CONCLUSION ON PESTICIDES PEER REVIEW

EFSA Journal

APPROVED: 28 July 2021

doi: 10.2903/j.efsa.2021.6817

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

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Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Spain, and co-rapporteur Member State, the Netherlands, for the pesticide active substance clofentezine and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The conclusions were reached on the basis of the evaluation of the representative use of clofentezine as an acaricide on citrus, pome fruits, strawberry, tomatoes and aubergine. The peer review also provided considerations on whether exposure to humans and the environment from the representative uses of clofentezine can be considered negligible, taking into account the European Commission's draft guidance on this topic. 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. An evaluation of data concerning the necessity of clofentezine as acaricide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods is also presented.

Keywords: clofentezine, peer review, risk assessment, pesticide, acaricide

Requestor: European Commission

Question number: EFSA-Q-2016-00222 and EFSA-Q-2018-00905

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Note: This scientific output, approved on 28 July 2021, supersedes the previous output published on 20 July 2009 (EFSA, 2009b).

Declarations of interest: The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Acknowledgements: EFSA wishes to thank the rapporteur Member State, Spain, for the preparatory work on this scientific output.

Suggested citation: EFSA (European Food Safety Authority), Alvarez F, Arena M, Auteri D, Borroto J, Brancato A, Carrasco Cabrera L, Castoldi AF, Chiusolo A, Colagiorgi A, Colas M, Crivellente F, De Lentdecker C, Egsmose M, Fait G, Gouliarmou V, Ferilli F, Greco L, Ippolito A, Istace F, Jarrah S, Kardassi D, Kienzler A, Leuschner R, Lava R, Linguadoca A, Lythgo C, Magrans O, Mangas I, Miron I, Molnar T, Padovani L, Parra Morte JM, Pedersen R, Reich H, Santos M, Sharp R, Szentes C, Terron A, Tiramani M, Vagenende B and Villamar-Bouza L, 2021. Conclusion on the peer review of the pesticide risk assessment of the active substance clofentezine. EFSA Journal 2021;19(8):6817, 35 pp. https://doi.org/10.2903/j.efsa.2021.6817

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.

Summary

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

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), Spain, and co-rapporteur Member State (co-RMS), the Netherlands, received an application from ADAMA Agriculture BV for the renewal of approval of the active substance clofentezine. In addition, ADAMA Agriculture BV submitted an application for maximum residue levels (MRLs), as referred to in Article 7 of Regulation (EC) No 396/2005.

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

It is concluded that clofentezine meets the cut-off criteria for non-approval, laid down in Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 as amended by Commission Regulation (EU) No 2018/605 concerning endocrine-disrupting potential. As part of the renewal procedure, the applicant provided further information aimed at demonstrating that the exposure of humans to clofentezine was negligible under realistic conditions of use. Clofentezine has therefore been assessed under the provisions of negligible exposure to satisfy point 3.6.5 of Annex II of Regulation 1107/2009 as amended by Commission Regulation (EU) No 2018/605. Furthermore, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting evidence regarding the necessity of clofentezine to control a serious danger to plant health. The evaluation of the data regarding this derogation request is presented in Appendices C and D of this conclusion.

Following completion of the peer review, the following conclusions are derived.

The representative uses of clofentezine by foliar spraying by broadcast air assisted sprayer, boom sprayer or knapsack sprayer as an acaricide on citrus, pome fruits, field strawberry, tomato, aubergine in SEU; pome fruits, strawberry in CEU and spray applications in permanent and non-permanent greenhouses (such as walk-in tunnel) on strawberry, tomato and aubergine in SEU and/or CEU and on tomato in permanent greenhouses in CEU as proposed by the applicant, result in a sufficient acaricidal **efficacy** against the target organisms.

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 clofentezine or the representative formulation.

In the area of **mammalian toxicology**, one critical area of concern was identified since clofentezine is considered to meet the criteria for endocrine disruption for humans for the T modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605. In relationship with the consumer's risk assessment, the aneugenic potential and the general toxicity profile of metabolites 2-CBN, 2-CBZ and AE C593600 should be further investigated. As first tier for the negligible exposure assessment according to the available draft Technical Guidance Document on assessment of negligible exposure, the operator exposure estimates are exceeding 10% of the acceptable operator exposure level (AOEL) for manual application on strawberry or tomato/aubergine, for outdoor uses (EFSA model) and indoor uses (EFSA model + EUROPOEM II). Worker exposure estimates exceed 10% of the AOEL for the outdoor uses on high crops and all indoor uses. Exposure estimates for residential children exceed 10% of the AOEL for all outdoor uses. As second tier, the margin of exposure for the critical effect is below 1,000 for operators during manual application on strawberry or tomato/aubergine (outdoor uses and indoor uses with EFSA model + EUROPOEM II). A margin of exposure below 1,000 is also observed for workers in case of outdoor use on citrus or pome fruit, and indoor use on strawberry, tomato and aubergine; and for residential children in all outdoor uses.

The **consumer risk assessment**, both for the representative uses and maximum residue level (MRL) application uses, could not be conducted because the residue definitions for primary crops and processed commodities cannot be finalised in view of the identified data gaps to address the general toxicity and the magnitude of residues of the relevant compounds included in the residue definitions. Furthermore, the livestock exposure assessment could not be finalised. As regards the negligible exposure assessment according to the available draft Technical Guidance Document on assessment of

negligible exposure, the outstanding residue data from residue field trials for pome fruit, strawberry and tomato do not allow a conclusion whether residues of clofentezine will be below 0.01 mg/kg or the limit of quantification (LOQ) of the analytical method. In a limited number of valid residue field trials on citrus, residues above 0.01 mg/kg for both clofentezine and 2-CBN are quantified.

In view of the data gaps identified to finalise the proposed residue definitions for risk assessment in primary crops and in processed commodities and to conduct reliable consumer intake calculations through the diet and drinking water, **MRLs** cannot currently be proposed for the intended uses.

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses, with the notable exception that information was not available regarding the effect of water treatments processes on the nature of residues of the clofentezine transformation products AE C593600, 2-CBA, 2-CBN, 2-CBZ that might be present in surface water, when surface water is abstracted for the production of drinking water. Consequently, the consumer risk assessment could not be finalised.

In the area of **ecotoxicology,** a high long-term risk to birds and/or mammals was identified for all uses of clofentezine, except those in permanent greenhouses. A high long-term risk to aquatic organisms was concluded for the parent compound for citrus and pome fruits, even considering mitigation measures such as 20 m no-spray buffer zones. For tomatoes, aubergines and strawberry (field and walk-in tunnels), a mitigation measure comparable to 10 m no-spray buffer zones was necessary to address the long-term risk to aquatic organisms from clofentezine. For bees and other non-target arthropods, the reproductive risks were not deemed sufficiently addressed, considering the ovicidal mode of action of the active substance, and the available data, leading to an issue not finalised. For soil organisms, a high risk for earthworms was identified for the uses in pome fruits and strawberry (field and walk-in tunnels).

Clofentezine is considered to meet the criteria for **endocrine disruption** for humans for the thyroid (T) modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605, leading to a critical area of concern. The endocrine-disrupting properties of clofentezine for non-target organisms according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be concluded based on the available data, however, since clofentezine meets the criteria for the T-modality in humans, additional testing was not considered necessary.

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Background

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

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

In accordance with Article 1 of the Regulation, the RMS, Spain, and the co-RMS, Netherlands, received an application from ADAMA Agriculture BV for the renewal of approval of the active substance clofentezine. In addition, ADAMA Agriculture BV submitted an application for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[4]. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (the Netherlands), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on clofentezine in the RAR, which was received by EFSA on 6 March 2018 (Spain, 2018). The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, ADAMA Agriculture BV, for consultation and comments on 29 October 2018. 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 3 January 2019. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 2 April 2019. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues 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.

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

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

[3] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

[4] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

In addition, in accordance with the provisions of Commission Implementing Regulation (EU) No 2018/1659, following a consultation with Member States at the Pesticide Peer Review Experts' Meeting 11 (Mammalian Toxicology, 2–5 September 2019), the applicant was given the opportunity to submit, within a period of 3 months, additional information to address the approval criteria set out in point 3.6.5 and/or point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605[5], and/or documentary evidence demonstrating that clofentezine may be used such that exposure is negligible, or the conditions for the application of the derogation under Art.4(7) of Regulation (EC) No 1107/2009 are met.

Subsequently, the applicant provided further information aimed at demonstrating that the exposure of humans to clofentezine was negligible under realistic conditions of use, for use as acaricide in flower bulbs (indoor bulb immersion (bathing)), i.e. a non-representative use which was not part of the dossier for renewal of approval. Clofentezine has therefore been assessed under the provisions of negligible exposure to satisfy point 3.6.5 of Annex II of Regulation 1107/2009. However, since the legislation does not provide for changes to the representative uses during the renewal process which were not part of the supplementary dossier submitted for the renewal, an assessment of negligible exposure is presented for the representative uses only. Furthermore, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting evidence regarding the necessity of clofentezine to control a serious danger to plant health. The evaluation of the data regarding this derogation request is presented in the Appendices C and D of this conclusion. A public consultation on the draft Art 4(7) scientific report and the revised RAR on the endocrine and negligible exposure assessments made available after the 3-month clock stop was conducted between November 2020 and January 2021. All comments received, including from the applicant and Member States, were collated in the format of a commenting table (on the draft Art 4(7) scientific report) and reporting table (on the revised RAR on the assessment of the endocrine-disrupting properties and negligible exposure assessment).

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, including the negligible exposure assessment and the evaluation of the data regarding the necessity of clofentezine to control a serious danger to plant health which cannot be contained by other available means, and on the proposed MRLs took place with Member States via a written procedure in June–July 2021.

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 of clofentezine as an acaricide on citrus, pome fruits, strawberry, tomatoes and aubergine, as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review are presented in the conclusion. MRLs were assessed in cherry and courgette in addition to the representative uses.

In addition, the peer review also provided considerations on whether exposure to humans and the environment from the representative uses of clofentezine can be considered negligible, taking into account the European Commission's draft guidance on this topic. An evaluation of data concerning the necessity of clofentezine as acaricide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods is also presented (see Appendices C and D).

A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for clofentezine according to Annex II of Regulation (EC) No 1107/2009 are summarised in Appendix A.

A key supporting document to this conclusion is the peer review report (EFSA, 2021), 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:

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

- the comments received on the RAR;
- the reporting tables (3 April 2019 and 12 February 2021[6]);
- the evaluation tables (June 2021);
- 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 (Spain, 2021), 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 and its background documents would not be accepted to support any registration outside the EU for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Clofentezine is the ISO common name for 3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine (IUPAC).

The representative formulated product for the evaluation was 'Apollo 50 SC (MCW-8927)', a suspension concentrate (SC) containing 500 g/L clofentezine.

The representative uses evaluated comprise field applications by foliar spraying by broadcast air assisted sprayer, boom sprayer or knapsack sprayer as an acaricide to control a number of different species including *Tetranychid, Eriophid* and *Tarsonemid* mites, on a wide range of crops including citrus, pome fruits, strawberry, tomato, aubergine in SEU; pome fruits, strawberry in CEU and spray applications by boom sprayer or knapsack sprayer in permanent and/or non-permanent greenhouses on strawberry, tomato and aubergine in SEU/CEU. Full details of the good agricultural practices (GAPs) can be found in the list of end points in Appendix B.

Data were submitted to conclude that the representative uses of clofentezine proposed at SEU and CEU level result in a sufficient acaricidal 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 (European Commission, 2000a,b, 2010).

The proposed specification for clofentezine was based on batch data from industrial scale production. The proposed minimum purity is 980 g/kg. There is no requirement to change the EU reference specification for clofentezine. The specification meets the requirements of the FAO specification 418/TC (April 2007), developed under the new procedure.

The main data regarding the identity of clofentezine and its physical and chemical properties are given in Appendix B.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical material and the representative formulation. CIPAC methods also exist for the determination of the active substance in the technical material and in the formulation (418/TC/M/3 and 418/SC/M/3).

Residues of clofentezine in food and feed of plant origin can be monitored by LC-MS/MS with LOQs of 0.01 mg/kg in all commodity groups, however a data gap was identified for information on the extraction efficiency. The residue definition for monitoring in food of animal origin was defined as sum of clofentezine and 4-hydroxy-clofentezine, expressed as clofentezine, applicable for all livestock animals or alternatively, as 4-hydroxy-clofentezine applicable for ruminants and as clofentezine applicable for poultry. Adequate LC-MS/MS methods are available for monitoring the components of the residue definition in meat, liver, fat, milk and eggs with LOQs of 0.01 mg/kg.

Residues of clofentezine in soil can be monitored with LC-MS/MS with a LOQ of 0.01 mg/kg. Adequate LC-MS/MS method is available to monitor residues of clofentezine in surface water and

[6] Reporting Table following consultation on the revised RAR on the assessment of the endocrine disrupting properties and negligible exposure assessment made available after the 3-month clock stop.

drinking water, with a LOQ of 0.05 μg/L. LC-MS/MS method is available to monitor clofentezine residues in air with an LOQ of 0.3 μg/m^3.

Clofentezine and the metabolite 4-hydroxy-clofentezine were proposed as the monitoring residue definition for body fluids and tissues. LC-MS/MS method exists for the determination of residues of clofentezine in blood with a LOQ of 0.05 mg/L. A data gap was identified for a method for the determination of the residues of 4-hydroxy-clofentezine in body fluids.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion (European Commission, 2003, 2012a; EFSA 2014c; EFSA PPR Panel, 2012; ECHA, 2017) and the available draft Technical Guidance Document on assessment of negligible exposure (European Commission, 2015).

Clofentezine was discussed at the Pesticide Peer Review Experts' Meeting 11 in September 2019.

In the technical specification no toxicologically relevant impurities were identified. Therefore, the technical specification is considered covered by the batches tested in toxicological studies.

Following **oral administration** to the rat, mouse, rabbit and dog excretion of clofentezine was rapid and complete. The majority of elimination is taking place in the first 48 h post-dosing (80–90%) and was complete by 96 h. The major route of excretion is via faeces. Urinary levels range from 2% in the dog to 36% in the rabbit. In rat and mouse, urinary levels are 20–26%. Comparative *i.v.*, oral dosing and biliary excretion studies confirm oral absorption of 50%. Clofentezine is widely distributed with highest levels in the liver. Metabolism data from rats show that after oral dosing unchanged clofentezine was the major component in faeces (50% excreted unchanged; the rest was metabolised to more than 20 minor metabolites) whereas the material excreted in rat urine consisted mainly of metabolites. The two main metabolic pathways were hydroxylation and formation of a monochlorosulfur derivative. Clofentezine was metabolised by both rat and human liver microsomes and no unique human metabolite was observed.

Clofentezine and the metabolite 4-hydroxy-clofentezine are proposed for monitoring purpose in body fluids and tissues.

Clofentezine is of low **acute** oral, dermal and inhalation **toxicity**. Clofentezine is not a skin and eye irritant and not a skin sensitiser. Clofentezine is not phototoxic in the 3T3 NRU-PT test; however, it is a UVB absorber and the 3T3 NRU-PT test might not be suitable to test for UVB absorber (data gap, see Section 10).

Short-term oral administration to mice, rats and dogs produced liver enlargement as the main toxicological effect. The liver enlargement was in the most cases associated with centrilobular hepatocyte enlargement. The overall short-term no observed adverse effect level (NOAEL) is 1.7 mg/kg body weight (bw) per day, based on increased liver weight and increased cholesterol level observed in the 1-year dog study.

Based on the submitted *in vitro* and *in vivo* data, including an *in vivo* micronucleus study with proof of bone marrow exposure, **genotoxic potential** is unlikely for clofentezine.

Long-term toxicity NOAEL in rats is 1.72 mg/kg bw per day, based on increased relative liver weights in both sexes with associated histopathology (centrilobular hepatocyte enlargement and vacuolisation, focal cyst degeneration of hepatocytes, focal hepatocyte necrosis and fat deposits in males and telangiectasis in females) and increased T4 levels in males observed in the 2-year study at 17.3 mg/kg bw per day. Carcinogenicity NOAEL in rat is established at 1.72 mg/kg bw per day, based on increased incidence of thyroid follicular cell tumours (adenocarcinoma) observed in males. Long-term toxicity lowest observed adverse effect level (LOAEL) in mice is established at 5.0 mg/kg bw per day, based on eosinophilic hepatocytes in males observed at the lowest dose tested in the long-term/carcinogenicity study. Carcinogenicity NOAEL in mice is established at 56.9 mg/kg bw per day, based on liver tumours[7] observed in females.

In the **multigenerational** rat toxicity study, the parental NOAEL is 4 mg/kg bw per day, based on increased relative liver weight of successive generations (F1 and F2 males, associated with minimal histopathological changes in F1 males) and reduced body weight of successive generations (F1 and F2 males & females). The NOAEL for neonatal toxicity is 4 mg/kg bw per day, based on decreased F2A pup weight observed on day 21 *post partum*. The NOAEL for reproductive toxicity is set at 27.8 mg/kg bw per day, the highest tested dose.

[7] CLP process in parallel agreed on no classification for carcinogenicity (ECHA, 2020).

In the rat, relevant maternal NOAEL is 1,280 mg/kg bw per day based on decreased body weight gain and increased relative liver weights (10%), observed when corrected for the uterine contents, associated with histopathology (staining and enlargement of centrilobular hepatocytes). The NOAEL for **developmental toxicity** is 3200 mg/kg bw per day, the highest dose tested.

In the rabbit, relevant maternal NOAEL is 250 mg/kg bw per day, based on decreased body weight gain. The NOAEL for developmental toxicity is set at 1,000 mg/kg bw per day based on reduced foetal weight.

Clofentezine did not show potential for **neurotoxicity** or **immunotoxicity**.

Based on the available data (including bacterial *in vitro* gene mutation assay, mammalian cell gene mutation assay and mammalian cell *in vitro* chromosome aberration assay), genotoxicity potential of 2-CBN, 2-CBZ and AE C593600 **metabolites** is unlikely, however aneugenicity has not been assessed (data gap, see Section 9.1.1). The metabolite 2-CBN has been shown to be more acutely toxic than clofentezine. No repeat dose toxicity studies are available nor reliable quantitative structure–activity relationship (QSAR) analysis for general toxicity for the above-mentioned metabolites (data gap, see Section 9.1.1). The metabolite 4-hydroxy-clofentezine can be considered as a major rat metabolite when taking into account the limited oral absorption of the parent, and therefore, its toxicity is considered covered by the reference values of the parent compound.

The acceptable daily intake (**ADI)** of clofentezine is established at 0.017 mg/kg bw per day, based on the 2-year rat study and applying an uncertainty factor of 100. The ADI is supported by the NOAEL set in the 1-year dog study and the LOAEL set in the 2-year mouse study (when considering an uncertainty factor (UF) of 300 to the LOAEL). An ADI value of 0.02 mg/kg bw per day was established in the previous assessment, on the same basis and applying the same UF (the difference with previous value is due to rounding) (EFSA, 2009b; European Commission, 2012b).

The acceptable operator exposure level (**AOEL)** of clofentezine is established at 0.013 mg/kg bw per day, based on the 90-day rat study and using an uncertainty factor of 100 and correction for oral absorption of 50%. The AOEL is supported by the 90-day mechanistic rat study. An AOEL of 0.01 mg/kg bw per day was established in the previous assessment, on the same basis and applying the same UF (the difference with previous value is due to rounding) (EFSA, 2009b; European Commission, 2012b).

Acute reference dose (**ARfD**) and acute AOEL (**AAOEL**) values were not considered necessary for clofentezine, as in the previous assessment (EFSA, 2009b; European Commission, 2012b).

Dermal absorption values for formulated clofentezine (MCW-8927) are 0.02% for the concentrate and 2% for the spray dilution based on triple pack approach.

For the tractor-mounted and knapsack applications on citrus, pome fruits, strawberries, tomatoes and aubergines, the predicted **operator exposure** is below the AOEL without use of personal protective equipment (PPE). For the indoor uses on strawberries, tomatoes and aubergines, according to the ECPA glasshouse model (not validated at EU level) and the EFSA model (M/L) and EUROPOEM II (A), the predicted operator exposure is below the AOEL with use of PPE during application.

For **residents** (children and adults), covering also bystanders in the absence of AAOEL, the exposure estimates are below the AOEL for the representative uses covered by the EFSA model. As regards the indoor uses, the application in non-permanent structures is covered by the exposure for outdoor uses, while for the application in permanent structures, at least the exposure to vapour should be considered and respective results in exposure estimates are below the AOEL.

For **workers** re-entering the treated crops, the predicted exposure is below the AOEL for all representative uses, without the use of PPE according to the EFSA model.

With regard to **negligible exposure** assessment according to the available draft guidance (European Commission, 2015), as first tier, the exposure estimates exceed 10% of the AOEL for **operators** during manual outdoor application with knapsack on strawberry, tomato and aubergine with the use of PPE, and during indoor uses (strawberry, tomato, aubergine) with the use of PPE when calculated with the EFSA model (mixing/loading) and EUROPOEM II (application). For tractor-mounted outdoor applications on citrus, pome fruit, strawberry, tomato and aubergine, and for indoor uses (strawberry, tomato, aubergine) with the ECPA model (not validated at EU level), both with the use of PPE, the exposure estimates do not exceed 10% of the AOEL (see Appendix B and Section 8.1).

The exposure estimates for **workers** exceed 10% of the AOEL for the outdoor uses on high crops (citrus, pome fruit) and all indoor uses (strawberry, tomato, aubergine) with the use of gloves; worker exposure estimates are below or equal to 10% of the AOEL for the outdoor applications on strawberry, tomato and aubergine with the use of gloves.

The exposure estimates for **residential** children are higher than 10% of the AOEL for all outdoor uses. For indoor uses, at least the exposure to vapour should be considered and respective results in exposure estimates are below 10% of the AOEL.

As second tier assessment according to European Commission (2015), the margin of exposure between the non-dietary exposure estimates and the systemic NOAEL for the critical effects is below 1,000 for operators during manual application on strawberry, tomato and aubergine (outdoor uses and indoor uses with EFSA model + EUROPOEM II); for workers in case of outdoor use on citrus or pome fruit, and indoor use on strawberry, tomato and aubergine; and for residential children in all outdoor uses (see Appendix B).

It is noted that the RMS, co-RMS and one MS disagree with the approach of negligible exposure according to the draft Technical Guidance (European Commission, 2015) and support the use of real exposure studies, if available, to demonstrate that exposure values are below the limit of quantitation to fulfil the criteria of negligible exposure.

3. Residues

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

Clofentezine was discussed at the Pesticides Peer Review Experts' Meeting 16 in September 2019.

3.1. Representative use residues

Metabolism upon foliar application was investigated in different fruit crops (apple, peach and grape). Despite several shortcomings that were identified in the studies, the results were considered congruent and suitable to elucidate the metabolism in fruit crops with clofentezine as the major residue (up to 90% total radioactive residue (TRR) in peaches) and 2-CBN below 10% TRR.

The **residue definition** for **monitoring** is proposed as clofentezine and the **residue definition for risk assessment** is set as 'clofentezine and 2-CBN'. The way the risk assessment residue definition should be expressed is pending on further clarification on the toxicological profile of metabolite 2-CBN since its aneugenicity assessment and general toxicity are outstanding (see data gap in Section 2). Both residue definitions apply only to fruit crops following foliar treatment.

Storage stability has been established only in apple (high water), orange pulp (high acid), peel (other) and whole orange for 2-CBN, and in orange pulp (high acid) and whole orange for clofentezine, and a current good laboratory practice (GLP) and guideline compliant study suggests that clofentezine is not stable in orange peel. Therefore, a data gap is identified for guideline-compliant storage stability studies with clofentezine and 2-CBN for high water commodities covering the representative uses in pome fruit (only clofentezine), tomato and aubergine, and for high acid commodities covering the representative use in strawberries.

In support of the critical GAPs (cGAPs), residue field trials for all representative uses were provided and assessed considering independency and whether both clofentezine and 2-CBN were analysed using a valid analytical method and covered by acceptable storage stability data for both compounds. In the light of these considerations, EFSA concluded that only two trials with oranges and two trials with mandarins analysing for clofentezine and 2-CBN in whole fruit fulfilled all criteria and are acceptable. Consequently, data gaps have been identified for independent residue field trials (six trials with mandarin in SEU and six trials with orange in SEU, eight trials with pome fruit, respectively, in NEU and SEU, eight trials with strawberry, respectively, in NEU, SEU and indoor, and eight trials with tomato, respectively, in NEU, SEU and indoor), compliant with the cGAPs analysing for clofentezine and 2-CBN, and supported by storage stability data for both substances. It is noted that a storage stability study is ongoing and the independent residue field trials analysing for clofentezine and 2-CBN, which are currently not supported by storage stability data might, depending on the outcome of the study, be considered as valid.

Clofentezine is persistent in soil requiring the investigation of its fate in rotational crops.

A guideline compliant metabolism study in rotational crops covering the seasonal application rate demonstrated no residues above 0.01 mg eq/kg in lettuce. In cereals and root plant parts the residues were mainly located in the unextractable fraction (85% TRR for grain) and identification/ characterisation of the extractable residue was performed only in hay and straw where clofentezine was the only identified residue (7.6 %, 0.009 mg eq/kg in straw). From this study it can be concluded that residues in rotated crops are not expected from the proposed uses of clofentezine.

Clofentezine is stable under pasteurisation conditions, but slightly degrades to AE C593600 (12.4% TRR) under baking, brewing, boiling conditions and completely decomposes to form AE C593600 (78% TRR), 2-CBN (5% TRR) and 2-CBZ (17% TRR) under sterilisation conditions. A separate high temperature hydrolysis study for 2-CBN which is included in the residue definition for risk assessment was not provided. Pending the toxicological assessment of this compound (see data gap in Section 2) and the results of the requested residue field trials analysing for 2-CBN, additional data addressing the behaviour of this compound at representative processing procedures might be required. It was noted that in all the trials on strawberries and tomatoes, the levels of the residues in the unprocessed commodities were low and not representative of the residue levels expected in the GAP-compliant residue field trials on these crops. Furthermore, the experimental design of the processing residue trials on tomatoes reflected pasteurisation and cooking only and not sterilisation, and residue analysis was performed on peeled tomato and not on the raw agricultural commodity (RAC). In view of the identified deficiencies, two processing trials, respectively, on strawberries and tomatoes, are requested which are supported by storage stability data, representative of the highest residue levels observed in the GAP-compliant residue trials on these crops, employing processing conditions relevant for these commodities (for tomato including a sterilisation step) and analysing for all compounds formed under these conditions (data gap).

Considering the instability of clofentezine in orange peel and the fact that the samples (incl. peel and pulp separately) in the presented processing trials with oranges were stored for up to 6 months the available data might not reflect the true residues in the whole orange as calculated from peel and pulp data. Therefore, two processing trials with citrus, supported by storage stability data, employing processing conditions relevant for this commodity (e.g. juice and marmalade production) and analysing for all compounds formed under these conditions are required (data gap). In case storage stability of clofentezine could be demonstrated in citrus peel in the on-going storage stability study, this data gap could become redundant but a sound argumentation as to why the new storage stability results should overrule the current ones should be provided. Due to these data gaps and the pending toxicological assessments of AE C593600, 2-CBZ and 2-CBN (see data gaps in Section 2) the **residue definition for risk assessment for processed commodities** remains open.

The dietary burden calculation is pending on the provision of a sufficient number of valid residue field trials for citrus and apple supported by storage stability data.

A recent guideline compliant storage stability study revealed instability of clofentezine in bovine muscle and a tendency for degradation in all other matrices (from 3 months onwards in liver and fat). The picture for the metabolite 4-hydroxy-clofentezine is similar. One metabolism study with poultry, though not triggered as the crops under evaluation are not used as feed item, and several studies with ruminants are available. All of the ruminant studies had one but mainly several deficiencies and were not fully guideline compliant. The only ruminant study in which identification/characterisation was performed revealed 4-hydroxy-clofentezine as major metabolite in liver, kidney, fat and milk. Clofentezine was not recovered in those matrices and it is not clear whether this is due to instability or whether a complete metabolisation has taken place. However, extractable radioactivity in muscle was too low for identification. In poultry matrices, besides clofentezine that was the major compound of the residues, 4-OH and/or 3-OH clofentezine (no analytical distinction) was also recovered in all matrices except in eggs where no analysis was performed. The overall evidence from the studies is sufficient to derive residue definitions for the representative uses; it is noted that in the light of additional uses in the future, guideline-compliant metabolism studies with acceptable metabolites' identification in all commodities (in particular in egg and ruminant muscle) may be requested. As the toxicity of the metabolite 4-OH clofentezine is covered by the toxicological reference values of the parent compound the **animal residue definition for risk assessment** is set as sum of clofentezine and 4-hydroxy-clofentezine, expressed as clofentezine (for ruminants and provisionally for poultry). For the **animal residue definition for monitoring,** two options are proposed: (1) 4-hydroxy-clofentezine for ruminants and clofentezine for poultry, or as an enforcement method is available analysing for both substances (2) sum of clofentezine and 4-hydroxy-clofentezine, expressed as clofentezine, applicable to all livestock animals. In the existing feeding studies a common moiety analytical method was used which could not or only partly capture the 4-hydroxy-clofentezine rendering the studies supportive only. For the representative uses, the need for feeding studies will need to be reconsidered after the finalisation of the dietary burden calculation.

Given that no residue data were presented, and all the representative uses are on melliferous crops before and during flowering, a data gap is identified for a study investigating the residue levels in pollen and in bee products for human consumption resulting from residues taken up by honeybees from crops at blossom for all representative uses (see Section 10).

Currently a consumer risk assessment cannot be performed as the risk assessment residue definitions for primary crops and processed commodities are not finalised due to missing information on the toxicity of a number of metabolites impacting the expression of the respective residue definitions and due to missing information on the magnitude of residues of clofentezine and relevant compounds included in the risk assessment residue definition for primary crops and processed commodities, and the pending livestock exposure assessment.

As regards the **negligible exposure assessment** according to the available draft Technical Guidance Document on assessment of negligible exposure (European Commission, 2015), the outstanding residue data from residue field trials for pome fruit, strawberry and tomato do not allow a conclusion whether residues of clofentezine will be below 0.01 mg/kg or the LOQ of the analytical method. In a limited number of valid residue field trials on citrus, residues above 0.01 mg/kg for both clofentezine and 2-CBN are quantified.

The consumer risk assessment from the consumption of drinking water is also not finalised considering the lack of appropriate information to address the effect of water treatment processes on the nature of residues of some of clofentezine's transformation products, potentially present in surface water, when surface water is abstracted for drinking water (see Section 4).

3.2. Maximum residue levels

In support of the MRL applications for the intended uses in tomato, aubergine, cherries and courgettes, residue field trials were provided. It is noted that the GAPs for tomatoes and aubergines are the same as the representative uses. Therefore, the data gaps related to the representative use in tomatoes apply also to the MRL application. None of the trials was supported by storage stability data leading to a data gap for guideline-compliant storage stability studies with clofentezine and 2-CBN for high water commodities covering the MRL application uses for courgette and cherry (see section 9.2.1). The data sets for cherry and courgette were not complete with respect to minimum number of residue field trials and/or results for 2-CBN. Consequently, data gaps have been identified for independent residue field trials (eight trials with cherry in NEU, four trials with courgette in NEU while 8 trials in SEU and indoor and eight trials with tomato, respectively, in NEU, SEU and indoor), compliant with the cGAPs, analysing for clofentezine and 2-CBN, and supported by storage stability data for both substances (see Sections 9.1.1 ad 9.2.1). It is noted that a storage stability study is ongoing and the independent residue field trials analysing for clofentezine and 2-CBN, which are currently not supported by storage stability data might, depending on the outcome of the study, be considered as valid.

As none of the crops is used as feed, there is no impact on the livestock dietary burden from these uses.

Processing studies are missing for tomatoes, cherries and courgettes but the processing factors can be extrapolated from the representative uses in apple to cherry and to courgettes from tomato (see data gap identified for the representative uses under Section 3.1), and therefore, no data gap is needed for the MRL uses.

The consumer risk assessment cannot be performed as the risk assessment residue definitions for primary crops and processed commodities are not finalised due to missing information on the toxicity of a number of metabolites impacting the expression of the respective residue definitions and due to missing information on the magnitude of residues of clofentezine and relevant compounds included in the risk assessment residue definition for primary crops and processed commodities.

In view of the data gaps identified to finalise the proposed residue definitions for risk assessment in primary crops and in processed commodities and to conduct reliable consumer intake calculations through the diet and drinking water, MRLs cannot currently be proposed for the intended uses.

4. Environmental fate and behaviour

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, clofentezine exhibited moderate to high persistence, forming the major (> 10% applied radioactivity (AR)) metabolites AE C593600 (max. 13% AR) and 2-CBA (max. 11% AR), which exhibited very low to low and low persistence, respectively. Metabolite 1,2-DCBH (max. 7% AR) also reached levels triggering identification and assessment and exhibited low to moderate persistence. Mineralisation of the [^{14}C- tetrazine] radiolabels to carbon dioxide accounted for 20–47% AR after

120 days. The formation of unextractable residues (not extracted by microwave acetonitrile/water or Soxhlet dichloromethane followed by Soxhlet methanol/water) for these radiolabels accounted for 21–33% AR after 120 days. In an anaerobic soil incubation, clofentezine exhibited medium persistence forming no novel metabolites. The aerobic metabolite AE C593600 was not formed in this anaerobic soil incubation. In a laboratory soil photolysis study, clofentezine degraded more rapidly than in the dark control forming the major metabolite 2-CBN (max. 17% AR), which exhibited very low persistence in incubations under aerobic conditions in the dark. Clofentezine exhibited slight mobility or was immobile in soil. 1,2-DCBH was immobile, AE C593600 exhibited low soil mobility, 2-CBN exhibited medium soil mobility and 2-CBA exhibited very high soil mobility. It was concluded that the adsorption of all these compounds was not pH dependent. In satisfactory field dissipation studies carried out at three sites in Germany, two in the UK, one in Italy and one in Bulgaria (spray application to the soil surface on bare soil plots) clofentezine exhibited moderate to very high persistence. Sample analyses were only carried out for the parent clofentezine. The laboratory persistence of the metabolites did not trigger the need for field investigation according to the data requirements. Field study DegT50 values for clofentezine were derived following normalisation to FOCUS reference conditions (20°C and pF2 soil moisture) following the EFSA (2014b) DegT50 guidance. The field data endpoints were not combined with laboratory values to derive modelling endpoints as following the DegT50 guidance the laboratory and field values were considered to represent different populations. The field DegT50 values were used to derive the DegT50 used as input in FOCUS modelling.

In laboratory incubations in dark aerobic natural sediment water systems, clofentezine exhibited moderate persistence, partitioning to sediment and forming the major metabolites AE C593600 (max. ca. 22% AR in water, exhibiting moderate to very high persistence in the alkaline systems investigated) and 2-CBA (max. 20% AR in water exhibiting moderate persistence in the more acidic systems investigated). The unextractable sediment fraction (not extracted by acetonitrile then acetonitrile/ water) was a sink for the [^{14}C- tetrazine] radiolabels, accounting for 35–37% AR at study end (100–105 days). Mineralisation of these radiolabels accounted for 45–46% AR at the end of the study. The rate of decline of clofentezine in a laboratory sterile pH 5 buffered aqueous photolysis experiment was enhanced relative to that occurred in the dark aerobic sediment water incubations. The transformation products formed were 2-CBN (max. 34% AR), 2-CBZ (max. 15% AR) and 2-CBA (max. 7% AR). The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC) calculations) were carried out for the metabolites 2-CBA, 2-CBN, 2-CBZ and 1,2-DCBH using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance clofentezine and AE C593600 appropriate step 3 (FOCUS, 2001) and for clofentezine step 4 calculations were available.[8] The step 4 calculations appropriately followed the FOCUS (FOCUS, 2007) guidance, regarding no-spray drift buffer zones of up to 20 m being implemented for the drainage and runoff scenarios (representing a 59–93% spray drift reduction). The SWAN tool (version 5) was appropriately used to implement this spray drift mitigation in the simulations.

For the representative permanent greenhouse uses, the necessary surface water and sediment exposure assessments (PEC calculations) were carried out for parent clofentezine using a modification of the FOCUS (2001) step 3 approach. The modifications were changing the standard SWASH calculated spray drift deposition values to those coming from a 0.1% emission of clofentezine from greenhouses being re-deposited on adjacent surface water bodies. Whilst hydrology was simulated using the standard FOCUS climate files with water fluxes via runoff and drainage simulated as usual, pesticide fluxes in the runoff and drainage were set to zero. This approach of 0.1% emission is referred to in FOCUS (2008) air guidance as being appropriate, except when applications are made with ultra-low volume application techniques when 0.2% emission is prescribed. The applicant was requested to provide the surface water exposure assessments for permanent greenhouses as described in the EFSA (2014a) guidance on emissions from protected crop production systems that includes example scenarios implemented in the GEM model. An assessment using example scenarios implemented in the GEM model was not provided, so has been identified as a data gap (see Section 10).[9]

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

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

[9] Note that there was a minority view expressed by one Member that had the opinion that this data gap could have led to the identification of an assessment not finalised for aquatic organisms from some uses in permanent greenhouses.

5.5.4[8]. The potential for groundwater exposure from the representative uses by clofentezine and its soil transformation products AE C593600, 2-CBN, 2-CBA and 1,2-DCBH above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios.

The applicant provided some information in relation to clofentezine concentrations being low at the points of abstraction of surface water for the production of drinking water. This was the measures proposed to reduce spray drift that are needed to protect aquatic organisms combined with its expected partitioning to sediment and degradation in surface water as demonstrated in the available aerobic mineralisation study (DT_{50} 5.6 days at 4 μg/L). For metabolite 1,2-DCBH indicated to be immobile in soil and only formed in soil, its concentration would also be low at the points of abstraction of surface water for the production of drinking water. However, information to address clofentezine's other transformation products that can be present in surface water was not available. This has led to the identification of a data gap and results in the consumer risk assessment not being finalised (see sections 3 and 9.1.1) regarding the effect of water treatments processes on the nature of residues of AE C593600; 2-CBA; 2-CBN; 2-CBZ that might be present in surface water, when surface water is abstracted for the production of drinking water.

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix B. A key to the wording used to describe the persistence and mobility of the compounds assessed can be found in Appendix E.

Clofentezine has the potential for long range atmospheric transport consequent to aerosols that will be formed at the time of spraying and is having a calculated atmospheric DT_{50} above the trigger of 2 days (FOCUS, 2008 air guidance).

5. Ecotoxicology

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

Some specific aspects related to the environmental risk assessment of clofentezine were discussed at the Pesticide Peer Review Experts' Meeting 14 (September 2019).

Despite limited information is available on the presence of impurities, the batches used in the ecotoxicity studies are considered representative of the technical specification.

Suitable acute and reproductive data with clofentezine were available for **birds**. A low acute risk was concluded for all representative uses at the screening step. A low reproductive risk was concluded at the tier 1 for most uses, including uses in permanent greenhouses; a high risk was identified for small insectivorous birds (relevant for all uses in orchards), and for frugivorous birds (relevant for late uses on fruiting vegetables, i.e. BBCH 71–89, in southern EU, under field or non permament greenhouses). For the uses in orchards, information was available concerning the identification of potential focal species, refined values of PT and PD. All these aspects were discussed at the expert meeting[10]. Uncertainties were identified about: (1) the lack of a full temporal overlap between the studies used for the focal species identification and the GAP; (2) the representativeness of the available studies for less intensively managed (and more traditional) orchards, which may represent a realistic worst-case scenario for the proposed ecological refinements; (3) the presence of a unique study for PT estimation in the central EU zone, and its representativeness for different types of orchard structures. Nevertheless, the available studies were used to refine the risk assessment. Based on this information, a low risk could be concluded for the orchard uses in central EU, while a high risk was still identified for the uses in south EU (citrus and pome fruits). For the uses on fruiting vegetables the only accepted refinement was the use of tomato-specific RUDs from the default database included in EFSA (2009a), though some MS still rejected these. This refinement is not applicable to the uses on aubergines. A high risk for frugivorous birds was still identified for the uses on fruiting vegetables (tomatoes and aubergines) in field or walk-in tunnels.

Suitable acute and reproductive toxicity data were also available for assessing the risk to **wild mammals**; the reproductive endpoint was discussed and agreed during the expert meeting.[11] A low acute risk was concluded for all representative uses at the screening step. On the contrary, on the basis of a tier 1 risk assessment, a high long-term risk was identified for a number of feeding guilds and for all the uses in which exposure is likely to occur. A low risk was instead concluded for the uses

[10] See Expert's consultation point 5.1 at the Pesticide Peer Review Experts' Meeting 14 (September 2019) (EFSA, 2021).
[11] See Expert's consultation point 5.2 at the Pesticide Peer Review Experts' Meeting 14 (September 2019) (EFSA, 2021).

in permanent greenhouses, due to lack of significant exposure. Several refinement strategies were considered by the RMS and discussed in the expert meeting.[12] Among those, only the refinement of deposition values was deemed acceptable, for all crops but strawberries, and not all MS were in favour. The refined risk assessment still indicated a high long-term risk for small herbivorous mammals (all uses on pome fruits and citrus, tomatoes and aubergines, late use on strawberry), frugivorous mammals (late uses on pome fruits, citrus, tomatoes and aubergines), large herbivorous mammals (early uses on strawberry) and small omnivorous mammals (early uses on strawberry).

None of the **plant metabolites** of clofentezine occurred at high levels, therefore an assessment of the dietary risk posed by plant metabolites was not presented for either birds or mammals. The metabolite 2-CBN presents an acute toxicity to rats considerably higher than the parent (more than a factor of 10). No long-term data are available, and the acute data alone are not sufficient to prove that the metabolite is more reproductively toxic than the parent after long-term exposure. This metabolite was, however, never formed in plant metabolism studies at TRR levels $\geq$ 10% and only in some residue trials it could be quantified at very low concentrations slightly above 0.01 mg/kg. All in all, a low risk can be concluded using a weight of evidence approach, however in future it should be carefully considered whether other uses may pose an issue.

A low risk from the consumption of contaminated water was concluded at the screening level for both birds and mammals for clofentezine and its metabolites AE C593600, 1,2-DCBH, 2-CBA and 2-CBN. The conclusion applies to all uses included in the GAP. For the metabolites, a screening assessment was conducted assuming a toxicity 10 times higher than the parent. It is worth noting that this outcome would not change for 2-CBN, even when the available endpoint is used.

A low risk from secondary poisoning was concluded for both birds and mammals for clofentezine and its metabolites AE C593600 and 1,2-DCBH, presenting a log P_{ow} > 3. The conclusion applies to all uses included in the GAP. For the metabolites, a screening assessment was conducted assuming 10 times higher toxicity than the parent.

Several valid studies with clofentezine (either alone or as formulated representative product) were available, covering the relevant **aquatic taxa**.

For fish (acute and long term), aquatic invertebrates (acute), sediment dwelling organisms and algae a low risk from clofentezine was concluded for all representative uses.

Aquatic invertebrates (i.e. *Daphnia magna* and *Americamysis bahia* for the acute and long-term assessment, respectively) were identified as the most sensitive group. The endpoint selection for the long-term risk assessment was discussed at the experts' meeting[13] where an NOEC of 3.3 μg a.s./l was chosen for use in risk assessment. Using this long-term endpoint, a low risk could be concluded for the uses in permanent greenhouses. For all other uses a high long-term risk was identified, which could only be resolved using mitigation measures such as no-spray buffer zone of 10 m in tomato, aubergine and strawberry. A mitigation measure corresponding to a 20 m no-spray buffer zone was still insufficient to conclude low risk in citrus (all scenarios) and pome fruits (all scenarios, as only the ponds at D4, D5 and R1 had indications of low risk).

Acute studies with relevant **metabolites** (i.e. for surface water: AE C593600, 2-CBN, 2-CBA, 1,2-DCBH and 2-CBZ; for sediment: AE C593600) were also generally available. When this was not the case, risks were quantified assuming a 10-fold higher toxicity than the parent compound. Based on the available information, a low acute risk could be concluded for all metabolites in all use scenarios. The chronic toxicity of AE C593600 was investigated in *Chironomus riparius*. Based on this study and FOCUS Step 3 calculations, a low risk could be identified for sediment dwelling organisms. However, long term toxicity studies were not submitted for aquatic species other than *Chironomus riparius* (data gap for metabolites, see Section 10).

The acute (contact and oral) and chronic toxicity was investigated in adult **honey bees** using the representative formulation. Additionally, larval toxicity was investigated in two studies, one of which being a repeated exposure design.

A low risk was concluded for the uses in permanent greenhouses, due to lack of significant exposure. For all other uses, an acute risk assessment following the SANCO Guidance on Terrestrial ecotoxicology (European Commission, 2002a) was not available. However, a Tier-1 acute (oral and contact) and chronic risk assessment (adults and larvae) according to EFSA (2013) was available, which indicated low risk for all the representative uses. Nonetheless, the effects assessment to honey

[12] See Expert's consultation point 5.4 at the Pesticide Peer Review Experts' Meeting 14 (September 2019) (EFSA, 2021).
[13] See Expert's consultation point 5.5 at the Pesticide Peer Review Experts' Meeting 14 (September 2019) (EFSA, 2021).

bees was discussed at the experts' meeting,[14] with particular reference to the effects and risk characterisation for bee brood, including eggs. Based on the available data, the following conclusions were drawn: (i) the EC_{10} from the repeated exposure larval test was to be used in risk assessment; (ii) considering the ovicidal mode of action of clofentezine, and the lack of a comprehensive tier I risk assessment covering effects on eggs – the hazard characterisation in honey bee brood (i.e. including eggs) should be further addressed (data gap and assessment not finalised, see Section 9.1.1); (iii) risks to adults and brood from the relevant metabolite 2-CBN occurring in pollen and nectar need further consideration, pending on the evaluation of the residue data set. However, after the experts' meeting it was clear that this metabolite was never detected in plant metabolism studies at TRR levels above 10%. Therefore, according to EFSA (2013), the risk assessment for 2-CBN is covered by the parent compound and no further assessment was deemed required. A suitable assessment of accumulative effects and sublethal effects (e.g. hypopharyngeal glands (HPGs)) was not available (data gap, see Section 10). Furthermore, no risk assessment was performed to address the oral exposure via puddle water (data gap, see Section 10). Finally, toxicity data were not available for **bumble bees or solitary bees**.

For **non-target arthropods** other than bees, the representative formulation was tested on the standard test species *Typhlodromus Pyri* and *Aphidius rophalosiphi*. Additionally, two tests on *Trichogramma cacoeciae* and *Poecilius cupreus* were submitted.

A low risk was concluded for the uses in permanent greenhouses, due to lack of significant exposure. For other uses, based on toxicity data and the Tier-1 risk assessment, a high in-field risk was concluded for the applications in citrus, pome fruits, strawberries and tomatoes.

Therefore, extended laboratory studies using the representative formulation were performed with the test species *Aphidius rhopalosiphi*, *Typhlodromus pyri*, *Aleochara bilineata* and *Orius laevigatus*. Based on these Tier-2 studies, and using a vegetation distribution factor of 10, the risk could be quantitatively refined.

The risk to non-target arthropods was further discussed at the expert's meeting.[15] Specifically, since clofentezine is an acaricide with ovicidal action, the experts concluded that particular consideration should be given to the reproductive risk assessment in *Typhlodromus pyri*. For this species a Tier-2 test was available, where direct effects on eggs, but not other reproductive endpoints were investigated. Therefore, the experts agreed that a more comprehensive characterisation of reproductive hazards to *Typhlodromus pyri* was needed, ensuring that both effects in eggs and reproduction of emerging individuals are addressed (data gap and assessment not finalised, see Section 9.1.1).

The chronic toxicity was investigated in **earthworms** and other **soil macroorganisms** (i.e. *Folsomia candida* and *Hypoaspis aculeifer*). Additionally, the toxicity was investigated using the representative formulation and all relevant metabolites (2-CBA, AE C593600 and 2-CBN), except 1,2-DCBH, for which a surrogate hazard assessment was performed, assuming a 10-times higher toxicity than the parent compound. Based on this body of evidence and the Tier-1 risk assessment, a low long-term risk could be concluded for all representative uses, except those on pome fruits and strawberries. Specifically, for the uses in pome fruits and strawberries grown in the open field or open protected structure (e.g. walk-in tunnels), a high risk for earthworms was concluded. The risk for earthworms in strawberries grown in permanent greenhouses was considered low, due to the lack of significant exposure. For metabolites, a low risk to soil organisms was concluded for all representative uses.

For **soil microorganisms,** low risk was concluded for all representative uses from the representative formulation and metabolites 2-CBA, AE C593600 and 2-CBN. However, a soil nitrogen transformation study was not performed with 1,2-DCBH (data gap, see Section 10).

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

6. Endocrine disruption properties

With regard to the assessment of the endocrine disruption (ED) potential of clofentezine **for humans** according to the ECHA/EFSA guidance (2018), in determining whether clofentezine interacts with the oestrogen, androgen and steroidogenesis (EAS) and thyroid (T) mediated pathways, the number and type of effects induced and the magnitude and pattern of responses observed across studies were considered. Additionally, the conditions under which effects occur were considered, in

[14] See Expert's consultation point 5.7 at the Pesticide Peer Review Experts' Meeting 14 (September 2019) (EFSA, 2021).
[15] See Expert's consultation point 5.6 at the Pesticide Peer Review Experts' Meeting 14 (September 2019) (EFSA, 2021).

particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in overt toxicity. The assessment is therefore providing a weight-of-evidence analysis of the potential interaction of clofentezine with the EAS and T signalling pathways using the available evidence in the data set.

The **T-modality** has been considered sufficiently investigated and T-mediated adversity (histological changes in the thyroid) and T-mediated endocrine activity (changes in thyroid hormones and thyroid-simulating hormone (TSH)) have been observed in rats. Based on the available data set and the mode of action (MoA) analysis, it was concluded that the ED criteria for T-modality are met for clofentezine (Scenario 1b of the EFSA/ECHA (2018) ED Guidance), leading to a critical area of concern (see Section 9.1.2).

EAS-mediated adversity and EAS-mediated endocrine activity have not been observed, but the **EAS modalities** have not been sufficiently investigated. Therefore, further data need to be generated before a conclusion on whether or not the ED criteria are met for the EAS-modalities can be drawn (Scenario 2a(iii) of the EFSA/ECHA (2018) ED Guidance). A ToxCast oestrogen receptor (ER) model is available and negative for clofentezine, therefore, there is no need to further explore the E modality. According to the EFSA/ECHA GD (2018), the following tests are needed to investigate the A and S modalities:

- A study in line with OECD Test Guideline (TG) 458 (Stably Transfected Human Androgen Receptor Activation Assay (AR STTA) assay).
- Aromatase assay (human recombinant) OPPTS 890.1200 (US EPA 2009 In: Endocrine Disruptor Screening Program Test Guidelines. Office of Prevention, Pesticides and Toxic Substances (OPPTS), US EPA, Washington (DC).
- A study in line with OECD TG 456 (H295R Steroidogenesis assay).
- A study in line with OECD TG 441 (Hershberger Assay) in case OECD TG 456, OPPTS 890.1200 and OECD TG 458 are negative.

If the above tests are negative, the active substance will not meet the ED criteria for EAS modalities. However, in case of positive result/s based on the above tests for at least one modality, additional testing might be needed:

- OECD TG 443 (with the inclusion of cohort 1B) or OECD TG 416 (including additional endpoints in accordance with the EFSA (2020) technical report: 'Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology'.

However, in the context of this assessment, since clofentezine is already considered as an endocrine disruptor for the T-modality, additional testing to investigate the A and S-modalities is not needed.

EFSA also noted that the applicant submitted additional data which were not considered in the assessment due to the late submission. These include mechanistic studies conducted in human and rat test systems to support the ED assessment of the T modality.[16]

The outcome of the assessment reported above for humans do not apply to **wild mammals as non-target organisms.** The adversity observed in mammalian species is based on changes in thyroid histology. Based on the recommendations of the EFSA/ECHA (2018) Guidance and on common practice, effects at organ level are not considered relevant at population level. No other more apical effects were identified in the mammalian data set.

For non-target organisms other than mammals, neither the endocrine activity nor endocrine adversity was sufficiently investigated. Additional data would be needed to draw a conclusion on the endocrine disrupting properties of clofentezine on non-target organisms for both T- and EAS-modalities, i.e. a test according to OECD Test Guideline 231 (Amphibian Metamorphosis Assay) and 229 (Fish Short Term Reproduction Assay). A test according to OECD Test Guideline 248 (Xenopus Eleutheroembryonic Thyroid Assay) was performed. However, the assay was not submitted in due time and therefore it could not formally be considered.[17] It is also noted that based on the Mode of Action identified in mammals, a test according to OECD TG 248 is not considered suitable to exclude endocrine disrupting properties in non-mammalian species.

[16] It is acknowledged that the applicant commissioned some additional studies to address the ED properties of the substance, which could however not be considered in the peer review; for further details with the list of the commissioned studies and their availability, refer to Evaluation Table, column 5 entry under experts' consultation point 2.6 (EFSA, 2021).

[17] It is acknowledged that the applicant commissioned some studies to address the ED properties of the substance, which could however not be considered in the peer review; for further details refer to Evaluation Table, column 5 entry under experts' consultation point 5.8 (EFSA, 2021).

Based on the above considerations, the assessment of the endocrine disrupting properties of clofentezine for **non-target organisms** according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be concluded (see section 9.1.1). However, no further data were requested taking into account that clofentezine was considered to meet the criteria for endocrine disruption for human health for the T modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605.

Regarding human health, considerations on the **negligible exposure** are reported in section 2 (mammalian toxicology) and section 3 (residues) of this document.

Regarding the environment, the available PEC in soil, surface water and sediment for all the representative uses assessed are above levels that can be routinely measured[18]. There will be exposure of clofentezine via food items of non-target organisms for the representative field uses, as these organisms will enter fields on the same day an application is made.

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

Table 1: Soil

Compound (name and/or code)	Ecotoxicology
Clofentezine	High risk for earthworms (relevant for uses in pome fruits and strawberry, except permanent greenhouses)
AE C593600	Low risk
2-CBN (soil photolysis)	Low risk
2-CBA	Low risk
1,2-DCBH	Low risk for earthworms and soil macroorganisms. Data gap for soil microorganisms (relevant for all representative uses)

Table 2: Groundwater[(a)]

Compound (name and/or code)	> 0.1 µg/L at 1 m depth for the representative uses[(b)] Step 2	Biological (pesticidal) activity/relevance Step 3a.	Hazard identified Steps 3b. and 3c.	Consumer RA triggered Steps 4 and 5	Human health relevance
clofentezine	No	Yes	–	–	Yes
AE C593600	No	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed
2-CBN (soil photolysis)	No	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed
2-CBA	No	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed
1,2-DCBH	No	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed	Not triggered for the representative uses assessed

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or relevant lysimeter.

[18] In line with the ethos of FAO/WHO (2009) further discussed in EFSA Scientific Committee (2012) and limits of analytical quantification needed for monitoring methods set out in European Commission (2021).

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Clofentezine	High long-term risk for all representative uses, except (i) all permanent greenhouse uses; (ii) uses in tomato, aubergine and strawberry with mitigation measures comparable to 10 m no-spray buffer zone.
AE C593600	Low acute risk. Data gap to address long-term risk to aquatic organisms other than sediment dwellers, for which low risk was concluded.
2-CBN	Low acute risk. Data gap to address long-term risk to aquatic organisms.
2-CBA	Low acute risk. Data gap to address long-term risk to aquatic organisms.
2-CBZ	Low acute risk. Data gap to address long-term risk to aquatic organisms.
1,2-DCBH (from soil)	Low acute risk. Data gap to address long-term risk to aquatic organisms.

Table 4: Air

Compound (name and/or code)	Toxicology
Clofentezine	Rat LC50 > 5.2 mg/L (4 h, nose-only)

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

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

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

8.1. Particular conditions proposed for the representative uses evaluated

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

Representative use	Citrus	Strawberry		Pome fruits	Tomato aubergine	
	Field	Field and walk-in tunnel	Permanent Greenhouse	Field	Field and walk-in tunnel	Permanent Greenhouse
Operator standard exposure	No RMM needed	No RMM needed	Use of PPE is required[(a)]	No RMM needed	No RMM needed	Use of PPE is required[(a)]
Operator negligible* exposure	Use of PPE is required[(b)]	Use of PPE is required[(c)]	Use of PPE is required[(d)]	Use of PPE is required[(b)]	Use of PPE is required[(c)]	Use of PPE is required[(d)]
Worker standard exposure	No RMM needed	No RMM needed	No RMM needed	No RMM needed	No RMM needed	No RMM needed
Worker negligible* exposure	RMM insufficient	Use of gloves	RMM insufficient	RMM insufficient	Use of gloves	RMM insufficient

Representative use	Citrus	Strawberry		Pome fruits	Tomato aubergine	
	Field	Field and walk-in tunnel	Permanent Greenhouse	Field	Field and walk-in tunnel	Permanent Greenhouse
Bystander/ resident standard exposure	Buffer strip 5 m	Buffer strip 2–3 m	Buffer strip 2–3 m	Buffer strip 5 m	Buffer strip 2–3 m	Buffer strip 2–3 m
Bystander/ resident negligible* exposure	RMM insufficient for residential children	RMM insufficient for residential children	Buffer strip 2–3 m	RMM insufficient for residential children	RMM insufficient for residential children	Buffer strip 2–3 m
Risk to aquatic organisms		RMM equivalent to 10 m no-spray buffer zone			RMM equivalent to 10 m no-spray buffer zone	

*: For negligible exposure, RMMs are reflected in the table in case they would lead to exposure below or equal to 10% of the AOEL. In order to give a clear overview, it is also mentioned when RMMs are not needed or are insufficient to lead to an exposure level meeting the criteria for standard or negligible exposure. For further details and considerations as regards negligible exposure assessment please refer to Section 2 and Appendix B.

(a): Gloves (M/L&A) + impervious clothing (A)[ECPA model]; gloves + chemical protective coverall type 6 (A)[EUROPOEM II].

(b): For tractor-mounted applications: gloves, RPE (FP2, P2 and similar) during ML&A; soluble bags (M/L), closed cabins (A) [EFSA, 2014c].

(c): For tractor-mounted applications: gloves, RPE (FP2, P2 and similar) during ML&A; soluble bags (M/L) [EFSA, 2014c]. However, for manual application it is not possible reach exposure levels below 10% of AOEL (see also Appendix B).

(d): Gloves and RPE (mask A1P2) during ML&A, hood/face shield + impervious clothing during A [ECPA model]. However, with the EFSA model combined to EUROPOEM it is not possible to reach exposure level below 10% of the AOEL (see also section 2 and Appendix B).

8.2. Particular conditions proposed for the maximum residue level applications

No particular conditions are proposed for the MRL applications.

9. Concerns and related data gaps

9.1. Concerns and related data gaps for the representative uses evaluated

9.1.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for one or more of the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[19] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

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

[19] 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.

1) The consumer dietary risk assessment could not be concluded since the risk assessment residue definitions for fruit crops and for processed commodities could not be finalised, and the livestock exposure assessment is outstanding (see Section 3.1).

   a) Guideline-compliant storage stability studies with clofentezine and 2-CBN for high water commodities covering the representative uses in pome fruit (only clofentezine), tomato and aubergine, and for high acid commodities covering the representative use in strawberries are requested (relevant for the representative uses in pome fruit, tomato, aubergine and strawberry; see Section 3.1).
   b) Data gap for 6 independent residue field trials with mandarin in SEU and 6 trials with orange in SEU compliant with the cGAP, analysing for clofentezine and 2-CBN and supported by storage stability data for both substances (relevant for the representative use in citrus; see Section 3.1).
   c) Data gap for 8 independent residue field trials with pome fruit, respectively, in NEU and SEU compliant with the cGAP, analysing for clofentezine and 2-CBN and supported by storage stability data for both substances (relevant for the representative use in pome fruit; see Section 3.1).
   d) Data gap for 8 independent residue field trials with strawberry, respectively, in NEU, SEU and indoor compliant with the cGAP, analysing for clofentezine and 2-CBN and supported by storage stability data for both substances (relevant for the representative use in strawberry; see Section 3.1).
   e) Data gap for 8 independent residue field trials with tomato, respectively, in NEU, SEU and indoor compliant with the cGAP, analysing for clofentezine and 2-CBN and supported by storage stability data for both substances (relevant for the representative uses in tomato and aubergine; see Section 3.1).
   f) Two processing trials, respectively, on strawberries and tomatoes, supported by storage stability data, representative of the highest residue levels observed in the GAP-compliant residue trials on these crops, employing processing conditions relevant for these commodities (for tomato including a sterilisation step) and analysing for all compounds formed under these conditions (relevant for the representative uses in strawberries, tomatoes and aubergine; see Section 3.1).
   g) Two processing trials with citrus, supported by storage stability data, employing processing conditions relevant for this commodity (e.g. juice and marmalade production) and analysing for all compounds formed under these conditions (relevant for the representative use in citrus; see Section 3.1).
   h) Further assessment of the toxicological profile of 2-CBN: aneugenicity assessment and general toxicity profile was not available (relevant for the representative uses on fruit crops; see Sections 2 and 3.1).
   i) Further assessment of the toxicological profile of AE C593600: aneugenicity assessment and general toxicity profile was not available (relevant for all representative use; see Sections 2 and 3.1).
   j) Further assessment of the toxicological profile of 2-CBZ: aneugenicity assessment and general toxicity profile was not available (relevant for the representative uses in tomatoes and pome fruit; see Sections 2 and 3.1).

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 abstraction of surface water that might contain the transformation products AE C593600, 2-CBN, 2-CBA and 2-CBZ (see Sections 3 and 4).

   a) Information to address the effect of water treatment processes on the nature of metabolites AE C593600; 2-CBA; 2-CBN; 2-CBZ that have the potential to be present in surface water, when surface water is abstracted for drinking water was not available. Probably in the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. Should this consideration indicate that novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them would need to be addressed (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 4).

3) The risk to honey bees is not finalised with regard to the effects that the active substance may have on potentially sensitive life stages (i.e. honey bee eggs) (see Section 5).

   a) A valid effect study designed to cover effects on eggs or egg laying was not available (e.g. a suitable semi-field, colony-level assessment), considering the ovicidal mode of action of the substance (relevant for all representative uses except those in permanent greenhouses; see Section 5).

4) The risk to non-target arthropods is not finalised with regard to the effects that the active substance may have on potentially sensitive species (i.e. *Typhlodromus pyri*) and life stages (i.e. eggs and egg laying phase) (see Section 5).

   a) A valid effect study designed to address the reproductive toxicity in *T. Pyri* covering both effects on eggs and other reproductive endpoints (i.e. egg laying/fecundity) was not available, considering the ovicidal mode of action of the substance (relevant for all representative uses except those in permanent greenhouses; see Section 5).

5) The assessment of the endocrine disrupting properties of clofentezine for non-target organisms could not finalised for EATS modalities based on the available information (see Section 6).

9.1.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

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

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

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

6) Clofentezine is considered to meet the criteria for endocrine disruption for humans for the T modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (see Section 6).

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

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8.1, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6).

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

Representative use		Citrus	Pome fruits	Strawberry	Strawberry	Tomato aubergine	Tomato aubergine
		Field	Field	Field and walk-in tunnel	Permanent Greenhouse	Field and walk-in tunnel	Permanent Greenhouse
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]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[(b),(c)]	X[(b),(c)]	X[(c)]		X[(b),(c)]	
	Assessment not finalised						
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified		X[(e)]	X[(e)]			
	Assessment not finalised	X[3,4]	X[3,4]	X[3,4]		X[3,4]	
Risk to aquatic organisms	Risk identified	X[(d)]	X[(d)]				
	Assessment not finalised						
Groundwater exposure to active substance	Legal parametric value breached						
	Assessment not finalised						
Groundwater exposure to metabolites	Legal parametric value breached						
	Parametric value of 10 µg/L[(a)] breached						
	Assessment not finalised						

In addition to the issues indicated below, clofentezine is considered to meet the criteria for endocrine disruption for humans for the T modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605, whilst the assessment of the endocrine disrupting properties for non-target organisms according to the scientific criteria for the determination of endocrine disrupting properties as set out in point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, could not be finalised based on the available information. For considerations as regards negligible exposure assessment please refer to Sections 2, 3, 6 and Appendix B.

The superscript numbers relate to the numbered points indicated in Sections 9.1.1 and 9.1.2. Where there is no superscript number, see footnotes and Sections 2 to 7 for further information.

(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).
(b): High reproductive risk identified for birds, after consideration of refinements.
(c): High reproductive risk identified for wild mammals, after consideration of refinements.
(d): High long-term risk was identified for aquatic invertebrates for all scenarios at FOCUS Step 4.
(e): High long-term risk was identified for earthworms.

9.2. Issues related to the maximum residue level applications

9.2.1. Issues not finalised under the maximum residue level applications

1) The consumer dietary risk assessment could not be concluded since the risk assessment residue definitions for fruit crops and for processed commodities could not be finalised (see Section 3.2).

   a) Guideline-compliant storage stability studies with clofentezine and 2-CBN for high water commodities covering the MRL application uses for courgette and cherry are requested (relevant for all MRL application use, see Section 3.2).
   b) Data gap for 8 independent residue field trials with cherry in NEU compliant with the cGAP, analysing for clofentezine and 2-CBN and supported by storage stability data for both substances (relevant for the MRL application use in cherry; see Section 3.2).
   c) Data gap for 4 independent residue field trials with courgette in NEU and 8 trials each in SEU and indoor, compliant with the cGAP, analysing for clofentezine and 2-CBN and supported by storage stability data for both substances (relevant for the MRL application use in courgette; see Section 3.2).
   d) Further assessment of the toxicological profile of 2-CBN: aneugenicity assessment and general toxicity profile was not available (relevant for all MRL application uses; see Sections 2 and 3.2).
   e) Further assessment of the toxicological profile of AE C593600: aneugenicity assessment and general toxicity profile was not available (relevant for all MRL application uses; see Sections 2 and 3.2).

9.2.2. Consumer risk identified under the maximum residue level applications

None identified.

10. List of other outstanding issues

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

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

- Extraction efficiency of the procedures used in the monitoring methods for plant commodities was not addressed (relevant for all representative uses evaluated; see Section 1).
- Method for the determination of the residues of 4-hydroxy-clofentezine in body fluids (relevant for all representative uses evaluated; see Sections 1 and 2).
- Clofentezine was not phototoxic in the OECD 3T3 NRU-PT test. However, the OECD 3T3 NRU-PT might not allow concluding properly on the phototoxicity potential of clofentezine since it is an UVB absorber and the 3T3 NRU-PT test might not be an appropriate test for UVB absorbers. It is noted however that phototoxicity testing applying the new version of the OECD TG 432 (June, 2019) would allow for proper assessment of UVB absorbers (relevant for all representative uses evaluated; see Section 2).
- A study investigating residue levels in pollen and in bee products for human consumption resulting from residues taken up by honeybees from crops at blossom (relevant for all representative uses evaluated, see Section 3.1).
- PEC surface water calculations and subsequent risk assessments for permanent greenhouses in accordance with the corresponding EFSA guidance (2014a) appendices for protected crops were not available (relevant for the representative uses evaluated in permanent greenhouses; see Section 4).
- Identification of unknowns formed at > 10% AR in the available indirect sterile natural water aqueous photolysis study was not available (relevant for all representative uses evaluated; see section 4 of the evaluation table in the peer review report, EFSA, 2021).

- Further data to address the risk to honeybees from sublethal effects (e.g. effects on HPG) and via exposure to puddle water (relevant for all representative uses except permanent greenhouses, see Section 5).
- Further data to address the chronic toxicity of metabolites (i.e. AE C593600, 2-CBN, 2-CBA, 2-CBZ and 1,2-DCBH) to all aquatic organisms, except sediment dwellers (relevant for all representative uses, see Section 5).
- Further data to address the effects of 1,2-DCBH in soil microorganisms (relevant for all representative uses; see Section 5).

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Abbreviations

1/*n*	slope of Freundlich isotherm
λ	Wavelength
ε	decadic molar extinction coefficient
a.s.	active substance
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AAOEL	acute acceptable operator exposure level
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
AR	androgen receptor
ARfD	acute reference dose
AV	avoidance factor
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary cells
CI	confidence interval
CIPAC	Collaborative International Pesticides Analytical Council Limited
CL	confidence limits
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
DT_{50}	period required for 50% dissipation (define method of estimation)
EAS	oestrogen, androgen and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community
f(twa)	Time-weighted average factor
FAO	Food and Agriculture Organization of the United Nations
FID	flame ionisation detector
FIR	food intake rate
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC	gas chromatography
GM	geometric mean
GS	growth stage
HPG	hypopharyngeal glands
HQ	hazard quotient
HR	hazard rate
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry

iv	Intravenous
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).
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography–mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
M/L	mixing and loading
mm	millimetre (also used for mean measured concentrations)
MOA	mode of action
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PHI	preharvest interval
PIE	potential inhalation exposure
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
PT	proportion of diet obtained in the treated area
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
RBC	red blood cells
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
RPE	respiratory protective equipment
SC	suspension concentrate
SFO	single first-order
SMILES	simplified molecular-input line-entry system
TK	technical concentrate
TRR	total radioactive residue
TSH	thyroid-stimulating hormone (thyrotropin)
TWA	time-weighted average
UF	uncertainty factor
UV	Ultraviolet
W/S	water/sediment
w/v	weight per unit volume
w/w	weight per unit weight
WBC	white blood cell
WG	water-dispersible granule
WHO	World Health Organization

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

Properties		Conclusion[(a)]
CMR	Carcinogenicity (C)	Clofentezine is not considered to be carcinogenic according to point 3.6.3 of Annex II of Regulation (EC) 1107/2009 (confirmed in RAC Opinion adopted on 11 June 2020 (ECHA, 2020)).
	Mutagenicity (M)	Clofentezine is not considered to be mutagenic according to point 3.6.2 of Annex II of Regulation (EC) 1107/2009 (confirmed in RAC Opinion adopted on 11 June 2020 (ECHA, 2020)).
	Toxic for Reproduction (R)	Clofentezine is not considered to be toxic for reproduction according to point 3.6.4 of Annex II of Regulation (EC) 1107/2009 (confirmed in RAC Opinion adopted on 11 June 2020 (ECHA, 2020)).
Endocrine disrupting properties		Clofentezine is considered to meet the criteria for endocrine disruption for humans for the T modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605. The endocrine disrupting properties of clofentezine for non-target organisms according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be concluded.
POP	**Persistence**	Clofentezine is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Long-range transport	
PBT	**Persistence**	Clofentezine is not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Toxicity	
vPvB	**Persistence**	Clofentezine is not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	

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

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

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2021.6817

Appendix C – Evaluation of data concerning the necessity of clofentezine as acaricide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods

Appendix C can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2021.6817

Appendix D – Data collection set

Validated Excel files submitted by MS (Austria, 2020; Belgium, 2020; Germany, 2020; Spain, 2020; the Netherlands, 2020; Poland, 2020) and evaluated by EFSA.

Appendix D can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2021.6817

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

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

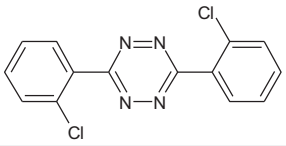
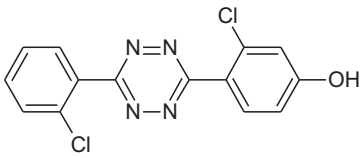
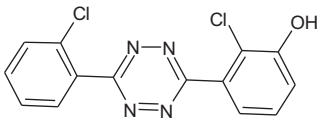
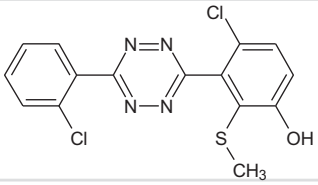
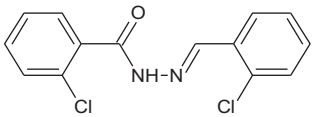
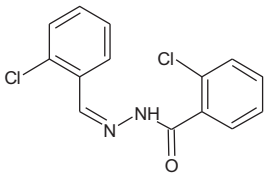
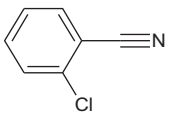
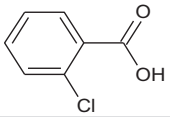
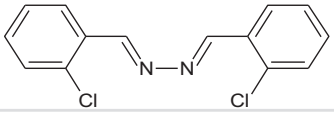
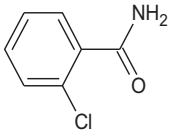
Note these classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

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

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

Based on McCall et al. (1980).

Appendix F – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/ InChiKey[b]	Structural formula[c]
clofentezine	3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine Clc1ccccc1c1nnc(nn1)c1ccccc1Cl UXADOQPNKNTIHB-UHFFFAOYSA-N	
4-hydroxy-clofentezine 4-OH clofentezine	3-chloro-4-[6-(2-chlorophenyl)-1,2,4,5-tetrazin-3-yl]phenol Oc1ccc(c2nnc(nn2)c2ccccc2Cl)c(Cl)c1 URIZMMOZTBABJU-UHFFFAOYSA-N	
3-OH clofentezine	2-chloro-3-[6-(2-chlorophenyl)-1,2,4,5-tetrazin-3-yl]phenol Oc1cccc(c2nnc(nn2)c2ccccc2Cl)c1Cl YNKXOHAAMDSSSI-UHFFFAOYSA-N	
2-methylthio-3-OH clofentezine	4-chloro-3-[6-(2-chlorophenyl)-1,2,4,5-tetrazin-3-yl]-2-(methylsulfanyl)phenol Clc1ccccc1c1nnc(nn1)c1c(Cl)ccc(O)c1SC CSFKNLZGMXYBSH-UHFFFAOYSA-N	
AE C593600 Hydrazide-hydrazone HH (2-chlorobenzylidene) hydrazide 2-chlorobenzoic acid hydrazide Chlorobenzoic Hydrazone FBC 93600	2-chloro-*N*′-[(*E*)-(2-chlorophenyl) methylene]benzohydrazide O=C(N/N=C/c1ccccc1Cl)c1ccccc1Cl ICLDPNCVCPWYFE-RQZCQDPDSA-N or 2-chloro-*N*′-[(*Z*)-(2-chlorophenyl) methylidene]benzohydrazide O=C(N\N=C/c1ccccc1Cl)c1ccccc1Cl ICLDPNCVCPWYFE-MFOYZWKCSA-N	 
2-CBN AE F023666	2-chlorobenzonitrile N#Cc1ccccc1Cl NHWQMJMIYICNBP-UHFFFAOYSA-N	
2-CBA AE C500233	2-chlorobenzoic acid OC(=O)c1ccccc1Cl IKCLCGXPQILATA-UHFFFAOYSA-N	
1,2-DCBH 1,2-di(2-chlorobenzylidene) hydrazine	2-chlorobenzaldehyde [(*E*)-(2-chlorophenyl)methylene]hydrazone Clc1ccccc1/C=N/N=C/c1ccccc1Cl WQRRWZFEJAGOIY-BEQMOXJMSA-N	
2-CBZ AE F092117	2-chlorobenzamide O=C(N)c1ccccc1Cl RBGDLYUEXLWQBZ-UHFFFAOYSA-N	

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2019.1.1 ACD/Labs 2019 Release (File version N05E41, Build 110555, 18 July 2019).
(c): ACD/ChemSketch 2019.1.1 ACD/Labs 2019 Release (File version C05H41, Build 110712, 24 July 2019).