STATEMENT

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Review of the residue definitions for risk assessment of pyrethroids forming common metabolites

European Food Safety Authority (EFSA)

Abstract

In accordance with Article 31 of Regulation (EC) No 178/2002, the European Commission mandated EFSA to issue a statement to determine if 3-phenoxybenzoic acid (PBA or 3-PBA) and 3-(4′-hydroxyphenoxy)benzoic acid (PBA(OH) or 4-OH-PBA) (metabolites common to several pyrethroid substances) should be included in the residue definitions for risk assessment, and if so to conclude on the appropriate definitions (crops, livestock and processed commodities, where necessary). EFSA prepared a statement containing conclusions and recommendations concerning the residue definitions for risk assessment of PBA and PBA(OH). The statement was circulated to Member States for consultation via a written procedure before finalisation.

Keywords: pyrethroids, common metabolites, residue definition, risk assessment, pesticide

Requestor: European Commission

Question number: EFSA-Q-2021-00163

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Declarations of interest: If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

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Summary

In February 2021, the European Commission mandated EFSA to issue a statement to determine if 3-phenoxybenzoic acid (PBA or 3-PBA) and 3-(4′-hydroxyphenoxy)benzoic acid (PBA(OH) or 4-OH-PBA) metabolites common to several pyrethroid substances should be included in the residue definitions for risk assessment, and if so to conclude on the appropriate definitions (crops, livestock and processed commodities, where necessary).

EFSA prepared a statement containing conclusions and recommendations concerning the residue definitions for risk assessment of pyrethroid common metabolites PBA and PBA(OH). The draft statement was circulated to Member States (MSs) for consultation via a written procedure. No comments were received by the set deadline of 20 April 2023.

Pyrethroid common metabolites, most notably metabolites PBA, PBA(OH) including their conjugated forms and 3-phenoxybenzaldehyde (PBAld) can account for a significant proportion of the residues in different food commodities when various pyrethroid active substances are used as pesticides.

In the remit of this statement, the provisional residue definitions for risk assessment for cypermethrins, including cypermethrin, alpha-cypermethrin, beta-cypermethrin, zeta-cypermethrin were reviewed.

The existing proposal for a residue definition for these active substances were confirmed as:

'cypermethrin including other mixtures of constituent isomers (sum of isomers)'.

A residue definition for risk assessment covering the group of related metabolites bearing the 3-phenoxybenzoyl moiety, notably the major metabolites PBA, PBA(OH) including their conjugated forms and PBAld, remains provisional. For the metabolite PBAld, the hazard characterisation is not yet completed pending the availability of aneugenicity data on this compound.

EFSA proposes that these data be submitted and evaluated as a prerequisite for proceeding with the assessment of how the whole group of related and common metabolites bearing the 3-phenoxybenzoyl moiety is to be considered for the consumer risk assessment.

Although the number of pyrethroid active substances approved in the EU as pesticides has decreased in the recent past, most of them are still internationally used, and CXLs as well as import tolerances for various imported products exist to meet the needs of international trade. Moreover, pyrethroid active substances are also used in other EU regulatory areas such as biocides and veterinary medicines, which present additional sources of possible dietary exposure of consumers to the pyrethroid common metabolites.

To assess whether the use of pyrethroid active substances in plant protection products, biocides and veterinary medicinal products can result in an overall significant dietary exposure to their common metabolites bearing the 3-phenoxybenzoyl moiety, a more comprehensive data base is required.

To derive a final conclusion on the need to establish a residue definition which covers the common metabolites bearing the 3-phenoxybenzoyl moiety resulting from the use of active substances belonging to the class of pyrethroids the following information is required:

- *In vitro* and/or *in vivo* micronucleus tests to address the aneugenicity of PBAld;
- Reliable residue data on the expected residue concentration of 3-PBA, PBA(OH) (including their conjugates) and PBAld in food resulting from the use of pyrethroids as active substances (a.s.) in plant protection products, biocides and veterinary medicinal products.

In order to obtain a more reliable residue database, EFSA proposes

- To request again MSs to screen the national authorisation databases whether information on the occurrence of pyrethroid metabolites 3-PBA, PBA(OH) (including their conjugates) and PBAld were provided and to share the data with EFSA and possibly involve applicants in data collection;
- To screen and evaluate pesticide monitoring data submitted to EFSA in the framework of Art. 31 of Regulation 396/2005 on pyrethroid metabolites 3-PBA, PBA(OH) (including their conjugates) and PBAld;
- To conduct a systematic literature review on occurrence data of pyrethroid metabolites 3-PBA, PBA(OH) (including their conjugates) and PBAld relevant for exposure of European consumers, considering also sources such as data provided to the JMPR and JECFA.

EFSA reiterates the proposal made to risk managers in previous outputs to consider whether an approach similar to that adopted for the triazole derivative metabolites (TDMs) could be chosen, given that various pyrethroid compounds are approved and that most of them form the same common metabolites, that pyrethroids are a broadly used substance class, and that the reference values of their common metabolites are in a similar order of magnitude as for the TDMs.

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Background

3-Phenoxybenzoic acid (PBA or 3-PBA) and 3-(4′-hydroxyphenoxy) benzoic acid (PBA(OH) or 4-OH-PBA) are metabolites that form during the breakdown of many active substances belonging to the pyrethroid group. Some pyrethroid active substances are approved for use in plant protection products in the European Union, for others import tolerances exist, and therefore consumers may be exposed to the metabolites through dietary intake.

As those metabolites are common to several active substances, a common assessment which considers all the available toxicity data concerning the relevant active substances is needed to ensure a harmonised assessment of all pyrethroid substances and to allow for a consumer risk assessment to be carried out.

In response to a mandate from the European Commission, the Panel on Plant Protection Products and their Residues (PPR Panel) of EFSA prepared a scientific opinion (EFSA-Q-2021-00118) on the toxicity profile of PBA and PBA(OH) metabolites common to several pyrethroid substances under Article 29 of Regulation (EC) No 178/2002[1] that was adopted in September 2022 (EFSA PPR Panel, 2022) providing advice on:

- The genotoxicity of PBA and PBA(OH), discussed controversially in the evaluation of the active substance lambda-cyhalothrin and gamma-cyhalothrin.
- Toxicological endpoints relevant for hazard characterisation of PBA and PBA(OH) according to Regulation (EU) 283/2013[2] for active substance and relevant for setting of health-based guidance values (HBGVs).
- Comparison of relevant general toxicity endpoints of PBA and PBA(OH) to their parent pyrethroid compounds as listed in the mandate.
- Derivation of HBGV for PBA and PBA(OH).

In its scientific opinion, EFSA concluded that:

- Based upon available experimental data, PBA and PBA(OH) do not raise a concern with respect to genotoxicity.
- PBA and PBA(OH) showed lower acute oral toxicity (based on LD_{50}) and different hazard (no neurotoxic mechanism) compared with their parent pyrethroid compounds.
- EFSA noted that limited data is available to evaluate the toxicity of common metabolites towards parent pyrethroid compounds.
- Based on limited data, it was concluded that PBA and PBA(OH) have different qualitative (no neurotoxic mechanism) and quantitative (higher no observed adverse effect levels (NOAELs)) toxicity compared to the parent compounds. For both metabolites, the acceptable daily intake (ADI) has been derived at 0.1 mg/kg body weight (bw) per day, based upon the overall NOAEL of 100 from the 28-day rat studies with 3-phenoxybenzaldehyde (PBAld) and PBA(OH) and an uncertainty factor (UF) of 1,000. The acute reference dose (ARfD) has been derived for PBA and PBA(OH) at 1 mg/kg bw based upon the overall NOAEL of 100 from 28-day rat studies with PBAld and PBA(OH) and UF of 100.

In the mandate, EFSA was also asked by European Commission assess the appropriateness of the existing residue definitions for plant and animal commodities (including processed commodities) established for active substances belonging to the class of pyrethroids (Q-2021-00163). Member States should be provided with an opportunity to submit comments on that assessment.

Therefore, in April 2023, EFSA prepared a draft statement to address the relevant point of the mandate as outlined above, which was circulated to Member States for commenting via a written procedure. No comments were received by 20 April 2023.

[1] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

[2] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with 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 93, 3.4.2013, p. 1–84.

1. Terms of Reference as provided by the requestor

In the light of some divergence of views between the Member States experts involved in the peer review process, the need to avoid unnecessary testing on vertebrate animals, and for ensuring harmonised assessments for the pyrethroid active substances, including for ongoing or future renewals, the Commission mandated EFSA to conduct the following tasks:

Step 1: preparatory work

The Commission asked EFSA, in cooperation with Member States, to collect all available evidence relevant for the completion of steps 2 and 3 considering information for all pyrethroid active substances for which these metabolites occur.

Step 2: toxicological characterisation

The Commission asked the Panel on Plant Protection Products and their Residues:

- to perform a literature review of published scientific literature to ensure the database is complete;
- to assess the available evidence in relation to the toxicity profile of the metabolites PBA and PBA(OH) and establish a toxicity profile for the metabolites PBA and PBA(OH), including the genotoxic potential, in particular indicating whether the metabolites are of lower or comparable toxicity to the parent substances. If possible, health-based reference values for the metabolites to be used in risk assessment should be derived.

Step 3: consideration of the impact on the consumer risk assessment

As soon as possible, in parallel to finalising the opinion of the Panel, EFSA should indicate to the Commission whether or not a follow up review of existing MRLs would be likely to become necessary, taking into account all available elements that possibly have an impact on the consumer risk assessment. Based on that, the Commission can then consider to request a follow up opinion under Article 43 of Regulation (EC) No 396/2005[3] (including data and scope to be considered), i.e. to carry out an assessment of dietary exposure to them from the use of multiple active substances.

Once the toxicological assessment in Step 2 is completed by the Panel, the Commission asks EFSA to provide a conclusion to determine if the metabolites should be included in the residue definitions for risk assessment, and if so to conclude on the appropriate definitions (crops, livestock and processed commodities, where necessary).

All information collected in Step 1 and identified in Step 2 (literature survey) should be considered. The issues and divergent views identified in the peer review process of the confirmatory information recently assessed (e.g. EFSA Technical Reports) and/or during the renewal evaluations should be taken into account by the Panel and EFSA. The current state of the art on assessment of toxicity, read-across and other alternative in silico and non-testing methods and tools should be considered, where appropriate.

2. Interpretation of the Terms of Reference for this statement

This statement covers 'Step 3 of the terms of reference (ToR): consideration of the impact on the consumer risk assessment', considering available evidence collected under 'Step 1: preparatory work' that is considered relevant for Step 3.

Step 2 has already been addressed in a scientific opinion of the PPR Panel of EFSA on the toxicity profile of PBA and PBA(OH) metabolites common to several pyrethroid substances (EFSA PPR Panel, 2022) and is also considered for Step 3 as required.

Regarding Step 3, in accordance with Article 31 of Regulation (EC) No 178/2002, EFSA was asked to conclude whether PBA and PBA(OH) (metabolites common to several pyrethroid substances) should be included in the residue definitions for risk assessment, and if so to conclude also on the appropriate definitions (crops, livestock and processed commodities, where necessary).

[3] 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.

In the accompanying letter to the mandate, the European Commission also asked EFSA to indicate whether or not a follow up review of existing MRLs would be likely to become necessary, taking into account all available elements that possibly have an impact.

In this letter it was further clarified that the following substances (some of which are no longer approved in the EU) could form common metabolites: gamma-cyhalothrin, lambda-cyhalothrin, alpha-cypermethrin, cypermethrin, beta- and zeta-cypermethrin, deltamethrin, etofenprox, tau-fluvalinate, fenvalerate, esfenvalerate, permethrin, fenpropathrin, cyfluthrin, beta-cyfluthrin and acrinathrin. This list might not be exhaustive but mentions the relevant pyrethroid active substances that are or until recently were approved for use in plant protection products in the EU or for which import tolerances exist.

In view of the forthcoming peer review on the renewal of the approval in accordance with Regulation (EC) No 1107/2009[4] for several of these substances, it was agreed with the requestor that for the active substances (a.s.) listed in Table 1, the residue definitions for risk assessment should be reviewed by EFSA and Member States in the remit of the peer review. These a.s. are therefore not assessed under the current statement.

Table 1: Pyrethroid active substances scheduled for assessment in the forthcoming peer review

Esfenvalerate	Renewal peer review is due shortly. An evaluation of the residue definition will be presented in the EFSA conclusion on the peer review of the pesticide risk assessment of the active substance esfenvalerate. See also fenvalerate.
Deltamethrin	Currently under renewal peer review. An evaluation of the residue definition will be presented in the EFSA conclusion on the peer review of the pesticide risk assessment of the active substance deltamethrin.
Tau-fluvalinate	Renewal peer review is due shortly. An evaluation of the residue definition will be presented in the EFSA conclusion on the peer review of the pesticide risk assessment of the active substance tau-fluvalinate.
Lambda-cyhalothrin	Renewal peer review will start shortly (expected in 2023). One of the isomers of lambda-cyhalothrin is gamma-cyhalothrin; the residue definition for both compounds should therefore be evaluated together and in the light of the most recent information received. An evaluation of the residue definition will be presented in the EFSA conclusion on the peer review of the pesticide risk assessment of the active substance lambda-cyhalothrin.
Gamma-cyhalothrin	Gamma-cyhalothrin is one of the isomers of the substance lambda-cyhalothrin. The residue definition for both compounds should therefore be evaluated together and in the light of the most recent information received in the context of the forthcoming renewal peer review of lambda-cyhalothrin. An evaluation of the residue definition, that will necessarily consider gamma-cyhalothrin as one isomer of lambda-cyhalothrin, will be presented in the EFSA conclusion on the peer review of the pesticide risk assessment of the active substance lambda-cyhalothrin. Furthermore, the review of the existing MLs for gamma-cyhalothrin according to Article 12 of Regulation (EC) No 396/2005is ongoing (initiated on 16 January 2023) and will present the latest risk assessment for this compound in a reasoned opinion.
Etofenprox	Renewal peer review is due shortly. An evaluation of the residue definition will be presented in the EFSA conclusion on the peer review of the pesticide risk assessment of the active substance etofenprox.

Furthermore, the requestor clarified that for actives substances (any ratio of constituent isomers) that are neither approved as pesticides in the EU nor subject to import tolerances, the review of the residue definition for risk assessment is not necessary because dietary exposure to pesticide residues of these compounds can be excluded (see Table 2). Hence, also these substances are not under the scope of the current assessment.

[4] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 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.

Table 2: Pyrethroid active substances for which the residue definition is not (re)assessed

Fenvalerate	Not approved in the EU. EFSA conclusion not available. Esfenvalerate is an isomer of fenvalerate. The non-isomeric common metabolites that could be formed from fenvalerate isomers could be assessed in the remit of the review of esfenvalerate.
Permethrin	Not approved in the EU. EFSA conclusion and MRL review not available. Peer-reviewed residue definition not available. The residue definition only needs to be assessed should an application for an import tolerance be received.
Fenpropathrin	Not approved in the EU. EFSA conclusion and MRL review not available. Peer=reviewed residue definition not available. An assessment will be provided by EFSA in the remit of an ongoing Art. 43 mandate for the assessment of non-approved active substances.
Cyfluthrin	Not approved in the EU. Based on the plant and livestock metabolism data available to EFSA, the common metabolites subject to this assessment are not formed.
Beta-cyfluthrin	Not approved in the EU. Based on the plant and livestock metabolism data available to EFSA, the common metabolites subject to this assessment are not formed.
Acrinathrin	Not approved in the EU and no CXLs in place. The residue definition only needs to be assessed should an application for an import tolerance be received.

Therefore, the scope of the current assessment can be summarised as:

The current review of the residue definition for risk assessment shall focus on cypermethrin and its different mixtures of constituent isomers including alpha-, beta- and zeta-cypermethrin since the active substance cypermethrin is approved until 31/1/2029[5].

EFSA shall provide a recommendation whether the common metabolites of active substances belonging to the pyrethroid group should be included in the residue definitions for risk assessment, and if so, to conclude on the appropriate definitions for crops, livestock and processed commodities, where necessary.

Assessment

3. General approach to derive proposals for risk assessment residue definitions

The residue definition for risk assessment is used by risk assessors to evaluate the potential risk of dietary intake of residues resulting from the application of a pesticide. According to the pertinent data requirements,[6] the following elements should be considered when judging which compounds are to be included in the residue definition:

- the toxicological significance of the compounds
- the amounts likely to be present in food and feed.

For the estimation of the potential and actual exposure it is important to consider also if the use of active substances is resulting in common metabolites or if it is also used as biocide or veterinary drug.

Therefore, when deriving residue definitions for risk assessment, aspects of toxicity (see Sections 4 and 5), occurrence and dietary exposure to residues (see Sections 7 and 8) need to be considered and the use-specific residue pattern in food of plant origin, including processed commodities, as well as in animal commodities that result from livestock exposure via feed needs to be taken into account.

To establish the specific residue pattern, metabolism studies in primary crops, rotational crops, livestock and studies on the nature of residues in processed commodities are screened. Metabolites that occur across several commodities and at significant proportions have a higher exposure potential and are therefore more likely to be included in the residue definition for risk assessment.

The toxicological evaluation of metabolites attempts a hazard characterisation, considering genotoxicity and general toxicity for regulatory assessments. It needs to be evaluated whether the

[5] Commission Implementing Regulation (EU) 2021/2049 of 24 November 2021 renewing the approval of the active substance cypermethrin as a candidate for substitution in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 420, 25.11.2021, p. 6–13.

[6] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market Text with EEA relevance. OJ L 93, 3.4.2013. p. 1–84.

toxicity of the metabolite is qualitatively and quantitatively similar to that of the active substance or other metabolites of interest, so that these compounds may need to be grouped together or potency factors derived to facilitate an appropriate risk assessment.

4. Toxicological information on the parent active substances

An overview of the toxicological reference values (TRVs) of the different cypermethrins is presented in Table 3.

Table 3: Toxicological information on the pyrethroid parent active substances

Active substance	TRV	Value	Reference	Comments
Alpha-cypermethrin	ADI	0.00125 mg/kg bw per day	EFSA (2018c)	Based on the pups LOAEL in a DNT study in rats, UF 200.
	ARfD	0.00125 mg/kg	EFSA (2018c)	Based on the pups LOAEL in a DNT study in rats, UF 200.
Beta-cypermethrin	ADI	0.0016 mg/kg bw per day	EFSA (2014)	Based on the LOAEL from a DNT study in rats, UF 300.
	ARfD	0.0016 mg/kg bw	EFSA (2014)	Based on the LOAEL from a DNT study in rats, UF 300.
Cypermethrin	ADI	0.005 mg/kg bw per day	EFSA (2018b)	Based on the 2-year rat study supported by the DNT study in rats, UF 100.
	ARfD	0.005 mg/kg bw	EFSA (2018b)	Based on the DNT study in rats, with additional UF of 30 to account for gavage route was not applied for the pups, and limited investigations performed during the study.
Zeta-cypermethrin	ADI	0.0015 mg/kg bw per day	EFSA (2022)	Based on a DNT study in rats, UF 100, supported by a 2-year study in rats performed with cypermethrin, UF 250.
	ARfD	0.0015 mg/kg bw	EFSA (2022)	Based on a DNT study in rats, UF 100.

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight; DNT: developmental neurotoxicity; LOAEL: lowest observed adverse effect level; UF: uncertainty factor.

5. Toxicological information on the pyrethroid common metabolites

PBA and PBA(OH) do not raise a concern with respect to genotoxicity. As regards general toxicity, PBA and PBA(OH) have different qualitative (no neurotoxic mechanism) and quantitative (higher NOAELs) toxicity compared to the parent pyrethroid compounds. For both metabolites, an **ADI** value of **0.1 mg/kg bw per day** and an **ARfD** value of **1 mg/kg bw** was derived (EFSA PPR Panel, 2022). Further details of the toxicological evaluation are given in Table 4.

Table 4: Toxicological information on the evaluated pyrethroid metabolites

Compound	HBGV	Value	Reference	Comments
PBA and PBA (OH)	ADI	0.1 mg/kg bw per day	EFSA PPR Panel (2022)	Based upon the overall NOAEL of 100 mg/kg bw per day from the 28-day studies with PBAld (NOAEL of 98.9 mg/kg bw per day) and PBA(OH) (NOAEL of 106.9 mg/kg bw per day) and UF of 1,000.
	ARfD	1 mg/kg bw	EFSA PPR Panel (2022)	Based upon the same overall NOAEL and UF of 100.

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight; NOAEL: no observed adverse effect level; UF: uncertainty factor.

It is noted that studies on general toxicity (regulatory studies and reliable public literature) conducted with PBAld were also collected and evaluated by the EFSA PPR Panel as part of the body of evidence (i.e. short-term toxicity studies with PBAld were evaluated to support the read-across for PBA). However, the PPR Panel did not collect and assess data on the genotoxicity potential of PBAld

nor did the PPR Panel derive reference values (or HBGVs) for PBAld because the assessment of this pyrethroid common metabolite was not requested by the requestor.

In general, it should be noted that for common metabolites where metabolite-specific data are available these should be used for the assessment of metabolites toxicity. Differently than in cases where a metabolite is unique to one parent molecule, in case of common metabolites the conclusion that metabolites share the toxicity of parent compound could be misleading since the exact parent compound may be unknown when the metabolite is detected in different matrices.

During the peer review of the active substances cypermethrin (EFSA, 2018b) and alpha-cypermethrin (EFSA, 2018c), limited toxicological data was assessed for PBAld. It was concluded that PBAld was unlikely to be more toxic than cypermethrin and alpha-cypermethrin based on the acute toxicity, genotoxicity and repeat-dose toxicity studies submitted with the two dossiers. PBAld did not induce gene mutation or clastogenicity; however, the different genotoxicity data-packages for PBAld submitted for the peer review of cypermethrin and alpha-cypermethrin did neither contain *in vitro* nor *in vivo* micronucleus tests. Hence, since aneugenicity was not addressed, a data gap was identified for PBAld. Since the derivation of reference values could be affected by the conclusion on aneugenicity, no reference values for PBAld are derived at present.

6. Occurrence data on the pyrethroid common metabolites

The data collection conducted under step 1 of the mandate was intended to collect data on the pyrethroid common metabolites identified/quantified in metabolism studies, residue trials, processing studies and livestock feeding studies. Responses were received from four Member States, of which only two Member States submitted information. The limited response rate to the data collection call may be explained by the fact that the metabolites were often not determined in the magnitude of residue studies with the different pyrethroid active substances or that the time was not sufficient to retrieve the information from the Member State databases.

The reported metabolism studies had all been previously reviewed by EFSA and did not present new information to be specifically considered for the reassessment of the residue definitions.

Only in few residue trials, 3-PBA seemed to have been analysed (cypermethrin, alpha-cypermethrin, esfenvalerate) as well as PBA(OH) and/or PBA in livestock feeding studies (e.g. tau-fluvalinate, lambda-cyhalothrin) as presented in Annex A. However, reliability of the results in the residue trials with cypermethrin and alpha-cypermethrin was compromised by insufficiently validated analytical methods, so that the number of relevant and acceptable residue trials is further reduced.

Therefore, for the time being, considerations of dietary exposure to pyrethroid common metabolites due to the use of pyrethroid active substances have still to be based mainly on information from the metabolism studies assessed during the peer review and MRL review, which provide only semi-quantitative information, hence, leading to greater uncertainty in the exposure estimates and limiting the possibilities for refinement of such estimates.

It is further noted that pyrethroid active substances are also relevant in other regulatory areas such as biocides and veterinary medicines, and therefore exposure to pyrethroid common metabolites can also result from additional sources. In the remit of the data collection with Member States, other potential sources of exposure were not addressed, although it would be important for an adequate risk assessment to evaluate their contribution to the overall dietary exposure of consumers to pyrethroid common metabolites.

7. Evaluation of the residue definitions for dietary risk assessment

Cypermethrin, alpha-cypermethrin, beta-cypermethrin, zeta-cypermethrin

The residue definitions for cypermethrins (different mixture of constituent isomers) were derived by the peer review of cypermethrin (EFSA, 2018b), alpha-cypermethrin (EFSA, 2018c), beta-cypermethrin (EFSA, 2014) and zeta-cypermethrin (EFSA, 2009), based on the evaluation of the metabolic pattern and the magnitude of residues of the different cypermethrins in primary and rotational crops, processed commodities, and food of animal origin.

The metabolites PBA, PBA(OH) including their conjugated forms and PBAld were found to be regularly present as residues. Depending on the pyrethroid pesticide-commodity combination, notably PBA and PBA(OH) including their conjugates were identified in plant and animal commodities at proportions that were comparable to that of their parent compounds.

Regarding processed commodities, the reviews of cypermethrin (EFSA, 2018b), alpha-cypermethrin (EFSA, 2018c) and zeta-cypermethrin (EFSA, 2009) consistently noted that 3-phenoxybenzaldehyde (PBAld) was a main degradation product in studies simulating processing as well as in processing trials. For beta-cypermethrin (EFSA, 2014), investigation of processing was not triggered and therefore nothing had been reported on the formation of PBAld.

The following residue definitions for risk assessment, derived by the most recent peer reviews of cypermethrin (EFSA, 2018b) and alpha-cypermethrin (EFSA, 2018c) for plant, animal and processed commodities, were provisional

- Cypermethrin including other mixtures of constituent isomers (sum of isomers),

The residue definition was proposed to be provisional, 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.

Considering that the metabolites PBA, PBA(OH) and PBAld lack the neurotoxic mechanism of their parent pyrethroid compounds (see Section 5), EFSA concludes that the inclusion of these metabolites in the current residue definition would not be appropriate. EFSA therefore confirms the previously derived residue definition for risk assessment for the cypermethrins (i.e. cypermethrin, alpha-cypermethrin, beta-cypermethrin, zeta-cypermethrin) as 'cypermethrin including other mixtures of constituent isomers (sum of isomers)' (**residue definition 1**).

However, in addition to this residue definition, the setting of a second residue definition for the consumer risk assessment, covering the common metabolites bearing the 3-phenoxybenzoyl moiety should be considered, i.e.

- sum of PBA, PBA(OH) (including their conjugates) and PBAld.

However, this **residue definition 2** remains provisional, pending completion of the toxicological assessment for PBAld (see Section 5) and an assessment how the toxicology of PBAld should be considered in the context of the whole group of related metabolites bearing the 3-phenoxybenzoyl moiety.

8. Dietary risk assessment

The most recent comprehensive risk assessment of residues of cypermethrins was performed in the reasoned opinion on the review of the existing maximum residue levels for cypermethrins according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2023). This risk assessment is still valid for the first residue definition for cypermethrin a.s. (including other mixtures of constituent isomers).

For the second residue definition proposed that was provisionally proposed in Section 7, currently, only a rough, indicative exposure estimate can be performed, based mainly on information from the metabolism studies assessed during the peer review and MRL review, leading to greater uncertainty in the exposure estimates and limiting the possibilities for refinement of such estimates (see Section 6).

For the cypermethrins, suitable residue trials with PBA and PBA(OH) seem not to be available. The results of the reported residue trials in different crops in which PBA was analysed were not considered sufficiently reliable. Metabolism studies can be used to estimate input residue levels for an exposure assessment of metabolites when quantitative residue studies with the metabolites are not available. However, this usually leads to greater uncertainty, because how well metabolism studies inform understanding of metabolite levels depends on the design of the study, and therefore, residue trials and feeding studies in which the metabolite levels are analysed are preferred.

Assuming similar residue levels of the sum of metabolites PBA and PBA(OH) compared to the parent cypermethrin residue levels (based on observations in metabolism studies in plant and livestock) and considering that the toxicity of PBA and PBA(OH) is much lower than that of the pyrethroid active substances (the derived ADI of 0.1 mg/kg bw per day was 20- to 80-fold higher for PBA and PBA(OH) than the ADIs derived for the different cypermethrins), it can be assumed that the residues of the active substances are the decisive factor for the consumer risk assessments and that a consumer health concern to consumers from exposure to the metabolites PBA and/or PBA(OH) is unlikely. Therefore, regarding the risk assessment for cypermethrins, it might not be necessary to establish the separate risk assessment residue definition including PBA and PBA(OH).

However, this approach would disregard the fact that the metabolites are common to several pyrethroid active substances and that the total dietary exposure to the group of related metabolites form the different sources might be substantially higher. Moreover, for the metabolite PBAld, the

derivation of reference values is still pending the availability of aneugenicity data on this compound and a risk assessment cannot be conducted for the time being for residues of PBAld.

It is further noted that pyrethroid active substances are also relevant in other regulatory areas such as biocides and veterinary medicines, and therefore exposure to pyrethroid common metabolites can also result from additional sources.

Based on the available information, EFSA is not able to derive a final recommendation whether the second residue definition covering the common pyrethoroid metabolites containing the 3-phenoxybenzoyl moiety should be established.

Conclusions and recommendations

Pyrethroid common metabolites, most notably metabolites PBA, PBA(OH) including their conjugated forms and PBAld can account for a significant proportion of the residues in different food commodities when various pyrethroid active substances are used as pesticides.

In the remit of this statement, the provisional residue definitions for risk assessment for cypermethrins, including cypermethrin, alpha-cypermethrin, beta-cypermethrin, zeta-cypermethrin were reviewed.

The existing proposal for a residue definition for these active substances were confirmed as:

'cypermethrin including other mixtures of constituent isomers (sum of isomers)'.

A residue definition for risk assessment covering the group of related metabolites bearing the 3-phenoxybenzoyl moiety, notably the major metabolites PBA, PBA(OH) including their conjugated forms and PBAld, remains provisional. For the metabolite PBAld, the hazard characterisation is not yet completed pending the availability of aneugenicity data on this compound.

EFSA proposes that these data be submitted and evaluated as a prerequisite for proceeding with the assessment of how the whole group of related and common metabolites bearing the 3-phenoxybenzoyl moiety is to be considered for the consumer risk assessment.

Although the number of pyrethroid active substances approved in the EU as pesticides has decreased in the recent past, most of them are still internationally used, and CXLs as well as import tolerances for various imported products exist to meet the needs of international trade. Moreover, pyrethroid active substances are also used in other EU regulatory areas such as biocides and veterinary medicines, which present additional sources of possible dietary exposure of consumers to the pyrethroid common metabolites.

To assess whether the use of pyrethroid active substances in plant protection products, biocides and veterinary medicinal products can result in an overall significant dietary exposure to their common metabolites bearing the 3-phenoxybenzoyl moiety, a more comprehensive data base is required.

To derive a final conclusion on the need to establish a residue definition which covers the common metabolites bearing the 3-phenoxybenzoyl moiety resulting from the use of active substances belonging to the class of pyrethroids the following information is required:

- *In vitro* and/or *in vivo* micronucleus tests to address the aneugenicity of PBAld;
- Reliable residue data on the expected residue concentration of 3-PBA, PBA(OH) (including their conjugates) and PBAld in food resulting from the use of pyrethroids as a.s. in plant protection products, biocides and veterinary medicinal products.

In order to obtain a more reliable residue data base, EFSA proposes

- To request again Member States to screen the national authorisation databases whether information on the occurrence of pyrethroid metabolites 3-PBA, PBA(OH) (including their conjugates) and PBAld were provided and to share the data with EFSA and possibly involve applicants in data collection,
- To screen and evaluate pesticide monitoring data submitted to EFSA in the framework of Art. 31 of Regulation 396/2005 on pyrethroid metabolites 3-PBA, PBA(OH) (including their conjugates) and PBAld,
- To conduct a systematic literature review on occurrence data of pyrethroid metabolites 3-PBA, PBA(OH) (including their conjugates) and PBAld relevant for exposure of European consumers, considering also sources such as data provided to the JMPR and JECFA.

EFSA confirms the proposal made in previous outputs that an approach similar to that adopted for the TDMs should be followed, given that various pyrethroid compounds are approved and that most of them form the same common metabolites, that pyrethroids are a broadly used substance class, and

that the reference values of their common metabolites are in a similar order of magnitude as for the TDMs (EFSA, 2018a).

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Abbreviations

a.s.	active substance
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CXL	codex maximum residue limit
DNT	developmental neurotoxicity
HBGV	health-based guidance value
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level

MRL	maximum residue level
MS	Member States
NOAEL	no observed adverse effect level
TDM	triazole derivative metabolite
ToR	Terms of Reference
TRV	toxicological reference value
UF	uncertainty factor

Annex A – Outcome of Member State data collection – residue trials and feeding studies with pyrethroids metabolites

Annex A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.8022