needed.

2. Mammalian toxicity

The toxicological profile of the active substance metrafenone was discussed at the Pesticides Peer Review Experts' Meeting PREV 18 (November 2019) and assessed according to the following guidance documents: European Commission (2003, 2012), EFSA PPR Panel (2012), EFSA (2014b) and ECHA (2017).

The toxicological profile of metrafenone was assessed based on toxicity studies that were not representative of the proposed updated reference specification for the active substance and those impurities currently declared in the specification. For those impurities currently declared, sufficient information was available to exclude the toxicological relevance of impurities and therefore the updated reference specification would be acceptable from the toxicological point of view. However, following a data requirement, EFSA considered that a new impurity, not currently specified, that is a starting material, would be considered a relevant impurity based on its hazards (Muta. 2 (H341) and Carc. 1B (H350)). However, a data gap is set in Section 1 to address the presence of the impurity in the technical material. The applicability of the threshold of toxicological concern (TTC) approach can be considered for setting a maximum content from the toxicological point of view, resulting in a maximum content of 0.01 g/kg in the reference specification for an exposure at the ADI level. EFSA noted that a Member State would propose to reduce the content to the lowest achievable level ('ALARA'[7] principle)

[7] ALARA: 'as low as reasonably achievable'.

in the reference specification. The Member State suggested 0.001 g/kg for the maximum content in the technical active substance of metrafenone.[8].

In the **toxicokinetics** studies, the oral absorption was estimated to be greater than 88%. There was low evidence for accumulation. Excretion of the substance was predominantly through faeces via bile. The main metabolic pathway identified was demethylation, hydroxylation and glucoronidation. No unique human metabolite is expected. The residue definition for body fluids is metrafenone. However, EFSA noted that metrafenone was extensively metabolised in rats and therefore this residue definition might not be appropriate (data gap, see Section 10).

In the **acute toxicity** studies, metrafenone has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant or a skin sensitiser.

A hazard concern for phototoxicity of metrafenone is identified based on positive results in the *in vitro* phototoxicity test. Further data (i.e. validated *in vivo* phototoxicity and photomutagenicity test and/or agreed methodology to assess the risk to phototoxic pesticide active substances) are needed to conclude on the phototoxicity potential, leading to a data gap and an issue that could not be finalised (see Section 9.1).

After **short- and long-term** repeated oral administration, the target organ of toxicity was the liver (increased weight, clinical chemistry, histopathological findings; rats, mice and dogs) and kidney after long-term exposure only (increased weight, nephropathy; mice, rats). The dog was the most sensitive species after short-term exposure and the mice and rat were similarly sensitive after long-term exposure. The relevant short-term oral NOAEL is lower than 50 mg/kg bw per day (1-year dog study; no NOAEL was identified). The relevant long-term oral NOAEL is 25 and 39 mg/kg bw per day in rats and mice, respectively (2-year rat and 18-month mouse studies). The carcinogenic potential was discussed during the peer review experts' meeting: the criteria for classification according to Regulation (EC) No 1272/2008[9] (ECHA, 2017) may be met for carcinogenic category 2 based on liver tumours in both species. There is currently no harmonised classification for metrafenone.

Based on the available **genotoxicity** studies metrafenone is unlikely to be genotoxic.

In multigeneration studies, the overall **reproductive** performance was not impaired; the agreed parental and offspring NOAELs are 39 mg/kg bw per day, whereas the reproductive NOAEL is 79 mg/kg bw per day. In the **developmental toxicity** studies, there was no evidence of teratogenicity. Metrafenone did not show potential for **neurotoxicity** and **immunotoxicity** in standard toxicity studies, neither in the acute and 28-day neurotoxicity study in rats nor in the 28-day immunotoxicity study in rat.

The agreed **acceptable daily intake** (ADI) is 0.25 mg/kg bw per day, based on liver toxicity observed at 260 mg/kg bw per day in the 2-year study in rat (NOAEL of 25 mg/kg bw). An uncertainty factor of 100 was applied. It is noted that during the previous peer review the same ADI was derived (EFSA, 2006).

The experts agreed that neither **acute reference dose** (ARfD), nor **acute acceptable operator exposure level** (AAOEL) was needed for metrafenone. No ARfD was derived during the previous peer review (EFSA, 2006).

The agreed systemic **acceptable operator exposure level** (AOEL) is 0.4 mg/kg bw per day based on decreased body weight gain in F1 males and reduced pup weight at 79 mg/kg bw per day (parental and offspring NOAEL of 39 mg/kg bw per day) in the multigeneration study in rats. An uncertainty factor of 100 was applied. No correction factor for oral absorption is needed to derive the AOEL. It is noted that during the previous peer review a slightly higher AOEL of 0.43 mg/kg bw per day was established based on the 13-week oral rat study.

The RMS estimated **non-dietary exposure** (i.e. operator, worker, bystander and resident) for both formulations for representative uses considering default dermal absorption values of metrafenone in 'BAS 560 02 F' and 'BAS 560 00 F' of 10% for the concentrate and of 50% for the dilution as input values according to EFSA PPR Panel (2012).

Considering the representative uses with 'BAS 560 00 F' as a fungicide in **cereals,** the maximum estimated operator exposure was below the AOEL (12% of the AOEL) without the use of personal protective equipment (PPE) during mixing and loading and application according to EFSA (2014b).

[8] Considering the data gap in Section 1, EFSA cannot conclude if the level of 0.001 g/kg is achievable.

[9] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, 1–1355.

Worker exposure was below the AOEL (4% of the AOEL, workwear but no PPE). Bystander and resident exposure was below the AOEL (maximum 8% of the AOEL; child resident).

Considering the representative uses with 'BAS 560 02 F' as a fungicide in **grapevine** (hand-held and tractor mounted applications), the maximum estimated operator exposure was below the AOEL (16% of the AOEL, tractor mounted) without the use of PPE during mixing and loading and application according to the EFSA (2014b) model. Worker exposure is above the AOEL according to the EFSA model. During the experts' meeting the experts supported the RMS proposal on the use of gloves as a refinement, however according to EFSA (2014b) no sufficient data were available to justify a proposed transfer coefficient factor with the use of workwear and gloves for re-entry activities in grapevine, and therefore EFSA considered not appropriate to use this refinement. Bystander and resident exposure was below the AOEL (maximum 24% of the AOEL; child resident).

The available information including toxicity studies with the **metabolites,** found as residues, indicated that:

- The genotoxicity and general toxicity profile of the metabolites CL 1500698, CL 1500702 and CL 434223 are assumed to be covered by the parent.
- The genotoxic potential of the metabolites CL 376991[10], CL 1023361, CL 1023362 and CL 1023363 is assumed to be covered by the parent, whereas for general toxicity a conclusion cannot be drawn (no further data are needed for the representative uses, see Section 3).
- Both the genotoxicity and general toxicity profile of metabolites CL 1500834 and CL 3000402 cannot be concluded. A data gap to address only the genotoxicity of these metabolites is identified according to the representative uses (see Section 3). For metabolite CL 1500834 genotoxicity data are available: CL 1500834 is genotoxic *in vitro* (micronucleus (MN) test) and not *in vivo* (MN test), however no sufficient proof of bone marrow exposure is available in the *in vivo* MN test, leading to a data gap (see Section 9.1).

3. Residues

The assessment in the residue section is based on the following guidance documents: OECD (2009, 2011), European Commission (2011, 2017) and JMPR (2004, 2007).

Metrafenone was discussed at the Pesticides Peer Review Experts' Meeting PREV 20 (November 2019).

The metabolism in plants, following foliar application, was investigated in fruit crops (grapes & cucumbers) at 2 N and cereals (wheat) at 2.7 N. In the grape metabolism study, the extracted radioactivity was sufficient according to the guideline but identification of metabolites was not performed in fruits. It was noted that berries as a whole fruit were not analysed, but as juice (fruit crash) and the remainder after juice extraction, separately. Assuming the results were summed up for each fraction, only the parent metrafenone was identified at 42 and 77 days after treatment (DAT) up to 53 and 25% of the total radioactive residues (TRRs) in grape berries. Several shortcomings were noted in the data reporting, such as the TRRs for grapefruits at all sampling points or the analytical attempts for further characterisation/identification in grapefruits. Thus, whether the grape metabolism study was guideline-compliant could not be concluded on and the experts agreed, unanimously, to ask for a clear and complete reporting of the data for this study (data gap, see Section 9.1). The metabolism study in cucumber was considered supportive only since it was conducted only with one label.

In the metabolism study on wheat, metrafenone was predominantly recovered in forage, hay and straw (i.e. 59% TRRs in forage, 14% TRRs in straw), while it occurred at lower proportion in wheat grains (8% of TRRs). The other part of the extracted radioactivity was defined as region of interests (ROI) most of which were constituted of multiple metabolites. The 'ROI 1' was the major unknown fraction found in wheat grain and hay, accounting for up to 21% TRRs in grains. Although this fraction was not further identified, it was reported as constituted of multiple components, individually accounting in absolute amounts for 0.001–0.07 mg/kg. Additional 'ROI' defined as individual compounds 'ROI 4' (CL 3000402), 'ROI 8' (CL 434223), 'ROI 9' (CL 376991) were also recovered in grains, accounting for less than 2% of TRRs each but in relevant absolute amount in straw (i.e. 0.32 mg/kg for CL 3000402). The fraction 'ROI 7', which comprises also metabolite CL 1500834, although recovered at < 10% TRRs in straw and grains, remained relevant for feed items accounting

[10] The toxicological profile of CL 376991 was not discussed during the experts' meeting. However, EFSA considered that the same conclusion applies to this metabolite given that it is also a hydroxylated form of the parent but minor rat metabolite.

in absolute amount for 0.55 mg/kg in straw. For the metabolites **CL 3000402** and **CL 1500834** the genotoxic potential was not ruled out and therefore a data gap was identified (see Sections 2 and 9.1), while for the compounds CL 434223 and CL 376991 no further data are required for the representative uses; the assessment of their toxicological properties is presented Section 2. Although the rate of radioactivity identification in wheat plants (straw, forage and grain) was not adequately addressed, the overall metabolic pattern could be depicted in cereals. Based on the overall evidence, the proposed **residue definition for enforcement and risk assessment** was proposed as metrafenone and it is limited to cereals only. For fruits, the residue definitions are proposed as metrafenone on a provisional basis.

Confined rotational crops metabolism studies were conducted in root crops (radish), leafy crops (lettuce) and pulses and oilseeds (rapeseed) at all plant-back intervals (PBIs) at an overdosed rate of 625 g a.s./ha (2.1 N) when compared with the annual dose of the representative GAP. The residue levels decreased significantly in the investigated crops from the first PBI to the third PBI (0.048–0.008 mg/kg). Overall, no quantifiable residues are expected in the succeeding crops and the same metabolic pattern as in primary crops was observed. Hence, the same residue definitions as for primary crops apply.

The stability of metrafenone in all crop categories was demonstrated for 24 months when stored at −20°C. The stability of metabolites CL 3000402, CL 434223 and CL 376991 was demonstrated in wheat grains when the samples are stored at −20°C for 31 months.

Field trials to support the representative GAPs were submitted in grapes, barley and wheat. The grape trials were conducted according to the representative GAP and they were analysed for metrafenone only. The number of trials was sufficient, supported by the storage stability and validated analytical method. On the contrary, the trials in wheat and barley were analysed for metrafenone and for the metabolites CL 3000402, CL 434223 and CL 376991. Only CL 3000402 was found in some trials above the LOQ (0.01 mg/kg). The trials in cereals were also supported by storage stability data and validated analytical method. However, the trials in barley and wheat, which deviate from the GAP (BBCH of the last application higher than 69), were not included in the assessment. Therefore, a data gap was identified for additional trials in barley and wheat to support the EU representative GAPs (see Section 9.1).

MRLs have not been proposed for any of the uses since the residue dataset for barley and wheat was incomplete and for grapes the residue definitions are provisional.

Metrafenone was demonstrated to be stable under the standard hydrolysis conditions of pasteurisation, baking/brewing/boiling and sterilisation. Processing trials were submitted for grapes, barley and wheat and processing factors were proposed (see details in Appendix B).

Livestock metabolism studies were conducted in ruminants and poultry with both labels of metrafenone. In ruminants, metrafenone was recovered in all tissues, milk (24% TRRs) and fat (85% TRRs) and was significantly present compared to liver (3% TRRs) and kidney (4% TRRs). Besides metrafenone, other 'ROI' were recovered in milk, kidney and liver. The 'ROI'-9, constituted of CL 1023361, CL 1023362 and CL 1500702, was found in liver and kidney at 13.2% TRRs and 13.6% TRRs respectively. The 'ROI'-13, constituted of CL 1500698 and CL 1023363, which, besides kidney (28% TRRs) and liver (21% TRRs) was also recovered in milk at 11% TRRs. The general toxicological properties of metabolites CL 1500698, CL 1023361, CL 1023362 and CL 1023363 were discussed in the mammalian toxicity section (see Section 2). In poultry, only metrafenone was identified in limited amount (2.2% TRRs in eggs) while the major part of the radioactivity remained unextracted (72% TRRs in muscle, 55% TRRs in eggs, 85% TRRs in liver). Although low level of TRR identification was reported, currently further investigation is not triggered by the representative and authorised uses. Considering all evidence, the **residue definition for monitoring and risk assessment** in ruminants is proposed as metrafenone only; for poultry it is proposed as metrafenone, by default.

Feeding studies were not submitted and are not triggered based on the results of overdosed metabolism studies showing that no residues above 0.01 mg/kg are expected in animal tissues at the calculated dietary burden considering the representative uses.

As regards the metabolism studies in fish, studies were not provided since the dietary burden was below 0.1 mg/kg on dry matter content. However, pending on the complete residue dataset on cereals, the dietary burden calculation might need to be reconsidered.

The consumer risk assessment has been conducted for grapes, barley and wheat by using the EFSA PRIMo 3.1 model. No consumer intake concern was identified, the chronic intake (TMDI) was calculated as maximum 12% of the ADI. The acute risk was not calculated since no ARfD was considered necessary. However, the consumer risk assessment should be regard as provisional only, in

the view of the data gaps identified for sufficient number of trials on cereals (barley and wheat) and pending on finalisation of the risk assessment residue definition for grapes.

As regards the magnitude of residues in bee products, three trials on nectar from combs and from bees' honey stomachs were collected at three time point intervals. The level of metrafenone in nectar from hives was 0.01 mg/kg at 1 day after treatment (DAT) and 5 DAT, and 0.02 mg/kg at 7 DAT. The level of residues in the honey stomach contents were 0.03 mg/kg at 1 DAT, 0.04 mg/kg at 5 DAT, and < 0.01 mg/kg at 7 DAT, showing a significant decrease of the residue levels. Based on these results it can be assumed that the current MRL of 0.05* mg/kg for metrafenone is sufficient for honey and bee products.

4. Environmental fate and behaviour

Metrafenone was discussed at the Pesticides Peer Review Experts' Meeting PREV 19 in November 2019.

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, metrafenone exhibited high to very high persistence with no significant metabolites formed. Mineralisation of the trimethoxyphenyl ring ^{14}C and bromophenyl ring ^{14}C radiolabels to carbon dioxide accounted for 1.8% and 1.5–5.3% AR after 120 days, respectively. The formation of unextractable residues for these radiolabels accounted for 19.4% and 17.4–24.8% AR after 120 days, respectively. Under anaerobic conditions metrafenone degraded faster than under aerobic conditions, forming a large number of degradation products, but none of them triggered further assessment. Photolysis on soil also contributes to the degradation of metrafenone, forming the major metabolites **CL 377160** (max. 18.9% AR), **CL 3000402** (max. 8.7% AR) and **CL 1500831** (max. 5.3% AR). Under aerobic conditions in the dark, metabolites CL 377160 and CL 3000402 exhibited low persistence and medium to high persistence, respectively. A data gap was identified for reliable degradation rates in soil for metabolite CL 1500831, which may be a mixture of enantiomers, though a conservative exposure assessment is available for this metabolite based on default soil DT_{50} of 1,000 days (see Section 10). In satisfactory field dissipation studies carried out at 4 sites in Europe (Germany, United Kingdom, Denmark and Northern France) with spray application to the soil surface on bare soil plots, metrafenone exhibited moderate to high persistence. Field study DT_{50} values were accepted as being reasonable estimates of degradation for the German and French trials and were normalised to FOCUS reference conditions (20°C and pF2 soil moisture) following the EFSA (2014a) DegT50 guidance. A default DT_{50} of 1,000 days was selected for the United Kingdom and Denmark trials. The field data endpoints were combined with laboratory values to derive modelling endpoints. Field dissipation studies for metabolite CL 3000402 were triggered, in line with the data requirement laid down in Regulation (EU) No 283/2013, par. 7.1.2.2.1 (data gap, see Section 10). Soil accumulation studies were conducted on two bare soil plots in Italy and Spain, and on two plots at a site in Germany, one cropped with vines and one cropped with cereals. The results indicated that, when used on bare ground southern conditions (Spanish and Italian trials), no significant long-term accumulation of metrafenone is expected, while in the case of the vine trial, the total soil residue concentration of metrafenone has reached a plateau by the study termination (6 years). For the cereals trial, a clear plateau of the measured concentrations was not reached after 6 years.

Metrafenone is expected to be immobile or exhibit low mobility in soil. CL 377160 exhibited slight soil mobility and CL 3000402 exhibited low to slight soil mobility. The peer review agreed that, for adsorption properties, the read across from data on metabolite CL 3000402 to metabolite CL 1500831 was acceptable.[11] It was concluded that the adsorption of metrafenone and its soil metabolites was not pH dependent.

In laboratory incubations in dark aerobic natural sediment water systems, metrafenone dissipated relatively rapidly from the water phase, with no metabolites triggering further assessment. The unextractable sediment fraction accounted for 16–26% AR at study end (100 days). Mineralisation of accounted for 2.6–12% AR at the end of the study. The rate of decline of metrafenone in a laboratory sterile aqueous photolysis experiment was similar to that occurred in the aerobic sediment water incubations. No chromatographically resolved component (excluding metrafenone) accounted for > 9% AR. The necessary surface water and sediment exposure assessments (predicted environmental

* MRL is proposed at the level of LOQ.

[11] See Expert consultation point 4.4 of the Report of the Pesticides Peer Review Experts' meeting PREV 19 (November 2019) (EFSA, 2023).

concentrations (PEC) calculations) were carried out for the soil metabolites CL 377160, CL 3000402 and CL 1500831, using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance metrafenone, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available[12]. The step 4 calculations appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 10 m being implemented for the representative uses on vines. The SWAN tool (version 3.2.0) was appropriately used to implement these mitigation measures in the simulations.

The necessary groundwater exposure assessments were appropriately carried out for metrafenone and its metabolites CL 377160, CL 3000402 and CL 1500831 using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3, with the exception that MACRO model was not run for the Châteaudun scenario. The potential for groundwater exposure from the representative uses by the active substance and its soil metabolites above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios.

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, when surface water is abstracted for drinking water. The conclusion of this consideration was that neither metrafenone nor any of its degradation products that trigger assessment (CL 377160, CL 3000402 and CL 1500831) would be expected to undergo any substantial transformation due to oxidation 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 B of this conclusion. A key to the persistence and mobility class wording used, relating these words to numerical DT and Koc endpoint values, can be found in Appendix C.

5. Ecotoxicology

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

Some specific aspects related to the environmental risk assessment of metrafenone were discussed at the Pesticide Peer Review Experts' Meeting PREV 21 in November 2019.

The information to support the compliance of the batches used in the ecotoxicological studies with the proposed updated technical specification was considered sufficient.

Acute and long-term oral toxicity data on **birds** and **mammals** were available with the active substance metrafenone. In addition, acute oral toxicity data on mammals were also available with the formulations for representative uses ('BAS 560 00 F' and 'BAS 560 02 F'). Based on the available data and risk assessment, low acute and long-term risk from dietary exposure to birds and mammals was concluded for all the representative uses. Low risk to birds and mammals from exposure to contaminated water and via secondary poisoning was indicated for all the representative uses.

Toxicity data were available on all the relevant taxa of **aquatic organisms** with the active substance metrafenone while acute toxicity data for fish, *Daphnia magna* and algae were available for each of the two representative formulations. Based on tier 1 data, a low risk to fish, sediment-dwelling organisms, algae and higher aquatic plants was concluded for all representative uses of metrafenone at FOCUS Step 3. A low risk to aquatic invertebrates was concluded for spring (1 and 2 × 150 g a.s./ha) and winter cereals (1 × 150 g a.s./ha and autumn application at 2 × 150 g a.s./ha) and grapes (early application; CEU and SEU) at FOCUS Step 3. A high acute and chronic risk to aquatic invertebrates at FOCUS Step 3 was indicated in scenario D2 (out of nine scenarios) for the representative use in winter cereals (spring application at 2 × 150 g a.s./ha), and in scenarios D6, R2 and R3 and scenarios R3 and D6 (out of five scenarios) for the representative use in grapes (late application) in CEU and SEU, respectively. A low risk for aquatic invertebrates for the representative use in grapes can only be concluded with appropriate risk mitigation measures for all scenarios failing at FOCUS Step 3, e.g. no-sprayed buffer zones of 10 m (FOCUS Step 4). Based on the ecotoxicity data available and risk assessment, a low risk to aquatic organisms was concluded for the pertinent aquatic metabolites.

Acute (contact and oral) ecotoxicity tests on **honeybees** were available for the active substance and the two formulations for representative uses. In addition, chronic studies on adult and larvae honeybees were available for one of the formulations for representative uses ('BAS 560 02 F'). The

[12] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

larval study did not last until adult emergence and no evidence supporting the absence of effects on pupation and emergence was provided. A semi-field study (i.e. OECD TG 75) on 'BAS 560 02 F' was available to assess the effects on bee brood. The risk assessment to honeybees was performed according to EFSA (2013). The screening risk assessment indicated a low acute and chronic risk to honeybee adults for all representative uses. A qualitative assessment of the bee brood was performed based on the outcome of the semi-field study on flowering *Phacelia tanacetifolia*, which reported no adverse effects on brood at an application rate of 330 g metrafenone/ha. Although this type of study presents some limitations (EFSA, 2013), the assessment can be considered suitable for concluding a low risk for bee brood for the representative uses. The risk via consumption of contaminated surface water and puddle water was assessed as low for all the representative uses. No assessment was available to address the risk to bees from exposure to guttation fluid. No information was available to perform a risk assessment for sub-lethal effects (data gap, see Section 10) and accumulative effects. No relevant metabolites of metrafenone were identified in plant parts and therefore the risk to bees from exposure to metabolites was not considered further. Toxicity data on bumble bees and solitary bees were not available.

Tier 1 toxicity tests on the **non-target arthropods** *Aphidius rhopalosiphi* (Hymenoptera: Aphiidae), and *Typhlodromus pyri* (Acari: Phytoseiidae) and glass-plate tests on *Chrysoperla carnea* (Neuroptera: Chrysopidae), *Poecilus cupreus* (Coleoptera: Carabidae) were available with the formulations for representative uses. In addition, an extended laboratory test on *T. pyri* and field studies with the predatory mites *T. pyri* and *Kampimodromus aberrans* (Acari: Phytoseiidae) were available with 'BAS 560 00 F' and 'BAS 560 02 F', respectively. On the basis of the available data and risk assessment, a low in-field and off-field risk to non-target arthropods was concluded for all the representative uses.

On the basis of the available data and risk assessment, low risk from metrafenone to **earthworms** and other **soil macroorganisms**, **soil microorganisms**, **non-target terrestrial plants** and **organisms in sewage treatment plants** was concluded for all the representative uses. Moreover, the risk assessment using the available data for the pertinent metabolites indicated a low risk to soil organisms for the representative uses.

6. Endocrine disruption properties

Metrafenone was discussed at the Pesticides Peer Review Experts' Meetings PREV 18 and 21 (November 2019) and at the Pesticides Peer Review Experts' TC 92 (18 January 2023).

With regard to the assessment of the endocrine disruption (ED) potential of metrafenone for **humans** according to the ECHA/EFSA guidance (2018), in determining whether metrafenone interacts with the oestrogen, androgen and steroidogenesis (EAS) and thyroid (T) mediated pathways, the number and type of effects induced, and the magnitude and pattern of responses observed across the available information were considered. Additionally, the conditions under which effects occur were considered, in particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in overt toxicity. The assessment is therefore providing a weight-of-evidence analysis of the potential interaction of metrafenone with the EAS and T signalling pathways using the available evidence in the dataset.

With regard to T-modality, the data set was considered complete and a pattern of T-mediated adversity was not identified. With regard to the EAS-modalities, the dataset was considered complete and a pattern of EAS-mediated adversity was not observed.

In conclusion, based on the available information[13] and according to the ECHA/EFSA guidance (2018), the ED criteria according to point 3.6.5 of Annex II to Regulation (EC) No 1107/ 2009, as amended by Commission Regulation (EU) 2018/605, are not met for the EAS- and T-modalities for the active substance metrafenone.

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms**.

For non-target organisms other than mammals, a Fish short-term reproduction assay (FSTRA, OECD TG 229) and a Xenopus Eleutheroembryo Thyroid Assay (XETA, OECD TG 248) were available.

[13] See expert consultation point 2.9 of the Report of the Pesticides Peer Review Experts' Meeting PREV 18 (November 2019) (EFSA, 2023).

The FSTRA did not show any evidence suggesting EAS-mediated endocrine activity. Therefore, in line with the EFSA/ECHA ED guidance (ECHA/EFSA, 2018), the ED criteria were not met for the EAS-modalities.

The results of the available XETA were discussed at the Pesticide Peer-Review Experts' TC 92. Based on a statistically significant increase in fluorescence greater than 12% in spiked mode for the lowest tested concentration[14] only, and in line with the decision tree in the OECD TG 248, the experts at the Pesticides Peer Review TC 92 agreed that the XETA should be considered as equivocal. In addition, it was noted that the data handling of the fluorescence results was not duly justified.[15] Considering the above results and the fact that the XETA was the only available study providing information on the ED properties of metrafenone for non-target organisms through the T-modality, a conclusion on whether the ED criteria are met for the T-modality for non-mammalian species could not be drawn (data gap and issue that could not be finalised, see Section 9.1).

Based on the available information, the assessment of the endocrine disruption potential of metrafenone according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, could not be finalised.

7. 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)	Ecotoxicology
Metrafenone	Low risk to soil organisms
CL 377160 (from photolytic degradation in soil)	Low risk to soil organisms
CL 3000402 (from photolytic degradation in soil)	Low risk to soil organisms
CL 1500831 (from photolytic degradation in soil)	Low risk to soil organisms

Table 2: Groundwater[(a)]

Compound (name and/or code)	> 0.1 µg/L at 1 m depth for the representative uses[(b)] Step 2	Biological (pesticidal) activity/ relevance Step 3a.	Hazard identified Steps 3b. and 3c.	Consumer RA triggered Steps 4 and 5	Human health relevance
Metrafenone	No	Yes	–	–	Yes
CL 377160 (from photolytic degradation in soil)	No	Not triggered	Not triggered	Not triggered	Not triggered
CL 3000402 (from photolytic degradation in soil)	No	Not triggered	Not triggered	Not triggered	Not triggered
CL 1500831 (from photolytic degradation in soil)	No	Not triggered	Not triggered	Not triggered	Not triggered

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or a relevant lysimeter. Ranges indicated for FOCUS scenarios include the result from the model giving the highest concentration at each scenario, as needed to comply with European Commission (2014a) guidance.

[14] See expert consultation point 5.3 of the Report of the Pesticides Peer Review Experts' TC 92 (January 2023) (EFSA, 2023).
[15] In the context of the RMS consultation on the draft EFSA Conclusion, and in a position paper shared by the applicant at the end of the peer review, the applicant informed about an additional statistical re-analysis of the results and about results of a preliminary study, which are available upon request (see Peer Review Report, RMS consultation on the draft EFSA Conclusion, EFSA, 2023). Those data were, however, not submitted for the peer review and could not be formally considered. However, based on preliminary consideration, the additional data are not considered to change the overall conclusion reached at the Peer Review Experts' TC 92.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Metrafenone	Low risk to aquatic organisms (considering mitigation measures for the representative use on grapes (late applications)) except for aquatic invertebrates for the representative use on winter cereals[(a)]
CL 377160 (from photolytic degradation in soil)	Low risk to aquatic organisms
CL 3000402 (from photolytic degradation in soil)	Low risk to aquatic organisms
CL 1500831 (from photolytic degradation in soil)	Low risk to aquatic organisms

(a): For the representative use on winter cereals (spring applications) at 2 × 150 g a.s./ha, high risk for aquatic invertebrates was identified in situations represented by the FOCUS scenario D2. A low risk to aquatic invertebrates was indicated for the remaining representative uses on winter cereals.

Table 4: Air

Compound (name and/or code)	Toxicology
Metrafenone	Low acute toxicity by inhalation to rats (> 5 mg/L air per 4 h (nose-only))

8. Particular conditions proposed to be taken into account by risk managers

Risk mitigation measures (RMMs) identified following consideration of Member State (MS) and/or applicant's proposal(s) during the peer review, if any, are presented in this section (see Table 5). These measures applicable for human health and/or the environment leading to a reduction of exposure levels of operators, workers, bystanders/residents, environmental compartments and/or non-target organisms for the representative uses are listed below. The list may also cover any RMMs as appropriate, leading to an acceptable level of risks for the respective non-target organisms.

It is noted that final decisions on the need of RMMs to ensure the safe use of the plant protection product containing the concerned active substance will be taken by risk managers during the decision-making phase. Consideration of the validity and appropriateness of the RMMs remains the responsibility of MSs at product authorisation, taking into account their specific agricultural, plant health and environmental conditions at national level.

Table 5: Risk mitigation measures proposed for the representative uses assessed

Representative use	Wheat, rye, oats, triticale	Barley	Wheat, Barley	Triticale, oats	Grapes (Wine, table)	Grapes (Wine, table)
	NEU and CEU MSs	NEU and CEU MSs	France	France	CEU MSs	SEU MSs
	1–2 appl	1–2 appl	1 appl	1 appl	3 appl	3 appl
Risk to aquatic organisms[(a)]					RMM equivalent to a no-spray buffer zone of 10 m is needed for 3/5 scenarios[(b)]	RMM equivalent to a no-spray buffer zone of 10 m is needed for 2/5 scenarios[(c)]

(a): Only needed for aquatic invertebrates as low risk to other aquatic taxa was concluded at FOCUS Step 3.
(b): D6, R2 and R3. Late applications only.
(c): D6 and R3. Late applications only.

9. Concerns and related data gaps

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 one or more of the representative uses in line with

the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011 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 Regulation (EC) No 1107/2009.

The following issues or assessments that could not be finalised have been identified, together with the reasons including the associated data gaps where relevant, which are reported directly under the specific issue to which they are related.

1) A hazard concern for phototoxicity of metrafenone is identified based on positive results in the *in vitro* phototoxicity test.
    a) Further data to address the phototoxic potential of metrafenone (i.e. validated *in vivo* phototoxicity test and photomutagenicity test and/or agreed methodology to assess the risk to phototoxic pesticide active substances) are needed to conclude; however it is noted that a validated *in vivo* phototoxicity or photomutagenicity test or agreed methodology to assess the risk to phototoxic pesticide active substances are currently not available (relevant for all representative uses evaluated, see Section 2).
2) The consumer risk assessment has not been finalised in view of the incomplete residue dataset on barley and wheat, while for grapes the residue definitions are provisional (see Section 3).
    a) Clear and complete reporting of data for the grape metabolism study needs to be provided in order to elucidate the metabolic pattern in fruits (relevant for the representative uses in grapes evaluated; see Section 3).
    b) Sufficient number of trials on barley (one for NEU and five for SEU) and wheat (three for NEU and four for SEU), fully compliant to support the representative GAPs in NEU and SEU needs to be provided (relevant for the representative uses in cereals evaluated; see Section 3).
    c) Data to address the genotoxic potential of metabolite CL 3000402 (relevant for all representative uses evaluated, see Section 2).
    d) Weight of evidence approach to conclude that the bone marrow was reached in the *in vivo* micronucleus test on CL 1500834 (relevant for all representative uses evaluated, see Section 2).
3) Since the available test (XETA) gave equivocal results, the assessment of the endocrine disruption potential of metrafenone for non-target organisms could not be finalised for the T-modality (see Section 6).
    a) Additional information to fully investigate the endocrine activity through the T-modality for non-target organisms (i.e. a valid and reliable XETA). If the XETA is positive, a mode of action (MoA) should be postulated and further data would be needed to further investigate adversity (i.e. a Larval Amphibian Growth and Development Assay (LAGDA)) (relevant for all representative uses evaluated, see Section 6).

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 Regulation (EC) No 1107/2009 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 Regulation (EC) No 1107/2009.

The following critical areas of concern are identified, together with any associated data gaps, where relevant, which are reported directly under the specific critical area of concern to which they are related.

Critical areas of concern were not identified.

9.3. Overview of the concerns identified for each representative use considered (Table 6)

(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 6.)

In addition to the issues indicated in the below table, the assessment of the endocrine disrupting properties of metrafenone for non-target organisms according to the scientific criteria for the determination of endocrine disrupting properties as set out in point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, could not be finalised.

Table 6: Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios

Representative use		**Wheat, rye, oats, triticale**	**Barley**	**Wheat, Barley**	**Triticale, oats**	**Grapes (Wine, table)**	**Grapes (Wine, table)**
		NEU and CEU MSs	**NEU and CEU MSs**	**France**	**France**	**CEU MSs**	**SEU MSs**
		1–2 appl	**1–2 appl**	**1 appl**	**1 appl**	**3 appl**	**3 appl**
Operator risk	Risk identified						
	Assessment not finalised						
Worker risk	Risk identified					X[(d)]	X[(d)]
	Assessment not finalised						
Resident/ bystander risk	Risk identified						
	Assessment not finalised						
Consumer risk	Risk identified						
	Assessment not finalised	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
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	1/9 FOCUS surface water scenarios[(c)]	1/9 FOCUS surface water scenarios[(c)]				
	Assessment not finalised						

Representative use		Wheat, rye, oats, triticale	Barley	Wheat, Barley	Triticale, oats	Grapes (Wine, table)	Grapes (Wine, table)
		NEU and CEU MSs	NEU and CEU MSs	France	France	CEU MSs	SEU MSs
		1–2 appl	1–2 appl	1 appl	1 appl	3 appl	3 appl
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						

The superscript numbers relate to the numbered points indicated in Section 9.1. Where there is no superscript number, see Sections 2–7 for further information.

(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

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

(c): For the representative use on winter cereals (spring applications) at 2 × 150 g a.s./ha, high risk for aquatic invertebrates was identified in situations represented by the FOCUS scenario D2.

(d): Worker exposure is above the AOEL according to the EFSA model. During the experts' meeting, the experts supported the RMS proposal on the use of gloves as a refinement, however according to EFSA (2014b) no sufficient data were available to justify a proposed transfer coefficient factor with the use of workwear and gloves for re-entry activities in grapevine, and therefore EFSA considered not appropriate to use this refinement.

10. List of other outstanding issues

Remaining data gaps not leading to critical areas of concern or issues not finalised but considered necessary to comply with the data requirements, and which are relevant for some or all of the representative uses assessed at EU level. Although not critical, these data gaps may lead to uncertainties in the assessment and are considered relevant.

These data gaps refer only to the representative uses assessed and are listed in the order of the sections:

- Five batch data for the content of the relevant impurity in the technical material (relevant for all representative use evaluated, see Section 1).
- Information on the content of the relevant impurity before and after storage of the formulations for representative uses (relevant for all representative use evaluated, see Section 1).
- Analytical methods for analysis of the relevant impurity in the technical material and in the formulations for representative uses (relevant for all representative use evaluated, see Section 1).
- Scientific justification to support the residue definition for body fluids given the extensive metabolism of metrafenone in mammals (relevant for all representative use evaluated, see Section 2).
- Reliable degradation rates in soil of the soil photodegradation product CL 1500831 (relevant for all representative uses evaluated; see Section 4).
- Field dissipation studies for the soil photodegradation product CL 3000402 triggered according to data requirement in Regulation (EU) No 283/2013, par. 7.1.2.2.1 (relevant for all representative uses evaluated; see Section 4).
- Further data to perform a risk assessment for sub-lethal effects on honeybees (relevant for all representative uses evaluated; see Section 5).

References

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

ECHA and EFSA (European Chemicals Agency and European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311, 135 pp. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN.

EFSA (European Food Safety Authority), 2006. Conclusion regarding the peer review of the pesticide risk assessment of the active substance metrafenone. EFSA Scientific Report 2006;58, 72 pp. https://doi.org/10.2903/j.efsa.2006.58r

EFSA (European Food Safety Authority), 2008. Opinion on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil. EFSA Journal 2008;6(1):622, 32 pp. https://doi.org/10.2903/j.efsa.2008.622

EFSA (European Food Safety Authority), 2009. Guidance on Risk Assessment for Birds and Mammals.

EFSA (European Food Safety Authority), 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus* spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp. https://doi.org/10.2903/j.efsa.2013.3295

EFSA (European Food Safety Authority), 2014a. EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662, 37 pp. https://doi.org/10.2903/j.efsa.2014.3662

EFSA (European Food Safety Authority), 2014b. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp. https://doi.org/10.2903/j.efsa.2014.3874 Available online, www.efsa.europa.eu/efsajournal

EFSA (European Food Safety Authority), 2023. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance metrafenone www.efsa.europa.eu.Available online

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2012. Guidance on dermal absorption. EFSA Journal 2012;10(4):2665, 30 pp. https://doi.org/10.2903/j.efsa.2012.2665

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290, 186 pp. https://doi.org/10.2903/j.efsa.2013.3290

European Commission, 2000a. Residues: guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414. SANCO/3029/99-rev. 4, 11 July 2000.

European Commission, 2000b. Technical material and preparations: guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414. SANCO/3030/99-rev. 4, 11 July 2000.

European Commission, 2002a. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002-rev. 2 final, 17 October 2002.

European Commission, 2002b. Guidance Document on Aquatic Ecotoxicology Under Council Directive 91/414/EEC. SANCO/3268/2001-rev. 4 final, 17 October 2002.

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

European Commission, 2010. Guidance Document on residue analytical methods. SANCO/825/00-rev. 8.1, 16 November 2010.

European Commission, 2011. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. SANCO 7525/VI/95-rev. 9 March 2011. pp. 1–46.

European Commission, 2012. Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003-rev 10.1, 13 July 2012.

European Commission, 2014a. Assessing potential for movement of active substances and their metabolites to ground water in the EU. Report of the FOCUS Workgroup. EC Document Reference SANCO/13144/2010-v. 3, 613 pp, as outlined in Generic guidance for tier 1 FOCUS groundwater assessment, v. 2.2 May 2014.

European Commission, 2014b. Guidance document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012. SANCO/2012/11251-rev 4, 12 December 2014.

European Commission, 2017. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev 10.3, June 2017.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2001. FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC. Report of the FOCUS Working Group on Surface Water Scenarios. EC Document Reference SANCO/4802/2001-rev. 2, 245 pp, as updated by Generic guidance for FOCUS surface water scenarios v. 1.4, May 2015.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2006. Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU Registration Report of the FOCUS Work Group on Degradation Kinetics. EC Document Reference SANCO/10058/2005-v. 2.0, 434 pp, as updated by the Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration, v. 1.1 December 2014.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2007. Landscape and mitigation factors in aquatic risk assessment. Volume 1. Extended summary and recommendations. Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment. EC Document Reference SANCO/10422/2005 v. 2.0 169 pp.

JMPR (Joint Meeting on Pesticide Residues), 2004. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Rome, Italy, 20–29 September 2004, 383 pp.

JMPR (Joint Meeting on Pesticide Residues), 2007. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Geneva, Switzerland, 18–27 September 2007, 164 pp.

Latvia, 2018. Renewal Assessment Report (RAR) on the active substance metrafenone prepared by the rapporteur Member State Latvia in the framework of Commission Implementing Regulation (EU) No 844/2012, October 2018. Available online: www.efsa.europa.eu

Latvia, 2023. Revised Renewal Assessment Report (RAR) on metrafenone prepared by the rapporteur Member State Latvia in the framework of Commission Implementing Regulation (EU) No 844/2012, February 2023. Available online: www.efsa.europa.eu

McCall P J, Laskowski D A, Swann R L, Dishburger H J, 1980. Measurements of sorption coefficients of organic chemicals and their use in environmental fate analysis. In: Test Protocols for Environmental Fate and Movement of Toxicants. In: Proceedings of the 94th Annual Meeting of the American Association of Official Analytical Chemists (AOAC). October 21–22, Washington, D.C. pp. 89–109.

OECD (Organisation for Economic Co-operation and Development), 2009. Guidance document on overview of residue chemistry studies. ENV/JM/MONO(2009)31, (28 July 2009).

OECD (Organisation for Economic Co-operation and Development), 2011. OECD MRL calculator: spreadsheet for single data set and spreadsheet for multiple data set, 2 March 2011. In: Pesticide Publications/Publications on Pesticide Residues. Available online: www.oecd.org

SETAC (Society of Environmental Toxicology and Chemistry), 2001. Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. ESCORT, 2.

Abbreviations

a.s.	active substance
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
CAS	Chemical Abstracts Service
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
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
HPLC-MS/MS	high-pressure liquid chromatography–tandem mass spectrometry
HR	hazard rate
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)
LAGDA	Larval Amphibian Growth and Development Assay
LOQ	limit of quantification
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
PHI	preharvest interval
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
RPE	respiratory protective equipment
SC	suspension concentrate
SMILES	simplified molecular-input line-entry system
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
WHO	World Health Organization

Appendix A – Consideration of cut-off criteria for metrafenone according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council

Properties		Conclusion[(a)]
CMR	**Carcinogenicity (C)**	Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process [Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended]: not available. According to the peer review, criteria for harmonised classification according to Regulation (EC) No 1272/2008 may be met for: Carc. Cat. 2 H351.
	Mutagenicity (M)	Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process [Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended]: not available. According to the peer review, criteria for harmonised classification as mutagenicity according to Regulation (EC) No 1272/2008 may not be met.
	Toxic for Reproduction (R)	Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process [Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended]: not available. According to the peer review, criteria for harmonised classification as toxic for reproduction according to Regulation (EC) No 1272/2008 may not be met.
Endocrine disrupting properties		The ED criteria for humans according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, are not met for the EAS- and T-modalities for the active substance metrafenone.. Non-target organisms: based on the available evidence the ED criteria are not met for the EAS-modalities for wild mammals and non-mammalian species. For the T-modality, the available study shows equivocal results, and therefore a conclusion whether the ED criteria according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 are met, could not be drawn.
POP	**Persistence**	Metrafenone is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Long-range transport	
PBT	**Persistence**	Metrafenone is not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/ 2009.
	Bioaccumulation	
	Toxicity	
vPvB	**Persistence**	Metrafenone is not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	

(a): Origin of data to be included where applicable (e.g. EFSA, ECHA RAC, Regulation).

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

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.8012

Appendix C – Wording EFSA used in Section 4 of this conclusion, in relation to DT and Koc 'classes' exhibited by each compound assessed

Wording	DT_{50} normalised to 20°C for laboratory incubations[16] or not normalised DT_{50} for field studies (SFO equivalent, when biphasic, the DT_{90} was divided by 3.32 to estimate the DT50 when deciding on the wording to use)
Very low persistence	< 1 day
Low persistence	1 to < 10 days
Moderate persistence	10 to < 60 days
Medium persistence	60 to < 100 days
High persistence	100 days to < 1 year
Very high persistence	A year or more

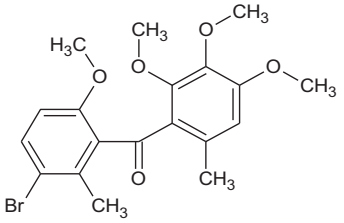
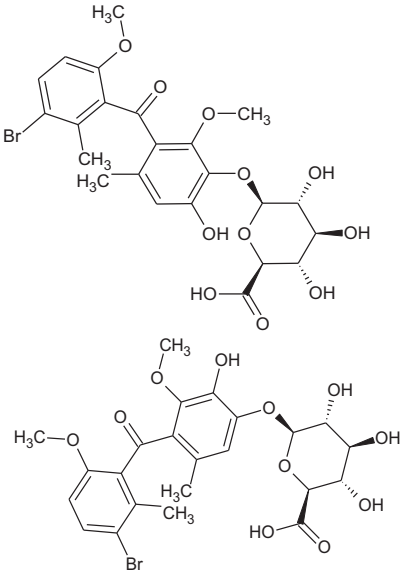
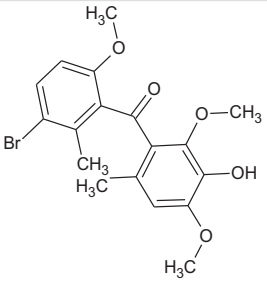
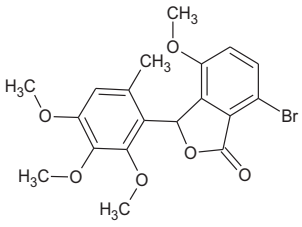
Note these classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

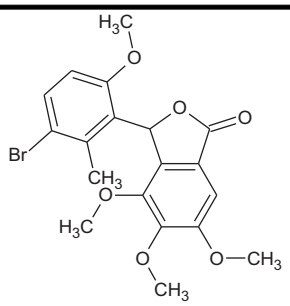
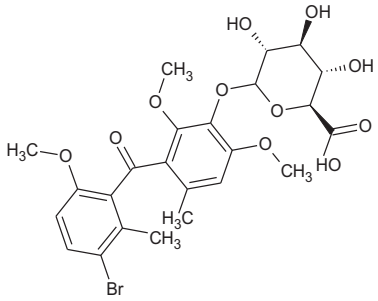
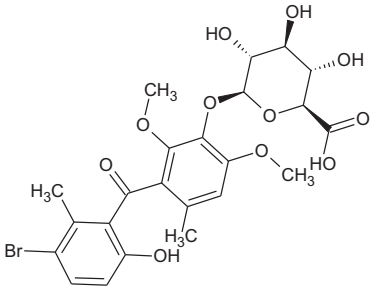
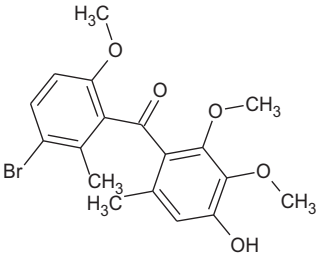
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0 to 50
High mobility	51 to 150
Medium mobility	151 to 500
Low mobility	501 to 2,000
Slight mobility	2,001 to 5,000
Immobile	> 5,000

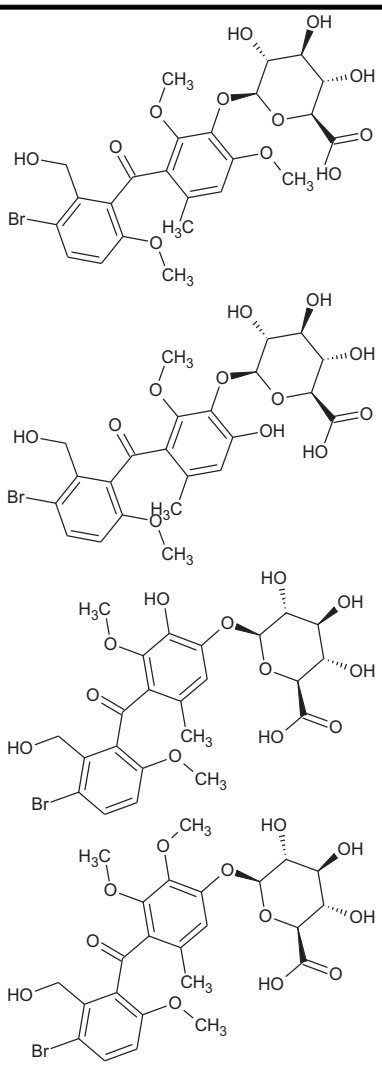
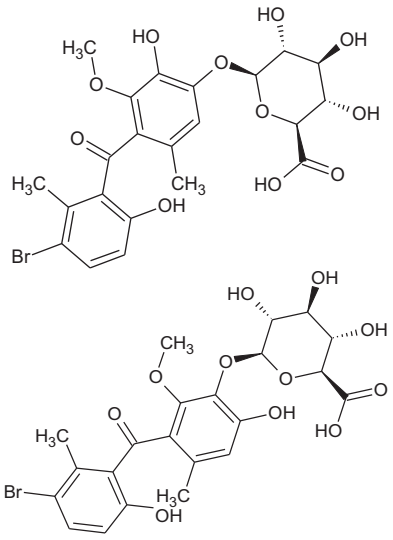
Based on McCall et al. (1980).

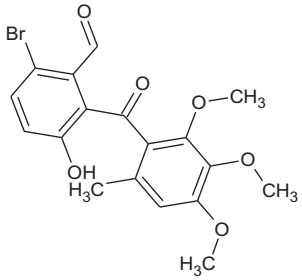
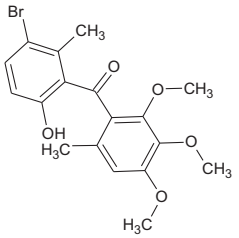
[16] For laboratory soil incubations normalisation was also to field capacity soil moisture (pF2/10 kPa). For laboratory sediment water system incubations, the whole system DT values were used.

Appendix D – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
metrafenone	3′-bromo-2,3,4,6′-tetramethoxy-2′,6-dimethylbenzophenone Cc1c(C(=O)c2c(C)cc(OC)c(OC)c2OC)c(ccc1Br)OC AMSPWOYQQAWRRM-UHFFFAOYSA-N	
CL 1023363	3-(3-bromo-6-methoxy-2-methylbenzoyl)-6-hydroxy-2-methoxy-4-methylphenyl β-D-glucopyranosiduronic acid Cc1c(Br)ccc(OC)c1C(=O)c1c(OC)c(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(O)cc1C QHSULTXSPKODFI-USFRMQJTSA-N 4-(3-bromo-6-methoxy-2-methylbenzoyl)-2-hydroxy-3-methoxy-5-methylphenyl β-D-glucopyranosiduronic acid Cc1c(Br)ccc(OC)c1C(=O)c1c(C)cc(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(O)c1OC STVUTAMREPWCBY-VLXBDIDVSA-N	
CL 377160	(3-bromo-6-methoxy-2-methylphenyl)(3-hydroxy-2,4-dimethoxy-6-methylphenyl)methanone Cc1c(C(=O)c2c(C)cc(OC)c(O)c2OC)c(ccc1Br)OC WNIXEQPZYAILKY-UHFFFAOYSA-N	
CL 3000402	7-bromo-4-methoxy-3-(2,3,4-trimethoxy-6-methylphenyl)-2-benzofuran-1(3*H*)-one Cc1cc(OC)c(OC)c(OC)c1C1OC(=O)c2c(Br)ccc(OC)c21 SJQUJJUCEGGODF-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CL 1500831	(3*RS*)-3-(3-bromo-6-methoxy-2-methylphenyl)-4,5,6-trimethoxy-2-benzofuran-1(3*H*)-one Cc1c(Br)ccc(OC)c1C1OC(=O)c2cc(OC)c(OC)c(OC)c21 DYAUQBHHYXMRNN-UHFFFAOYSA-N	
CL 1500698	3-(3-bromo-6-methoxy-2-methylbenzoyl)-2,6-dimethoxy-4-methylphenyl D-glucopyranosiduronic acid Cc1c(Br)ccc(OC)c1C(=O)c1c(OC)c(OC2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(OC)cc1C QTXHVSOHBMPYIE-ZJGKJBOUSA-N	
CL 1500702	3-(3-bromo-6-hydroxy-2-methylbenzoyl)-2,6-dimethoxy-4-methylphenyl β-D-glucopyranosiduronic acid Cc1c(Br)ccc(O)c1C(=O)c1c(OC)c(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(OC)cc1C BEYPWKRXFALITJ-USFRMQJTSA-N	
CL 434223	(3-bromo-6-methoxy-2-methylphenyl)(4-hydroxy-2,3-dimethoxy-6-methylphenyl)methanone Cc1c(C(=O)c2c(C)cc(O)c(OC)c2OC)c(ccc1Br)OC DIYDRBPRRLLMMK-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CL 1023361	3-[3-bromo-2-(hydroxymethyl)-6-methoxybenzoyl]-2,6-dimethoxy-4-methylphenyl β-D-glucopyranosiduronic acid OCc1c(Br)ccc(OC)c1C(=O)c1c(OC)c(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(OC)cc1C CGUREPJJWCTFIX-YPQORGHUSA-N 3-[3-bromo-2-(hydroxymethyl)-6-methoxybenzoyl]-6-hydroxy-2-methoxy-4-methylphenyl β-D-glucopyranosiduronic acid OCc1c(Br)ccc(OC)c1C(=O)c1c(OC)c(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(O)cc1C WZKZOCMHQCKLLI-USFRMQJTSA-N 4-[3-bromo-2-(hydroxymethyl)-6-methoxybenzoyl]-2-hydroxy-3-methoxy-5-methylphenyl β-D-glucopyranosiduronic acid OCc1c(Br)ccc(OC)c1C(=O)c1c(C)cc(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(O)c1OC WRZBRUJZGKGNIF-VLXBDIDVSA-N 4-[3-bromo-2-(hydroxymethyl)-6-methoxybenzoyl]-2,3-dimethoxy-5-methylphenyl β-D-glucopyranosiduronic acid OCc1c(Br)ccc(OC)c1C(=O)c1c(C)cc(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(OC)c1OC CSPMFHBJYHGWLA-YPQORGHUSA-N	
CL 1023362	4-(3-bromo-6-hydroxy-2-methylbenzoyl)-2-hydroxy-3-methoxy-5-methylphenyl β-D-glucopyranosiduronic acid Cc1c(Br)ccc(O)c1C(=O)c1c(C)cc(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(O)c1OC VQMGQUTVTOABSP-QSUZLTIMSA-N 3-(3-bromo-6-hydroxy-2-methylbenzoyl)-6-hydroxy-2-methoxy-4-methylphenyl β-D-glucopyranosiduronic acid Cc1c(Br)ccc(O)c1C(=O)c1c(OC)c(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c(O)cc1C UFDUXLFISUYYPL-NTKSAMNMSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CL 1500834	6-bromo-3-hydroxy-2-(2,3,4-trimethoxy-6-methylbenzoyl)benzaldehyde O=Cc1c(c(O)ccc1Br)C(=O)c1c(C)cc(OC)c(OC)c1OC SAERNGVBYBZYJJ-UHFFFAOYSA-N	
CL 376991	(3-bromo-6-hydroxy-2-methylphenyl)(2,3,4-trimethoxy-6-methylphenyl)methanone Cc1c(C(=O)c2c(C)cc(OC)c(OC)c2OC)c(O)ccc1Br CPHBTTLZNXTYMA-UHFFFAOYSA-N	

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 2019.1.1 ACD/Labs 2019 Release (File version N05E41, Build 110555, 18 July 2019).
(c): ACD/ChemSketch 2019.1.1 ACD/Labs 2019 Release (File version C05H41, Build 110712, 24 July 2019).