CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State Belgium and co-rapporteur Member State Germany for the pesticide active substance cypermethrin are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of cypermethrin as an insecticide on winter and spring cereals, winter and spring oilseed rape and potato. 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 identified.

Keywords: cypermethrin, peer review, risk assessment, pesticide, insecticide

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') 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. Cypermethrin is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), Belgium, and the co-rapporteur Member State (co-RMS), Germany, received an application from Cypermethrin Working Group Task Force consisting of Arysta LifeScience Benelux sprl (previously Agriphar S.A.) and SBM Développement for the renewal of approval of the active substance cypermethrin. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Germany), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on cypermethrin in the renewal assessment report (RAR), which was received by EFSA on 8 May 2017. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Cypermethrin Working Group Task Force consisting of Arysta LifeScience Benelux sprl (previously Agriphar S.A.) and SBM Développement, for comments on 9 August 2017. 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 16 October 2017.

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

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether cypermethrin can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of cypermethrin as an insecticide on winter and spring cereals, on winter and spring oilseed rape and potato, as proposed by the applicants. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the uses of cypermethrin according to the representative uses proposed at the European Union (EU) level result in a sufficient insecticidal efficacy against the target organisms.

In the area of identity, physical and chemical properties and analytical methods, data gaps were identified for additional validation data for the monitoring methods in plant matrices, milk and soil, for a monitoring method in body fluids and a method for the determination of the relevant impurity in the formulation.

In the area of mammalian toxicology, two data gaps were identified for further investigations of the endocrine-disrupting potential and for further assessment of the toxicological profile of metabolites (as identified in Section 3). Additionally, the assessment of the toxicological relevance of the impurities cannot be finalised and it cannot be concluded that the batches used in the (eco)toxicity studies were representative of the technical specification leading to a critical area of concern.

In the area of residues, several data gaps were identified and the residue definition for risk assessment in plant and animal commodities is provisional. The preliminary chronic and acute consumer risk assessment did not indicate exceedance of acceptable daily intake (ADI) or acute reference dose (ARfD) for any of the representative uses, although exposure of vulnerable consumer groups is very close to the ARfD (> 99% for infants consuming milk and milk products), and reduction of uncertainty in the provisional risk assessment by submission of further information is recommended.

Moreover, as outcome of the renewal review, specifically as for the lowered toxicological reference values, a prioritisation of the initiation of the existing maximum residue levels (MRLs) review of cypermethrins is recommended in view of indication of possible consumer intake concerns for a number of commodities.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level, with the notable exception that a data gap was identified for information on the effect of water treatment processes on the nature of residues of metabolites potentially present in surface water, when surface water is abstracted for drinking water.

This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

In the area of ecotoxicology, a number of data gaps were identified. The high risk to aquatic organisms, the high risk to bees and other arthropods was identified as critical areas of concern.

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Background

Commission Implementing Regulation (EU) No 844/2012[1] (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[2]. 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 up to 8 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS Belgium and co-RMS Germany received an application from Cypermethrin Working Group Task Force consisting of Arysta LifeScience Benelux sprl (previously Agriphar S.A.) and SBM Développement for the renewal of approval of the active substance cypermethrin. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Germany), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on cypermethrin in the RAR, which was received by EFSA on 8 May 2017 (Belgium, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, the Cypermethrin Working Group Task Force consisting of Arysta LifeScience Benelux sprl (previously Agriphar S.A.) and SBM Développement, for consultation and comments on 9 August 2017. 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 16 October 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicants' 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 applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 1 December 2017. On the basis of the comments received, the applicants' response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicants, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

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

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation 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 July 2018.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses

[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] 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.

of cypermethrin as an insecticide on winter and spring cereals, winter and spring oilseed rape and potato, as proposed by the applicants. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2018), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (1 December 2017);
- the evaluation table (24 July 2018);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Belgium, 2018), 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 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

Cypermethrin is the ISO common name for (*RS*)-α-cyano-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate or (*RS*)-α-cyano-3-phenoxybenzyl (1*RS*)-*cis-trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (IUPAC).

Cypermethrin contains three asymmetric carbon atoms, giving rise to four diastereomeric pairs of enantiomers. Some subsets of cypermethrin isomers have their own ISO common names: alpha-cypermethrin, beta-cypermethrin, theta-cypermethrin and zeta-cypermethrin.

The representative formulated product for the evaluation was 'Cypermethrin 500 EC', an emulsifiable concentrate (EC) containing 500 g/L cypermethrin.

The representative uses evaluated were field spray applications as an insecticide in winter and spring cereals for grain production only in the southern European Union (SEU); spray applications in winter and spring oilseed rape in Central and Northern Zone, as defined by the Regulation (EC) No 1107/2009 and spray applications in potato in the SEU. 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 cypermethrin according to the representative uses proposed at EU level result in a sufficient insecticidal efficacy against the target organisms following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

Conclusions of the evaluation

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

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

The proposed specifications for cypermethrin were based on batch data from industrial scale production. The members of the cypermethrin working group (CWG) proposed individual manufacturing specifications. The proposed minimum purity of the technical material was 950 g/kg for Arysta and 958 g/kg for SBM with the cypermethrin *cis*:*trans* ratio of 40:60 to 60:40 in both cases. Hexane was considered relevant impurity, however, of no concern at the levels specified. (see Section 2) The old reference specification was proposed as a reference specification for renewal with a minimum content of 920 g/kg cypermethrin. It should be noted that the minimum purity of the first inclusion was 900 g/kg and also that a FAO specification under the old procedure exists for cypermethrin: 332/TC/S/F (1993), published in 1995 (AGP:CP/316) with min. 900 g/kg cypermethrin

and the *cis*-isomer content between 40% minimum and 60% maximum of the declared cypermethrin content. The minimum purity and the ratio of *cis*:*trans*-isomers are meeting the requirements of the FAO specification.

Based on the batch data and the impurity profiles, EFSA disagrees with the proposed reference specification and proposes to update it according to the renewal data.

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

Adequate methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation. CIPAC methods are also available for the determination of cypermethrin in the technical material and representative formulation. A data gap was identified for a method for the determination of the relevant impurity in the formulation.

The residue definition for monitoring for food and feed of plant and animal origin was set to cypermethrin including other mixtures of constituent isomers (sum of isomers). A gas chromatography–mass spectrometry (GC–MS) multiresidue based method is available for monitoring *cis*-I, *cis*-II, *trans*-III and *trans*-IV cypermethrin isomers individually, summed to obtain total cypermethrin with a limit of quantification (LOQ) of 0.01 mg/kg cypermethrin, in all commodity groups. A data gap was, however, identified for linearity data for the confirmative ions used in the method.

The cypermethrin isomers (*cis*-I, *cis*-II, *trans*-III and *trans*-IV) can be determined individually in food and feed of animal origin using GC–MS with LOQs of 0.05 mg/kg total cypermethrin in meat, liver, kidney, fat; 0.005 mg/kg in milk and 0.01 mg/kg in egg, respectively. A data gap was identified for additional confirmatory data for the method for milk.

The residue definition for monitoring in the environmental matrices was defined as cypermethrin. The enantiomeric pairs of the diastereomers of cypermethrin can be determined in soil by GC–MS with a LOQ of 0.05 mg/kg of total isomers. Due to the absence of sufficient quantitative validation and acceptable validation data for confirmatory method (confirmative ions), a data gap was identified for guideline compliant method validation for the soil analytical method.

Residues of cypermethrin in drinking water can be monitored by gas chromatography-electron capture detection (GC-ECD) by determining the enantiomeric pairs of the diastereomers individually with a LOQ of 0.01 μg/L total cypermethrin and in surface water by GC–MS with a LOQ of 0.1 ng/L total cypermethrin. Monitoring cypermethrin residues in air as sum of the enantiomeric pairs of diastereomers is possible with GC–MS with a LOQ of 0.375 $\mu g/m^3$ total cypermethrin.

Residues of cypermethrin in the body fluids can be determined by GC–MS as the sum of the individual enantiomeric pairs of diastereomers with a LOQ of 0.01 mg/L total cypermethrin. The residue definition for monitoring in body fluids was defined as 4-OH-PBA sulfate and DCVA glucuronide, as a consequence a data gap was identified for an analytical method for the determination of the components of the residue definition.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on Dermal Absorption (EFSA PPR Panel, 2012) and Guidance on the Application of the CLP Criteria (ECHA, 2017).

Cypermethrin was discussed at the Pesticides Peer Review Experts' Meeting 175 in April 2018.

With regard to the newly proposed technical specification, hexane is a relevant impurity (maximum content to be defined once there is an agreed specification, see Appendix A, Section 1). QSARs analyses were provided for the other impurities but are not sufficient to exclude at least a genotoxic potential (data gap). Consequently, the assessment of the toxicological relevance of these impurities cannot be finalised and considering also the lack of knowledge about the detailed composition of the batches used in toxicity studies (e.g. at least for the critical studies), it cannot be concluded that these batches were representative of the new technical specification leading to a critical area of concern. Sufficiently validated analytical method has been reported in support of the developmental neurotoxicity study in rats (used for reference values).

For cypermethrin, the toxicokinetic data suggested a saturation effect at high dose. Considering all the available data and the high variability of the toxicokinetic results, the oral absorption value of 50% from the original peer review was still considered applicable to cypermethrin. After oral absorption,

cypermethrin is rapidly distributed in the body with the highest amounts of residues in fat. The limited metabolism includes hydrolytic cleavage of the ester bound and hydroxylation with cleavage of the ether bridge. The excretion is almost complete 72 h after single oral dose. The major metabolites identified were 4-OH-PBA sulfate and DCVA glucuronide. Regarding *in vitro* comparative metabolism, no significantly different metabolites were formed from human cells exposed to cypermethrin.

Cypermethrin is of moderate acute toxicity by the oral and inhalation route and of low acute toxicity by the dermal route. The acute test results allow the hazard identification of cypermethrin as a local irritant for the airways (STOT SE 3). Cypermethrin was not a skin sensitiser, irritant or phototoxic in the available studies.

In short-term dietary studies, the critical effect was neurotoxicity in the different species (rat, dog and mouse), and target organs also included liver and kidney (rat). The most sensitive species was the dog, with no observed adverse effect level (NOAEL) of 7.5 mg/kg body weight (bw) per day in the 2-year study. Based on neurotoxic effects (in dogs), the classification **STOT RE2 (H373)**[3] is proposed for cypermethrin.

Cypermethrin can be considered as unlikely to be **genotoxic** based on the available guidelines studies. Considering the positive results in a non-guideline repeat dose toxicity study in rabbits with a subsequent assessment of micronuclei formation in blood (Vardavas et al., 2016 in Belgium, 2018), the experts agreed that further scientific valid data should be provided in order to clarify these results and the mode of action for micronucleus formation and its possible link (causal or not) with inflammatory events (data gap).

For the long-term toxicity, two rat studies with cypermethrin and one mouse study were taken into account. The rat was the most sensitive species. Systemic toxicity in rats included increased urea, changes in kidneys (weight) and testes (tubular atrophy and calcification), with NOAELs of 0.5 and 7.5 mg/kg bw per day in the first and second rat study, respectively. In the absence of treatment-related tumours in rats and mouse, cypermethrin was concluded unlikely to be carcinogenic.

For the two **multigeneration** rat studies, the relevant parental NOAEL is 10 mg/kg bw per day based on decreased body weight and food consumption; the offspring NOAEL is 10 mg/kg bw per day based on decreased litter weight and histopathological findings in the liver, lung, lymph nodes and thymus; and the reproductive NOAEL is 10 mg/kg bw per day based on decreased survival of pups at birth. In the developmental studies with rats and rabbits, no evidence of embryotoxicity or teratogenicity was observed, and the maternal toxicity was limited to decreased body weight in rats. In a 15-day intact adult male rat assay (without measurement of hormonal activity), the NOAEL was 6 mg/kg bw per day based on decreased body weight gain. At the top dose, clinical signs of neurotoxicity, increased sperm abnormalities and weak decrease in seminal vesicle weight were also observed.

Cypermethrin is not classified or proposed to be classified as carcinogenic or toxic for reproduction category 2, on this basis, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine-disrupting (ED) properties are not met. On the basis of the available regulatory studies and literature findings, it was acknowledged that cypermethrin has endocrine-mediated activity but the potential for **endocrine disruption** could not be concluded upon (data gap).

In both acute and repeated dose **neurotoxicity** studies in rats with cypermethrin, an overall NOAEL of 25 mg/kg bw per day was identified. As regards developmental neurotoxicity (DNT study), only a lowest observable adverse effect level (LOAEL) was identified for parental animals based on clinical signs, and the developmental NOAEL of 15 mg/kg bw per day was based on functional observation battery (FOB) changes and testes/epididymis alterations. Regarding the potential link between pyrethroids and neurodegenerative diseases, the experts agreed that no robust animal or epidemiological studies exist indicating a causal relationship between Parkinson Disease and exposure to pyrethroids including cypermethrin.

Based on the available data, the immune system is not demonstrated to be a sensitive target regarding the toxicity of cypermethrin.

[3] It should be noted that proposals for classification made in the context of the evaluation procedure under Regulation (EC) No 1107/2009 are not formal proposals. Classification is formally proposed and decided in accordance with 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.

The **metabolites** including hydroxylated derivatives of cypermethrin and their conjugates are considered unlikely to be genotoxic or more toxic than the parent.

The metabolites including DCVA derivatives are also considered unlikely to be more toxic than the parent since DCVA glucuronide is a major rat metabolite.

Based on current available information in the dossier for cypermethrin, the conclusion for all metabolites with the 3-phenoxybenzoyl moiety such as 4-OH-PBA, 4-OH-PBA sulfate, 3-PBA and 3-PBAldehyde was that they could be initially considered unlikely to be of higher toxicity than the parent. Grouping was considered acceptable based on structurally similarities and metabolic pathway considerations. The conclusion on the toxicological properties for this group was based on the fact that 4-OH-PBA sulfate was also identified as a major rat metabolite and could be initially considered covered by the toxicity profile of the parent. For 3-PBAldehyde, it could be considered unlikely to be more toxic than cypermethrin based on acute toxicity, genotoxicity and repeat-dose toxicity studies. However, it was noted during the experts' meeting that further data including genotoxicity, were submitted for some common metabolites with lambda-cyhalothrin (EFSA, 2014b). These data have been submitted for the assessment of the confirmatory data on lambda-cyhalothrin, however they are not yet peer-reviewed by EFSA and a conclusion on these metabolites (3-PBA and 4-OH-PBA) cannot be currently drawn (data gap).[4] It is therefore further noted that the conclusions on this group of metabolites might need to be revised once confirmatory data on lambda-cyhalothrin are peer reviewed.

For the metabolite 3-OH-benzoic acid, the limited data available are insufficient to conclude on its toxicological profile and relative toxicity in comparison with the parent (no further data are requested regarding the representative uses).

No specific toxicological investigations were provided for the individual isomers in order to allow a conclusion on their relative toxicity (data gap, see also Section 3).

The **Acceptable Daily Intake** (ADI) is 0.005 mg/kg bw per day based on the 2-year rat study supported by the DNT study, and applying an uncertainty factor (UF) of 100. The **Acute Reference Dose** (ARfD) is 0.005 mg/kg bw per day based on the DNT study, and applying an additional UF of 10 to taken into account that the gavage route was not applied for the pups, and an additional UF of 3 based on the limited investigations during the study. The **Acceptable Operator Exposure Level** (AOEL) and **Acute Acceptable Operator Exposure Level** are both 0.0025 mg/kg bw per day based on the DNT study (also supported by the 2-year rat study for the AOEL), and applying a correction for an oral absorption of 50% and the same increased UF of 3000. It is noted that in the Review Report (European Commission, 2004), the ADI was 0.05 mg/kg bw per day based on the 2-year rat study (UF 100), the ARfD was 0.20 mg/kg bw based on the rat acute neurotoxicity study (UF 100), and the AOEL was 0.06 mg/kg bw based on the 90-day dog study (OA 50% and UF 100).

The dermal absorption values for cypermethrin in the product Cypermethrin 500 EC are 1% for the concentrate and 5% for the field dilution. The exposure estimates for operators, workers, bystanders and residents[5] were below the AOEL even without the use of personal protective equipment (PPE) (for operators according to the German Model and workers) for the representative uses.

3. Residues

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

3.1. Representative use residues

Metabolism of cypermethrin in plants was investigated in root crops (sugar beet, potatoes), cereals (wheat) and the pulses/oilseed category (oilseed rape). Additional data, not suitable as guideline-compliant metabolism studies though supportive to the acceptable metabolism studies are available in

[4] During the experts' meeting the RMS indicated that according to preliminary assessment reports on metabolites 3-PBA and 4-OH-PBA that the results are equivocal for genotoxicity. However, the confirmatory addendum on lambda-cyhalothrin was not available during the meeting. Please refer to experts' consultation 2.10 in the report of peer review 175 meeting (EFSA, 2018).

[5] EFSA noted that bystander and resident exposure were performed according to the original German Model (inhalation exposure to vapours is not taken into account). If inhalation exposure to default vapour concentration in air is taken into account (following UK approach and EFSA scheme) bystander and resident exposure would remain below the AOEL.

fruit crops (apples), leafy crops (cabbage, lettuce), cereals (maize) and the pulses/oilseed category (cotton, soybean). Some of the available studies were conducted separately with the *cis*-cypermethrin and *trans*-cypermethrin isomer pairs. Throughout all studies, the metabolic pathway of cypermethrin was similar with cypermethrin being the predominant compound of the residue. Metabolite DCVA, mainly under its conjugated form, was also occurring in significant proportions in some of the crops (cabbage, lettuce, sugar beet, maize and cotton), indicating cleavage of the molecule that would lead also to formation of its counterpart, namely metabolites with the 3-phenoxybenzoyl moiety such as 3-PBA, 3-PBAldehyde and 4-OH-PBA. Metabolite DCVA is unlikely of greater toxicity than its parent compound cypermethrin while for metabolites specific to the 3-phenoxybenzoyl moiety only preliminary conclusions have been possible with regard to their toxicity (see Section 2). An available metabolism study in maize with zeta-cypermethrin confirmed the metabolic pattern observed in the studies with cypermethrin.

In the metabolism studies conducted with cypermethrin, a notable change in the isomer ratio did not occur while isomerisation was observed in the studies with separate application of *cis*- and *trans*-cypermethrin isomers. *cis*-Cypermethrin showed the biggest change with up to ca 50% converted into *trans*-cypermethrin isomers, whereas less than 20% *trans*-cypermethrin was converted into *cis*-cypermethrin isomers. The observed tendency of isomerisation, if not in equilibrium, is consistent with observations in metabolism studies with alpha-cypermethrin, and needs to be taken into account when assessing active substances composed of isomers contained in cypermethrin but in different ratios.

A confined rotational crop study conducted at representative intervals after soil application of cypermethrin at an exaggerated rate (1 kg a.s./ha, 20 N) in wheat, sugar beet, lettuce and cotton demonstrated a steady decline of total residue levels in rotational crops over time. Transfer of residues from soil into crops is limited as for total residues of $\leq$ 0.05 mg/kg in the mature crops at any tested interval except for wheat, however the reliability of the reported residue levels may be affected by high residues in the control samples specifically for wheat. Based on the experiment conducted with (^{14}C-cyclopropane)-labelled cypermethrin in sugar beet (no other crop tested for this label), the data may indicate a preferential uptake of metabolites specific to the cyclopropane moiety, which is considered coherent with the formation rate of the major soil metabolite DCVA (*cis*- and *trans*-isomer, up to 47.4% applied radioactivity (AR)) reported in Section 4. Further identification of residues in rotational crops was not conducted, and was waived for the representative uses in view of the low residues observed in a 20 N study.

The effects of processing on the nature of cypermethrin residues have been investigated at test conditions representing boiling, pasteurisation and sterilisation. Cypermethrin was stable to hydrolysis under conditions simulating boiling, baking, brewing and pasteurisation while significant formation of DCVA and 3-PBAldehyde was observed under sterilisation conditions. A specific residue definition for processed commodities is currently not proposed and the definition for primary crops may be used once the assessment of the toxicological relevance of metabolites with the 3-phenoxybenzoyl moiety is finalised.

Based on the available information, the plant residue definition is proposed as 'cypermethrin including other mixtures of constituent isomers (sum of isomers)' for **monitoring** and as 'cypermethrin (sum of isomers)' for **risk assessment**. This residue definition should be considered provisional for risk assessment pending finalisation of the assessment of the genotoxic potential of 3-PBA and review of the preliminary conclusions in toxicology on the whole group of related metabolites bearing the 3-phenoxybenzoyl moiety (besides 3-PBA also, e.g. PBAldehyde, 4-OH-PBA) once the confirmatory data on lambda-cyhalothrin have been peer reviewed (see Section 2).

In livestock, poultry and ruminant metabolism studies conducted with cypermethrin showed a similar metabolic pattern in all matrices. Cypermethrin isomers were major residues in poultry whole eggs and in fat and in ruminant milk and fat. 3-PBA glycine was major in ruminant liver, kidney, muscle and in milk. DCVA free and conjugated was recovered at significant proportions in all matrices. Metabolism of isomers in animals was preferential, indicated by enrichment of the hen matrices by diastereomers having *S*-configuration at position 1 of the cyclopropane ring[6] and enrichment of ruminant matrices by *cis*-isomers particularly enantiomer (1*S cis* α*R*). The relative toxicity of individual isomers was not provided, but is required (data gap), specifically in view of the observation that in ruminant matrices the residues are enriched with the two enantiomers that constitute alpha-cypermethrin (lower reference values than cypermethrin).

[6] 1*S cis* α*S;* 1*S cis* α*R;* 1*S trans* α*S;* 1*S trans* α*R*.

The animal residue definition **risk assessment** is therefore provisionally set as 'cypermethrin including other mixtures of constituent isomers (sum of isomers)' and using a relative potency factor of 4 to account for the potential increase in toxicity of the residues in animal commodities until further information on the relative toxicity of the individual isomers has become available. Again, finalisation of the assessment of the genotoxic potential of 3-PBA and review of the preliminary conclusions in toxicology on the whole group of related metabolites with the 3-phenoxybenzoyl moiety is awaited to conclude on the animal residue definition for risk assessment.

The animal residue definition for **monitoring** is proposed as 'cypermethrin including other mixtures of constituent isomers (sum of isomers)'.

A metabolism study in fish with cypermethrin was not submitted although triggered (formal data gap), however, an available study in the alpha-cypermethrin dossier was considered suitable to address the question from a scientific point of view.

The number of acceptable residue field trials to support the representative uses was insufficient for barley and wheat (data gap) while sufficient data were available in oilseed rape and potato. Analysis of residues of cypermethrin was conducted with validated methods and integrity of samples during storage prior to analysis was demonstrated.

The available information is insufficient to rule out potential residues in pollen and bee products for human consumption (data gap).

Available rotational crop field trials had shortcoming that rendered them not reliable. However, the confined rotational crop study is considered sufficient to conclude that residue levels in rotational crops will unlikely exceed 0.01 mg/kg when the preceding crops are treated at GAP rate.

Processing residue trials were available to derive processing factors for several processed commodities with regard to residues of cypermethrin.

Whether the data available on the magnitude of residues in primary, rotational crops and processed commodities will be sufficient to address the relevant residues for consumer risk assessment is pending the review of the preliminary conclusions in toxicology on the whole group of related metabolites bearing the 3-phenoxybenzoyl moiety once the confirmatory data on lambda-cyhalothrin have been peer reviewed, including a final conclusion regarding the genotoxic potential of 3-PBA.

The chronic and acute consumer risk assessment conducted with the EFSA PRIMo rev. 2 did not result in an exceedance of ADI (41.3% NL child) and the ARfD (99.4% milk and milk products, UK infant) for the representative uses. Acute intakes of milk and milk products for vulnerable consumer groups are very close to the ARfD, applying the provisional risk assessment residue definition and provisional relative potency factor. EFSA therefore emphasises the importance of reducing uncertainty in the current assessment by providing further information on the relative toxicity of individual isomers in cypermethrin. The consumer dietary risk assessment is moreover provisional considering the data gaps identified for additional residue trials in barley and wheat and the pending assessment of the metabolites, most notably 3-PBA.

The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water that might contain metabolites DCVA, PBAcid and carboxamide (see Section 4).

3.2. Maximum residue levels

As outcome of the renewal review, specifically as for the lowered toxicological reference values, a prioritisation of the initiation of the existing MRLs review of cypermethrins is recommended. A screening assessment for all MRLs in place indicated a theoretical maximum daily intake (TMDI) corresponding to 1,212% of the ADI and a large exceedance of the ARfD for several commodities (top 3: > 5,300% oranges, > 3,500% grapefruit, scarole). It should be noted that the assessment is unrefined, however, it can be reasonably expected that exceedance of the toxicological reference values will occur for a number of commodities also in a refined risk assessment.

4. Environmental fate and behaviour

Cypermethrin was discussed at the Pesticides Peer Review Teleconference (TC) 172 in April 2018.

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, cypermethrin exhibited low to moderate persistence, forming the major (> 10% AR) metabolites DCVA (*cis*- and *trans*-isomer) (max. 47.4% AR), 3-PBA (max. 10.2% AR), which exhibited low to

moderate and very low to low persistence, respectively. Mineralisation of the cyclopropyl and phenyl rings ^{14}C-radiolabel to carbon dioxide accounted for 33.0–77.8% and 34.6–54.2% after 90 days, respectively. The formation of unextractable residues (not extracted by acetonitrile/water) for these radiolabels accounted for 28.4–36.4% AR after 120 days. In anaerobic soil incubations, degradation of cypermethrin was similar to the one under aerobic conditions, with the degradation pathway similar to that under aerobic conditions. In a soil photolysis study, metabolite carboxamide was formed at max. 18.9% AR and exhibited low persistence. Degradation endpoints in soil were presented for all the individual isomers of cypermethrin and shown difference in the rate of degradation between the isomers; this was taken into account in the exposure assessment.

Cypermethrin was immobile in soil. DCVA exhibited very high to low mobility, 3-PBA exhibited very high to slight mobility and carboxamide was immobile in soil. It was concluded that the adsorption of cypermethrin and its metabolites was not pH dependent. However, when deriving adsorption endpoints to be used for modelling for metabolites DCVA and 3-PBA, it was agreed to use soils with pH-$H_2O \geq 5.6$ (see meeting report of the pesticides peer review TC; EFSA, 2018).

Metabolites DCVA, 3-PBA and carboxamide are common metabolites with zeta-cypermethrin, gamma-cyhalothrin and beta-cypermethrin for which published EFSA conclusions are available (EFSA, 2009a, 2014a,c). Therefore, the reliable peer-reviewed agreed endpoints for degradation and adsorption in soils were added to the dataset of cypermethrin in order to derive endpoints to be used for modelling.

In satisfactory field dissipation studies carried out at two sites in Germany, one site in France and one site in Spain (spray application to the soil surface on bare soil plots in late spring), cypermethrin exhibited low to moderate persistence. Sample analyses were only carried out for the parent cypermethrin.

In laboratory incubations in dark aerobic natural sediment water systems, cypermethrin exhibited low persistence, forming the major metabolites DCVA (max. 66.1% AR in both water and sediment, exhibiting high persistence), 3-PBA (max. 25.4% AR in both water and sediment, exhibiting low to moderate persistence), and the unknown metabolite Unk1 (max. 12.2% AR in both water and sediment, exhibiting moderate to very high persistence). The unextractable sediment fraction (not extracted by acetonitrile/water) accounted for 10.1–18.8% AR at study end (100 days) for the cyclopropyl and phenyl ring ^{14}C radiolabel. Mineralisation of these radiolabels accounted for 25.1–68.8% AR at the end of the study. The rate of decline of cypermethrin in a laboratory sterile aqueous photolysis experiments was similar to that occurred in the aerobic sediment water incubations. Irradiation of phenyl- and cyclopropyl-labelled cypermethrin in sterile natural water resulted in formation of the major photodegradation products DCVA (max. 18.4% AR), and 3-PBA (max. 17.6% AR). Degradation endpoints in water/sediment were presented for all the individual isomers of cypermethrin and shown difference in the rate of degradation between the isomers; this was taken into account in the exposure assessment.

The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites DCVA, 3-PBA, and carboxamide using the FOCUS (2001) step 1 and step 2 approach (version 3.2 of the Steps 1-2 in FOCUS calculator). Two set of simulations were carried out in order to take into account the potential formation of the metabolites derived from a faster degradation of the parent: in one modelling, the geometric mean soil DT_{50} of the most stable isomer was used for cypermethrin and in the second modelling the geometric mean soil DT_{50} of the least stable isomer was used for cypermethrin. For the active substance cypermethrin, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available[7] and were performed using the geometric mean soil DT_{50} of the most stable isomer for cypermethrin. The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 91–93% spray drift reduction). The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. A further water–sediment study was conducted in order to identify metabolite Unk1; it was postulated that this metabolite resulted from further oxidation of metabolite DCVA. However, exposure and risk assessment were not provided for metabolite Unk1, therefore a data gap was identified (see Section 7).

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4[7] for the active substance cypermethrin and metabolite DCVA, 3-PBA and carboxamide. Two set of simulations were carried out in order to take into account the potential formation of the metabolites

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

derived from a faster degradation of the parent: in one modelling the geomean soil DT_{50} of the most stable isomer was used for cypermethrin and in the second modelling the geomean soil DT_{50} of the least stable isomer was used for cypermethrin. The potential for groundwater exposure from the representative uses by cypermethrin 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 cypermethrin and these metabolites.

The applicant did not provide appropriate information to address the effect of water treatments processes on the nature of the residues of metabolites DCVA, 3-PBA and carboxamide that might be present in surface water, when surface water is abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

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 following documents were considered for the risk assessments: European Commission (2002), SETAC (2001), EFSA (2009b), EFSA PPR Panel (2013a,b).

Several aspects of the hazard and risk assessment were discussed at the Pesticides Peer Review Meeting 177 in April, 2018.

As indicated in the mammalian toxicology section, a data gap was identified for the assessment of the toxicological relevance of the impurities and considering also the lack of knowledge about the detailed composition of the batches used in (eco)toxicity studies, it cannot be concluded that these batches were representative of the new technical specification leading to a critical area of concern.

Suitable toxicity data were available to assess the acute and reproductive risks to **birds** and **wild mammals**. For the risk via dietary exposure, a low acute and reproductive risk to birds and wild mammals was concluded for all representative uses based on the available risk assessments. A study investigating the potential for bioconcentration in fish was available and discussed at the experts' meeting. The experts raised several concerns but overall considered that the endpoint was sufficiently reliable for risk assessment given the margin of safety obtained in the risk assessment for fish-eating birds and mammals. A low risk to birds and mammals from secondary poisoning, exposure to contaminated water and from metabolites was concluded for all representative uses.

Toxicity data and risk assessments were available to assess the risk to **aquatic organisms** from cypermethrin and metabolites DCVA, 3-PBA and carboxamide. The available risk assessments using tier 1 toxicity endpoints for cypermethrin indicated a high acute and chronic risk to fish and aquatic invertebrates for all representative uses (FOCUS steps 1–3). A low risk was concluded only for algae (FOCUS step 3). The acute endpoint for fish was refined considering the geometric mean approach. For the aquatic invertebrates, agreed ecological threshold option (ETO) and ecological recovery option (ERO) regulatory acceptable concentration (RAC) values were available from mesocosm studies. As discussed at the experts' meeting, the ERO RAC is not considered suitable to cover the representative uses that include as well applications in autumn. Nevertheless, since aquatic invertebrates were the most sensitive group of organisms, these RAC values were considered for the conclusion on the risk assessment.

The risk assessments were also refined with exposure estimations at FOCUS step 4 (considering spray drift mitigation with a 20-m non-sprayed buffer zone). However, the risk assessments considering the ETO RAC or the ERO RAC, both indicated a high risk for all representative uses (for all FOCUS step 4 scenarios) (data gap and critical area of concern).

A low risk to aquatic organisms from the metabolites was concluded for all representative uses.

Toxicity data were available for both honey**bees** and bumblebees. Tier 1 risk assessments for honeybees, following both the Guidance Document on Terrestrial Ecotoxicology (European Commission, 2002) and also the EFSA Bee Guidance Document (EFSA PPR Panel, 2013a,b), were available. Both risk assessments indicated a high risk to honeybees. Numerous higher tier semi-field and field studies were available, which were as well discussed during the experts' meeting (spray applications on attractive flowering crops or on cereals made attractive with sugar solutions). It was agreed that, based on these data, a low risk to honeybees could not be concluded, even considering the results of those trials when the spray application was performed after the bee flight (i.e. evening application) (data gap and critical area of concern).

A low risk to honeybees from exposure via residues in surface water and guttation fluid was concluded considering the EFSA Bee Guidance Document (EFSA PPR Panel, 2013a,b). No appropriate

risk assessment was provided for the exposure via puddle water, however based on the assessments for guttation fluid, the risk from puddle water was concluded as low.

Acute contact and oral Tier 1 risk assessments for bumblebees, performed in accordance with EFSA Bee Guidance Document (EFSA PPR Panel, 2013a,b), were available indicating a high risk to bumblebees (data gap). No data and risk assessments were available for solitary bees.

No risk assessment was provided for the metabolites occurring in pollen and nectar (data gap, this was also identified as an issue that could not be finalised) or for cumulative effects.

On the basis of the tier-1 risk assessments a high in-field and off-field risk was indicated for **non-target arthropods**. Several higher tier field studies were available performed at both in-field and off-field exposure rates; these were discussed in the context of the risk assessment for the representative uses during the experts' meeting. For the in-field risk assessment, field studies performed in the United Kingdom and Italy were deemed as reliable and were concluded to show a low risk to in-field population of non-target arthropods for the representative uses. However, the experts agreed that the available studies were not suitable to cover situations where applications are performed in autumn (data gap). Two field studies, performed in the United Kingdom and France, investigated the effects to non-target arthropod populations at off-field exposure rates. Since some effects were observed at all tested rates, a no effect rate (NOER) could not be derived from these studies. As discussed in the experts' meeting risk mitigation measures could potentially mitigate the off-field risk, but it was not possible to establish a sufficient risk mitigation measure with the available data. Therefore, a low off-field risk to non-target terrestrial arthropods was not demonstrated (data gap and critical area of concern).

Sufficient toxicity data were available for the risk assessments for earthworms, other **soil macroorganisms** and **soil microorganisms** with the exception to soil mites (data gap). Considering the available data, a low risk to soil organisms was concluded for the active substance and the soil metabolites (3-PBA, DCVA and carboxamide) for all representative uses.

A low risk to **non-target terrestrial plants** and for **organisms involved in sewage treatment processes** was concluded for all representative uses.

The assessment of **endocrine properties** was discussed at the experts' meeting. Existing fish short-term reproduction assay and amphibian metamorphosis assay submitted at US-EPA were taken into consideration; however, the information was scarce, since the full study reports were not available (data gap). Moreover, it was agreed that, pending on the data gap identified in the mammalian toxicology section (see Section 2), further data may be needed to address the potential ED properties of cypermethrin for non-target organisms.

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

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Cypermethrin	Low to moderate persistence Single first-order and biphasic kinetics DT_{50} 2.0–24.2 days (DT_{90} 23.3–412 days; laboratory conditions at 20°C, 12.5–40% MWHC soil moisture) European field dissipation studies single first-order DT_{50} 9.3–31.2 days (DT_{90} 30.9–103.6 days)	Data gap
DCVA	Low to moderate persistence Single first-order DT_{50} 2.5–18.1 days (DT_{90} 8.3–60.1 days; laboratory conditions at 20°C, 12.5–45% MWHC soil moisture)	Data gap
3-PBA	Very low to low persistence Single first-order and biphasic kinetics DT_{50} 0.38–5.0 days (DT_{90} 1.3–16.0 days; laboratory conditions at 20°C, 12–50% MWHC soil moisture)	Data gap
Carboxamide	Low persistence Biphasic kinetics DT_{50} 1.5–2.9 days (DT_{90} 19–795 days; laboratory conditions at 20°C, 16.5–40% MWHC soil moisture)	Data gap

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 the representative uses[(a)]	Pesticidal activity	Toxicological relevance
Cypermethrin	Immobile K_{doc} 80,653–202,418 mL/g	No	Yes	Yes
DCVA	Very high to low mobility K_{Foc} 7–640 mL/g	No	No	Assessment not required
3-PBA	Very high to slight mobility K_{Foc} 47–2,078 mL/g	No	No	Assessment not required
Carboxamide	Immobile K_{doc} 14,609–57,376 mL/g	No	No	Assessment not required

K_{doc}: organic carbon linear adsorption coefficient; K_{Foc}: Freundlich organic carbon adsorption coefficient.
(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Cypermethrin	High risk to aquatic organisms
DCVA (soil, surface water/sediment)	Low risk to aquatic organisms
3-PBA (soil, surface water/sediment)	Low risk to aquatic organisms
Carboxamide (soil)	Low risk to aquatic organisms
Unk1 (surface water/sediment)	Data gap

Table 4: Air

Compound (name and/or code)	Toxicology
Cypermethrin	Harmful if inhaled

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 Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- Linearity data for the confirmative ions used in the method proposed for monitoring in plant commodities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Analytical method for the determination of the relevant impurity in the representative formulation (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Additional confirmatory data for the method for the determination of the residues in milk (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- A guideline-compliant method validation for the soil analytical method (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- A method for monitoring the compounds of the residue definition for body fluids (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 5).
- Further data to conclude on the (non)toxicological relevance of the impurities and on the representativeness of the batches used in the (eco)toxicity studies with regard to the new technical specification (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- Further investigations of the ED potential of cypermethrin, at least with a male pubertal assay (including dosage of hormones) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- Further investigations of the relevance of micronuclei formation in blood (Vardavas et al., 2016 in Belgium, 2018) and its possible link (causal or not) with inflammatory events (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Toxicity studies on 3-PBA and 4-OH-PBA submitted under confirmatory data on lambda-cyhalothrin (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- A fish metabolism study upon dietary exposure (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; Sections 2 and 3).
- The relative toxicity of the individual isomers to be addressed or an argumentation be provided how a sufficiently sound consumer dietary risk assessment can be conducted considering the change in isomer ratio in animal commodities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3)
- At least two additional trials on barley compliant with the SEU GAP (relevant for the representative uses in cereals in SEU; submission date proposed by the applicant: unknown; see Section 3)
- At least one independent, GAP-compliant supervised residue trial on wheat in SEU (relevant for the representative uses in cereals in SEU; submission date proposed by the applicant: unknown; see Section 3)
- Data on residue levels in pollen and bee products for human consumption as set out in current data requirements in Reg. 283/2013 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3)
- Exposure and risk assessment were not provided for metabolite Unk1 coming from water/sediment study (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 4 and 5).
- The effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water (Article 4 (approval criteria for active substances) 3. (b) of Regulation (EC) No 1107/2009) has not been assessed. In the first instance, a consideration of the processes of ozonation and chlorination may be considered appropriate. If an argumentation is made that concentrations at the point of extraction for

drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information are required to address the high risk to aquatic organisms (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further data are needed to address the high risk to honeybees (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further data are needed to address the high acute risk to bumble bees (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further data are needed to address the risk to bees from exposure to metabolites occurring in pollen and nectar (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information are required to address the in-field risk to non-target arthropods considering situations when autumn application is performed (relevant for representative uses on winter cereal or winter oil seed rape; submission date proposed by the applicant: unknown; see Section 5).
- Further data are needed to address the high off-field risk to non-target arthropods (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further data are needed to address the risk to soil mite (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Existing fish short-term reproduction assay and amphibian metamorphosis assay should be made available and taken into consideration to address the endocrine properties (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

8. Particular conditions proposed to be taken into account to manage 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 Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[8] 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.

1) The consumer dietary risk assessment is not finalised as for the provisional residues definitions for risk assessment in plant and animal commodities (pending finalisation of the assessment of the toxicity for the group of related metabolites bearing the 3-phenoxybenzoyl moiety, most notably the genotoxic potential of 3-PBA and the relative toxicity of individual isomers) and a data gap for additional residue trials in barley and wheat (see Section 3)
2) The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following

[8] 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.

abstraction of surface water that might contain metabolites DCVA, 3-PBA and carboxamide (see Sections 3 and 4).

3) The risk assessment to bees from exposure to metabolites occurring in pollen and nectar could not be finalised (see Section 5).

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

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

4) The risk assessments indicated a high risk to aquatic organisms (see Section 5).
5) The risk assessments indicated a high risk to bees (see Section 5).
6) The risk assessments indicated a high off-field risk to non-target arthropods (see Section 5).
7) The batches used in the (eco)toxicological studies could not be concluded as representative of the technical specification (see Sections 2 and 5).

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.)

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

Table 5: Overview of concerns

Representative use		Winter and spring cereals CEZ, NEZ	Winter and spring cereals SEZ	Winter oilseed rape	Spring oilseed rape	Potato
Operator risk	Risk identified					
	Assessment not finalised					
Worker risk	Risk identified					
	Assessment not finalised					
Resident/bystander risk	Risk identified					
	Assessment not finalised					
Consumer risk	Risk identified					
	Assessment not finalised	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified					
	Assessment not finalised					
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[5,6], X	X[5,6], X	X[5,6], X	X[5,6]	X[5,6]
	Assessment not finalised	X	X	X	X	X

Representative use		Winter and spring cereals CEZ, NEZ	Winter and spring cereals SEZ	Winter oilseed rape	Spring oilseed rape	Potato
Risk to aquatic organisms	Risk identified	X[4]	X[4]	X[4]	X[4]	X[4]
	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					

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.

(a): 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.

References

Belgium, 2017. Renewal Assessment Report (RAR) on the active substance cypermethrin prepared by the rapporteur Member State Belgium, in the framework of Commission Implementing Regulation (EU) No 844/2012, May 2017. Available online: www.efsa.europa.eu

Belgium, 2018. Revised Renewal Assessment Report (RAR) on cypermethrin prepared by the rapporteur Member State Belgium in the framework of Regulation (EC) No 1107/2009, March 2018. Available online: www.efsa.europa.eu

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

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, 32pp. https://doi.org/10.2903/j.efsa.2008.622

EFSA (European Food Safety Authority), 2009a. Conclusion regarding the peer review of the pesticide risk assessment of the active substance zeta-cypermethrin. EFSA Journal 2009;7(1):196r, 119 pp. https://doi.org/10.2903/j.efsa.2009.196r

EFSA (European Food Safety Authority), 2009b. Guidance on Risk Assessment for Birds and Mammals on request from EFSA. EFSA Journal 2009;7(12):1438, 358 pp. https://doi.org/10.2903/j.efsa.2009.1438

EFSA (European Food Safety Authority), 2014a. Conclusion on the peer review of the pesticide risk assessment of the active substance gamma-cyhalothrin. EFSA Journal 2014;12(2):3560, 93 pp. https://doi.org/10.2903/j.efsa.2014.3560

EFSA (European Food Safety Authority), 2014b. Conclusion on the peer review of the pesticide risk assessment of the active substance lambda-cyhalothrin. EFSA Journal 2014;12(5):3677, 170 pp. https://doi.org/10.2903/j.efsa.2014.3677

EFSA (European Food Safety Authority), 2014c. Conclusion on the peer review of the pesticide risk assessment of the active substance beta-cypermethrin. EFSA Journal 2014;12(6):3717, 90 pp. https://doi.org/10.2903/j.efsa.2014.3717

EFSA (European Food Safety Authority), 2018. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance cypermethrin. Available online: www.efsa.europa.eu

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), 2013a. 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 PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013b. 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, 2002. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002-rev. 2 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, 2004. Review report for the active substance cypermethrin. Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 15 February 2005 in view of the inclusion of cypermethrin in Annex I of Council Directive 91/414/EEC. SANCO/4333/2000-Final, 15 February 2005, 41 pp.
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. p. 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.
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. 1.3, December 2014.
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.
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.
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

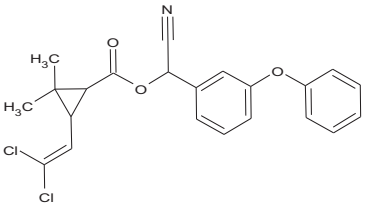
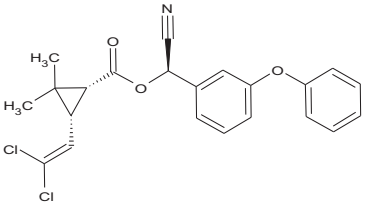
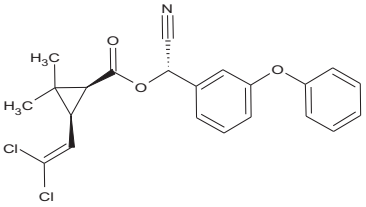
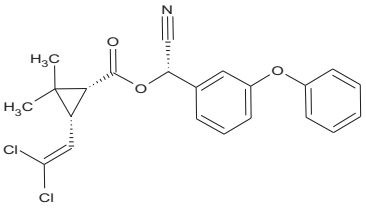
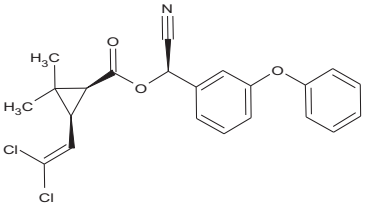
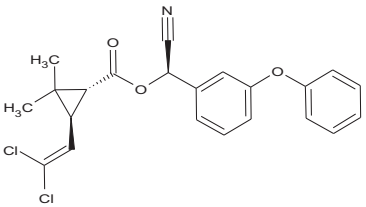
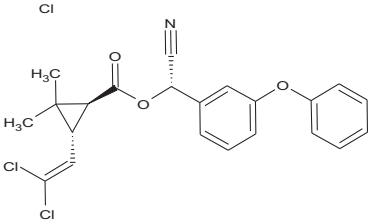
a.s.	active substance
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
CIPAC	Collaborative International Pesticides Analytical Council Limited
CWG	cypermethrin working group
DNT	developmental neurotoxicity
DT_{50}	period required for 50% dissipation (define method of estimation)

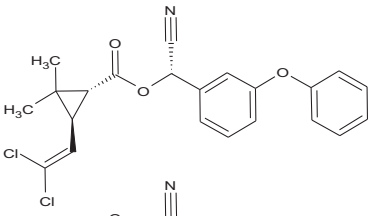
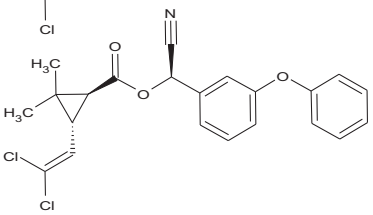
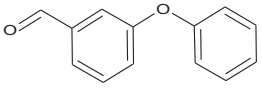
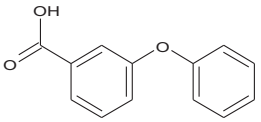
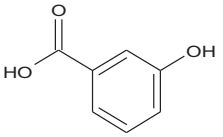
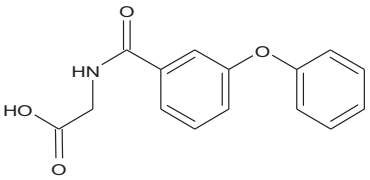
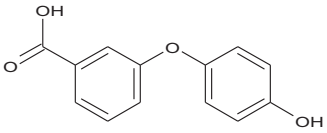
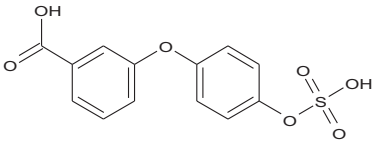
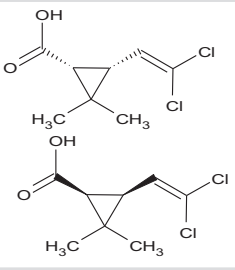
DT_{90}	period required for 90% dissipation (define method of estimation)
EC	emulsifiable concentrate
ECHA	European Chemicals Agency
ED	endocrine-disrupting
EEC	European Economic Community
ERO	ecological recovery option
ETO	ecological threshold option
FAO	Food and Agriculture Organization of the United Nations
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC	gas chromatography
GC-ECD	gas chromatography-electron capture detection
InChiKey	International Chemical Identifier Keys
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_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MRL	maximum residue level
MS	mass spectrometry
MWHC	maximum water-holding capacity
NOAEL	no observed adverse effect level
NOER	No Effect Rate
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
RMS	rapporteur Member State
SEU	southern European Union
SMILES	simplified molecular-input line-entry system
SWAN	surface water assessment enabler
TMDI	theoretical maximum daily intake
UF	uncertainty factor
WHO	World Health Organization

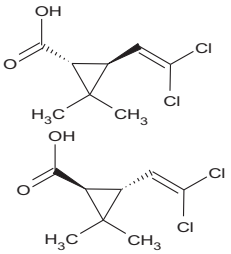
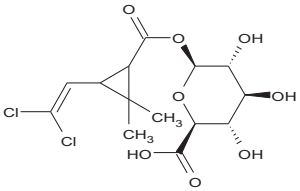
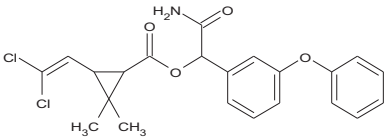
Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5402

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
cypermethrin	(*RS*)-α-cyano-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/C1C(C(=O)OC(C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-UHFFFAOYSA-N	
***Cis*-I** (1*R cis* α*R*)	(*R*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@H]1[C@@H](C(=O)O[C@@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-BJLQDIEVSA-N	
(and 1*S cis* α*S*)	(*S*)-α-cyano-3-phenoxybenzyl (1*S*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@@H]1[C@H](C(=O)O[C@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-QWFCFKBJSA-N (enantiomer: GUQZCTLEJXHSIH-JMSVTXOYSA-N)	
***Cis*-II** (1*R cis* α*S*)	(*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@H]1[C@@H](C(=O)O[C@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-NSHGMRRFSA-N	
(and 1*S cis* α*R*)	(*R*)-α-cyano-3-phenoxybenzyl (1*S*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@@H]1[C@H](C(=O)O[C@@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-WSTZPKSXSA-N (enantiomer: GUQZCTLEJXHSIH-RZAVTOELSA-N)	
***Trans*-III** (1*R trans* α*R*)	(*R*)-α-cyano-3-phenoxybenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@@H]1[C@@H](C(=O)O[C@@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-HBFSDRIKSA-N	
(and 1*S trans* α*S*)	(*S*)-α-cyano-3-phenoxybenzyl (1*S*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@H]1[C@H](C(=O)O[C@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-NLWGTHIKSA-N (enantiomer: GUQZCTLEJXHSIH-RBTQXQDPSA-N)	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
***Trans*-IV** (1*R trans* α*S*)	(*S*)-α-cyano-3-phenoxybenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@@H]1[C@@H](C(=O)O[C@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-GGPKGHCWSA-N	
(and 1*S trans* α*R*)	(*R*)-α-cyano-3-phenoxybenzyl (1*S*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/[C@H]1[C@H](C(=O)O[C@@H](C#N)c2cccc(Oc3ccccc3)c2)C1(C)C KAATUXNTWXVJKI-CMKODMSKSA-N (enantiomer: GUQZCTLEJXHSIH-TXXTYBRISA-N)	
3-PBAldehyde 3-PBAld	3-phenoxybenzaldehyde O=Cc1cc(Oc2ccccc2)ccc1 MRLGCTNJRREZHZ-UHFFFAOYSA-N	
3-PBA PBAcid	3-phenoxybenzoic acid O=C(O)c1cc(Oc2ccccc2)ccc1 NXTDJHZGHOFSQG-UHFFFAOYSA-N	
3-OH-benzoic acid	3-hydroxybenzoic acid OC(=O)c1cc(O)ccc1 IJFXRHURBJZNAO-UHFFFAOYSA-N	
3-PBA glycine	*N*-(3-phenoxybenzoyl)glycine O=C(O)CNC(=O)c1cc(Oc2ccccc2)ccc1 IHTUCGBIFBJPEK-UHFFFAOYSA-N	
4-OH-PBA	3-(4-hydroxyphenoxy)benzoic acid O=C(O)c1cc(Oc2ccc(O)cc2)ccc1 OSGCDVKVZWMYBG-UHFFFAOYSA-N	
4-OH-PBA sulfate	3-[4-(sulfooxy)phenoxy]benzoic acid OS(=O)(=O)Oc1ccc(cc1)Oc1cc(ccc1)C(=O)O VQSRFYGVVRDCSY-UHFFFAOYSA-N	
***cis*-DCVA**	(1*R*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid—(1*S*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (1/1) Cl\C(Cl)=C/[C@H]1[C@@H](C(=O)O)C1(C)C.O=C(O)[C@H]1[C@@H](/C=C(/Cl)Cl)C1(C)C QNOJQXYROGDZAX-LNDXSTFSSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
***trans*-DCVA**	(1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid—(1*S*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (1/1) Cl\C(Cl)=C/[C@@H]1[C@@H](C(=O)O)C1(C)C.O=C(O)[C@H]1[C@H](/C=C(/Cl)Cl)C1(C)C QNOJQXYROGDZAX-RPBIHNRISA-N	
DCVA glucuronide	1-*O*-{[(1*RS*,3*RS; 1RS,3SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropyl]carbonyl}-β-D-glucopyranuronic acid O=C(O[C@@H]1O[C@@H]([C@@H](O)[C@H](O)[C@H]1O)C(=O)O)C1C(/C=C(/Cl)Cl)C1(C)C SCDVRNUOLGVBJK-UUADDGCPSA-N	
carboxamide	(1*RS*)-2-amino-2-oxo-1-(3-phenoxyphenyl)ethyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate Cl\C(Cl)=C/C1C(C(=O)OC(c2cccc(Oc3ccccc3)c2)C(N)=O)C1(C)C APXUYVIALTYBMS-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2017.2.1 ACD/Labs 2017 Release (File version N40E41, Build 96719, 6 September 2017).
(c): ACD/ChemSketch 2017.2.1 ACD/Labs 2017 Release (File version C40H41, Build 99535, 14 Februrary 2018).