Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Chrysanthemum cinerariaefolium, extract from open and mature flowers of *Tanacetum cinerariifolium* obtained with hydrocarbon solvents

EC Number: 289-699-3
CAS Number: 89997-63-7

CLH-O-0000007334-76-01/F

Adopted

8 June 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CHRYSANTHEMUM CINERARIAEFOLIUM, EXTRACT FROM OPEN AND MATURE FLOWERS OF TANACETUM CINERARIIFOLIUM OBTAINED WITH HYDROCARBON SOLVENTS

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Chrysanthemum cinerariaefolium, extract from open and mature flowers of Tanacetum cinerariifolium obtained with hydrocarbon solvents
EC number: 289-699-3
CAS number: 89997-63-7
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2022	Germany		MemberState	1
Comment received				
Two separate CLH-reports for the extract from chrysanthemum cinerariaefolium have been provided in parallel, which differ by the solvent used for extraction (supercritical CO2 or hydrocarbon solvents). The proposed classification is the same and the chapters on toxicological endpoints are widely identical. In the report on the extract using supercritical CO2 this solvent is explicitly mentioned in the description of the toxicological studies (A2.2.-2.12) while in the report on the extract using hydrocarbon solvents the broader term "pyrethrum extract", which covers both, is used. This might indicate, that nearly all toxicological studies were performed with the extract using supercritical CO2 and a read across was performed to the extract using hydrocarbon solvents. This could be clarified and some more justification for the read across, if performed, would be helpful. As an UVCB of natural origin a variability in the content of the six pyrethrins (pyrethrin 1, cinerin 1, jasmolin 1, pyrethrin 2, cinerin 2 and jasmolin 2) might be possible. Some more general (and non-confidential) information about the variable content (e. g. ranges) would be helpful to understand, that the tested extracts are representative for all extracts in general. It is not clear, whether the DS is of the opinion, that all pyrethrins have similar toxicological properties. Then, some variability in the composition would not be relevant. It is noted, that the toxicological studies were performed with extracts, which included an additional solvent (EC 265-149-8; solvent range: 42.43-50.65%), but as elaborated in the CLH-report, this solvent is likely not the cause for the toxicological effects, which are reflected by the proposed classification.				

Furthermore, we would like to inform you about following formal errors:
• Section 2.1: Please delete the warning statement for pollinators since this is specific for the approval under the BPR and not relevant for the CLH report.
• Section 4.1: Please delete the paragraph about the fate and behavior in the environment based on the representative products' use since this is specific for the approval under the BPR and not relevant for the CLH report.
• Section 4.1: Please delete the effects assessment and summary table of PNEC values since this is specific for the approval under the BPR and not relevant for the CLH report.
• Section A.3.1 & A.3.2: Please delete the boxes "Value used in Risk Assessment" since these boxes are specific for the approval under the BPR and not relevant for the CLH report.

Dossier Submitter's Response

Thank you for your comment.

First of all, with regard to the first and third paragraphs (which can be considered as related), it should be noted that indeed the two substances only differ in the extraction method. Irrespective of the extraction method, the concentration of pyrethrins was adjusted with the solvent mentioned in the third paragraph (which is not responsible for the observed toxicological effects as it has a harmonised classification only as Asp. Tox. 1 - H304) leaving it in both cases at around 50%. This makes both extracts equivalent, since the same concentrations of active substance can be found in both extracts.

The DS prepared a detailed document for the justification of the read across among the different sources initially submitted (different extracts), which belonged to different active substances, and included this justification for read across and the TE justification between sources of the same active substance, *Chrysanthemum cinerariaefolium*, extract from open and mature flowers of *Tanacetum cinerariifolium* obtained with hydrocarbon solvents. Although it was prepared for the CAR, this DS is willing to provide this document to the RAC Secretariat, if necessary.

According to BPC APCP WG-III-2021, the reference specifications were amended to a maximum concentration of 78% total pyrethrin in the *Chrysanthemum* extract from hydrocarbon solvents. For the (eco)toxicological effects, the endpoints obtained from the studies as total pyrethrins should be converted to the extract considering this updated reference specification.

Regarding the second paragraph, we as DS can only prepare the CLH report on the basis of the information available. This means that the information is eminently provided by the industry, so there are no ranges over which to claim that these extracts are representative of all extracts. However, in our opinion, and without being able to go into more detail due to confidentiality issues, we think that the variability between *Chrysanthemum cinerariaefolium* species found in different regions does not represent a problem for the classification, taking into account that the reference specifications have to be met.

Finally, as regards formal errors, we agree that they should be deleted from the CLH report.

RAC's response

RAC thanks for the Member State comments and for the Dossier Submitter's clarification.

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	United Kingdom	Sumitomo Chemical rep BRA and MGK, SCJ and KPIC	Company-Manufacturer	2

Comment received

Please refer to the attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Chrysanthemum Cineranium extract HCS CLH-report commenting table_23.06.2022.pdf

Dossier Submitter's Response

1.1 The appendix was not available for public consultation as the information was confidential. However, it was relevant for ECHA to understand the role of the solvent.

1.2 The exact solvent concentration has not been disclosed in the CLH report at any point. Moreover, as this solvent is not part of the reference specifications of the active substance, this information is not confidential. The solvent identifier (CAS and EC numbers) is necessary to verify that this solvent has a harmonised classification and is not responsible for the effects observed in the (eco)toxicology studies. The concentrations of plant material and BHT have not been disseminated either. This information can also not be considered as confidential and could have relevance for the (eco)toxicological properties of the active substance.

1.3 Thank you for your comment. We hope that it will help to clarify its role in the manufacturing process of the active substance, but not in the alteration of its (eco)toxicological properties.

1.4, 4.1 to 4.3, A.1.1, A.2.1, A.3.1, A.3.3, A.3.5, A.3.6, A.3.8, A.3.10, A.3.12, A.3.13, A.3.15 to A.3.17, A.6.1 to A.6.3 and B.2 We agree that this information should be deleted from the CLH report since this is specific for the approval under the BPR.

1.5 The terminology is already consistent throughout the CLH report. In your example, "total pyrethrins" means pyrethrins+BHT+plant material+water as stated in page 7. Regarding the disclosure of the items listed in the definitions, our opinion can be found in point 1.2 of this comment.

2.1 Since the active substance is an UVCB, all components above a certain concentration are considered relevant, not only the active ones. Furthermore, as the full composition of the plant material has not been disclosed, this partial information cannot be considered confidential. Regarding batches in which the plant material and BHT were determined, we prefer not to go into detail as this information is considered confidential.

3.1, A.2.2 to A.2.8, A.3.2, A.3.4, A.3.7, A.3.9, A.3.11, A.3.18, A.3.19 and B.1 We agree this information should be redacted.

A.3.14 We agree these headings should be amended.

B.1 For DS, the ownership of the data was never completely clear as there were discrepancies between the owners. However, we have consulted the Applicants' contact

point for biocides in order to clarify the data ownership, and an amended version will be provided to ECHA.

B.3 and B.4 The information available in the 2008 RAR should not be redacted since it was made public. In the case of the studies after 2008, this information should be redacted.

B.4 This information has been extracted as is from the DAR and has not been altered to keep it true to Italy's assessment of the active substance under PPPR.

RAC's response

RAC thanks the Company for the comments and the Dossier Submitter for the clarification.

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2022	Italy		MemberState	3

Comment received

IT has recently provided the Assessment Report for pyrethrins as PPP active substance. We checked the studies presented for the CLH dossier and we noticed that some studies are missing for the section of mammalian toxicology, environmental fate and behavior and ecotoxicology. In the following one missing study per section is reported as an example: Acute oral toxicity, range finder & LD50 – rats Report No 86-5148A (1986); Degradation of [Cyclopentenone-2-14C]Pyrethrin I in Mußbach soil incubated under aerobic conditions at 20 °C in the dark.
Report No: AS501 (2017); Species Sensitivity Distribution of acute toxicity to fish Acute toxicity of refined pyrethrum concentrate on aquatic organism (fish) - Report No GAB-034/4-32/ SSD (2013).
Has the dossier submitter checked what was presented for pesticide renewal? Please, have a look on Volume 2 of the RAR containing the list of studies and Volume 1, with the proposal for classification, attached to this comment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Pyrethrins_RAR_Volume 1-2_2022-01-18.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Pyrethrins_RAR_01_Volume 1_2022-01-18.pdf

Dossier Submitter's Response

Thank you for your comment.

We are not sure that we have not included all the IT studies in PPP in the CLH report. The studies used as examples are already included in the CLH report. The studies from the RAR are included in Appendix VII of Part B (Appendices). These studies are in a separate appendix because we thought that their location in the CLH report would be simpler, because the CAR prepared under the BPR was used as a template. Moreover, we have not re-evaluated the DAR studies because we consider Italy's opinion is valid. For this reason, we have therefore left the information in Volume 3 intact for the RAC to take the decision it deems most appropriate.

For the sake of clarity, we can add here the classification proposed by Italy for PPPs and its comparison with the one proposed in this CLH report:

PPPR	BPR
Acute Tox. 4 (H302 & H332)	Acute Tox. 4 (H302 & H332) ATE_{oral} = 700 mg/kg bw $ATE_{inhalation}$ = 2.5 mg/L (dusts & mists)
Skin Sens. 1B (H317)	Skin Sens. 1B (H317)
STOT SE 1 (H370)	-
Asp. Tox. 1 (H304)	-
Aquatic Acute 1 (H400) M = 1000	Aquatic Acute 1 (H400) M = 100
Aquatic Chronic 1 (H410) M = 100	Aquatic Chronic 1 (H410) M = 10*

*This M-factor is proposed to be changed to 100 (please see comment 19).

RAC's response

Thank you for your comments. Indeed, RAC noted the missing studies and has included them in the opinion document.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2022	Netherlands		MemberState	4

Comment received

It is not clear why two reports have been prepared for the separate extractions when it was decided that the substances were technically equivalent and that a combined CAR should be produced. The dossier submitter is requested to elaborate on this.

Dossier Submitter's Response

Thank you for your comment.

Since the manufacturing methods are different, the active substances are different even though they have almost the same composition. For this reason, we consider it pertinent to present two separate CLH reports. In the discussion of WG-IV-2015 of biocides this issue was raised, and the conclusion was that they should be considered as separate active substances. This has been the basis for our decision.

Regarding the combined CAR, it was referred to the necessity to merge two dossiers submitted under different names (*Pyrethrins and Pyrethroids*, and *Chrysanthemum cinerariefolium extract*), which were combined into the unique dossier *Chrysanthemum cinerariaefolium, extract from open and mature flowers of Tanacetum cinerariifolium obtained with hydrocarbon solvents*, because the active substance in this case was the same, but different from *Chrysanthemum cinerariaefolium, extract from open and mature flowers of Tanacetum cinerariifolium obtained from supercritical CO_2*.

See explanation in Comment number 1.

RAC's response

RAC thanks for the Member State's comments and for the Dossier Submitter's clarification.

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2022	Germany	Pyrethrin Joint Venture	Company-Manufacturer	5
Comment received				
Comments concern legally wrong data ownership information stated in the CLH dossier. ECHA note – An attachment was submitted with the comment above. Refer to public attachment PJV comments_hydrocarbon solvent_non confidential.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment PJV comments_hydrocarbon solvent_confidential.zip ECHA note: ECHA checks the CLH report as received by the Dossier Submitter (DS) for accordance with the CLP regulation and subsequently publishes the report. Accordance check does not verify and ECHA has no mandate to verify the correctness of the information contained therein, particularly to assess the company's allegation concerning the ownership of the data reported in the reference list. Therefore, ECHA cannot itself make such changes to the CLH Report, nor can act on this allegation. However, the DS will further reply to your comment.				
Dossier Submitter's Response				
For DS, the relationship between the different data owners was never clear, especially when several of them appeared to be based outside the EU. This resulted in the data coming with the name of different owners in the two dossiers. DS never received clear information on this. It is not the responsibility of the DS to clarify this information or to intervene in legal problems that the owners of the data have with each other. However, we have asked the Applicants' contact point in order to clarify this issue. We have no objection to the modification of the relevant information once we have received this clarification. ECHA note – An attachment was submitted with the response from the dossier submitter. Refer to attachment CLH Chrysanthemum extract Hydrocarbon solvent.docx				
RAC's response				
ECHA note: ECHA has uploaded the revised CLH report with correct data owner information on its website.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2022	Germany		MemberState	6
Comment received				
It is stated in chapter A2.9.1 of the CLH-reports: "In male rats the incidences of adenoma were 5% (3 of 60 males) in both, the highest dose and the mid dose (3000 ppm and 1000 ppm (199 and 66 mg/kg bw/d extract))." However, these incidences could not be easily found in the table on p.123-126 of the report on the CO2-extract (p. 129-132 of the report of the hydrocarbon solvent-extract). It should be added from which data of the table the incidences of 5% are derived. It is mentioned in the CLH-report, that keratoacanthomas in rats and lung carcinomas in				

mice were increased, but no numeric values of the incidences are available. They should be added for completeness.
Dossier Submitter's Response
Thank you for your comment. The data is derived from table showing the microscopic findings in liver (p. 130-131). The combined incidence (SAC + DOS) for hepatocellular adenoma was 5% in males in both mid- and high-dose groups. Regarding the keratoacanthomas in rats and lung carcinomas in mice the highest incidences were 23,3 (males in high-dose group) and 5% (males in mid- and high-dose groups), respectively.
RAC's response
RAC thanks the Member State for the comment and the Dossier Submitter for the clarification. These values are included in the RAC background document (section "Supplemental information - In depth analyses by RAC").

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	7
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	8
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	9
Comment received				
-				
Dossier Submitter's Response				

RAC's response

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	10
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	11
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	12
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	13
Comment received				
According to RAR vol 3 (B.6.2.6 – skin sensitization, data point CA 5.2.6/05, LLNA study 2018b) did the preliminary study and the quantitative irritation test (QIT) not result in increases in ear thickness greater than 25% in any of the tested concentrations (2,5%, 5%, 10%, 25%, 50% and 100%). According to OECD 429 "the highest dose selected for the main LLNA study will be the next lower dose in the pre-screen concentration series that does not induce systemic toxicity and/or excessive local skin irritation". Therefore a higher concentration (undiluted) for the main study should have been chosen. It can not be ruled out, that a higher concentration could have given a higher EC3				

response and thereby a higher classification kategori (1A).
DEPA therefore suggest that the classification is H317 in kategori 1.

Dossier Submitter's Response

Thank you for your comment.

Since the substance is an UVCB, it is considered by default to be 100% pure. However pure chrysanthemum extract is too difficult to handle because of its high density, so it is diluted with a solvent. In addition, since the substance is stable without the solvent, the solvent is not part of its composition.

In the preliminary irritation study and in the QIT, the doses correspond to the dose of 50% of that stated, since it is 100% of the substance as received, which is diluted to 50% in the manufacturing process. In other words, a 100% dose would correspond to a 50% dose.

For this reason, and given the difficulty of handling the product at very high concentrations, we think it is justified to maintain the classification as Skin. Sens. 1B.

RAC's response

Thank you for the comment. According to subsequently provided data, as a reply to EFSA comment, higher doses were not tested since in the pre-test, skin irritation (alopecia, erythema) was observed at 50% pyrethrins. At 100% test concentration, lethality was also found. Also, the Applicant considered that since EC3 value is calculated using the results of the data points lying immediately above and below the SI value of 3, EC3 value and harmonised classification based on EC3 value would not change even if tested with concentrations higher than 25% (the highest dose tested).

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	14

Comment received

With reference to the RAR vol 1 (2.6.2.9) and vol 3 (B.6.2, B.6.6.2 and B.6.7) the Danish EPA suggest the classification STOT SE 1 – H370. It is elvaluated that the neurotoxic symptoms occurred below the doses relevant for the classification with H302.
According to the CLP (and Guidance on the application of the CLP criteria) significant toxicity can be functional disturbance which was seen in the studies (behavioral effects). The target organ is the nervous system.
LOAEL (in acute oral neurotox study) was 63 mg/kg bw/d for females and 125 mg/kg/bw/d for males, which is much below the LD50 for males and females. And even though there were some adaptive response there was also inconclusive evidence of minimal neuropathy – effects not normally seen in young rats (as in the study).

Dossier Submitter's Response

Thank you for your comment.

We do not agree with the classification as STOT SE 1 (H370) since the observed effects are neither significant nor severe. The guidance value ranges are only applicable in case the effects are of that severity. In the case that the effects from the acute oral toxicity study

were considered to be of sufficient severity, using the guidance value ranges the supported category is STOT SE 2 (H371) with a NOEL = 316 mg/kg. Moreover, in the acute inhalation toxicity study, the effects were transient, which is a significant discriminator, so maybe we could support the classification as STOT SE 3 (H336), taking into account also the neurotoxicity study, where there is insufficient evidence to link the chrysanthemum extract with the observed changes in the sciatic nerve. For these reasons, we do not support the classification in the STOT SE hazard class.
RAC's response
RAC agrees with the Member State's comment, and proposes the classification with STOT SE 1, H370 (nervous system). Doses at which neurological symptoms occurred are well below the guidance values, and well below the doses relevant for the classification with H302: Harmful if swallowed, or H332: Harmful if inhaled.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	15
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	16
Comment received				
To consider if the Pyrethrins technical should be seen as the actual substance since in practice it (pyrethrins technical) will be used as the active substance with the solvent (relevant impurity). Therefore it is suggested that it is classified with aspiration hazard, H304.				
Dossier Submitter's Response				
Thank you for your comment. Since the substance is stable without the solvent, the solvent is not part of its composition. For this reason, classification as Asp. Tox. 1 (H304) is not sustained.				
RAC's response				
Thank you for the comment. RAC notes that Pyrethrins technical contains more than 10% hydrotreated light petroleum distillate, which is classified as Asp. Tox. 1, H304. However, active substance, which is subject to classification, is not Pyrethrins technical, but total pyrethrins, which do not contain the solvent.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	17
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2022	France		MemberState	18
Comment received				
We agree with the aquatic acute and chronic toxicity classification that is proposed.				
Dossier Submitter's Response				
Thank you for your comment. Please see comment 19, some changes have been proposed.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
22.06.2022	Germany		MemberState	19
Comment received				
• Section A.3.1.1.1: Please check the reliability of the study "photolysis in water". The CAR states a reliability of 2. • Section A.3.1.2: Please delete the reference to the environmental risk assessment in the text regarding the study by Mori. • Section A.3.2.1: Please indicate in the tables whether the concentrations are nominal or measured. • Section A.3.2.1.1: In the description of the second acute immobilisation test with D.magna, an EC50 of 272.81 µg/L is mentioned for pyrethrin 1. Please change this to 61.08 µg/L as shown in table A77. • Section A.3.2.1: The early life stage test with fathead minnow is described as subacute. However, this study is a long-term study. Please revise. • Section A.3.2.1.2: In the text for the acute test with C.riparius, the numbers of immobile daphnids is				

mentioned instead of chironomids. Please revise.

• Section A.3.2.1.2:
In the summary table of acute/short-term toxicity to sediment dwelling organisms, please add that the test was done with the test material FEK-99.

• Section 4.1:
In Table 4.3, the temperature corrected DT50 in the sediment is 11.2 d at 12 °C (5.27 d at 20 °C) instead of 10 d. Please revise.

• Section A 6.1.3:
For the P assessment, the temperature corrected DT50 in the sediment is 11.2 d at 12 °C (5.27 d at 20 °C) instead of 10 d. Please revise.

• Appendix VII 2):
According to the appendix VII, there are studies from the approval as active substances used in plant protection products which show lower effect concentrations compared to the studies from the the approval as biocidal active substance. This could influence the derivation of the M-factors. I.e. for the chronic aquatic toxicity, there is a study with A.bahia with a NOEC of 0.25 µg total pyrethrins/L = 0.00025 mg total pyrethrins/L which is equivalent to 0.00038 mg/L of Chrysanthemum cinerariaefolium extract from HCS, without solvent (pyrethrins are at a concentration of 65.27% in the composition of the plant extract). This would lead to a M-Factor of 100. Classification should consider all available data and these studies were judged as reliable in the assessment of the active substance as plant protection product. Therefore, the M-factor should be derived based on these lower effect concentrations. Please adjust the classification accordingly or provide a rationale why these studies should not be considered.

Dossier Submitter's Response

• Section A.3.1.1.1:
The reliability of the study "photolysis in water" should be changed to 2 as stated in the CAR. Sorry for the mistake.

• Section A.3.1.2:
The reference to the environmental risk assessment in the text regarding the study by Mori should be deleted. Agreed and thank you for the comment.

• Section A.3.2.1:
The concentrations are measured except for the endpoint for algae, which is the solubility limit.

• Section A.3.2.1.1:
Thank you for this correction. The value should be 61.08 µg/L, as shown in table A77.

• Section A.3.2.1:
We agree. It should read "*A flow-through chronic toxicity test*".

• Section A.3.2.1.2:
The following text and the detailed table for **Immobile *Chironomus riparius*** should be deleted from the CLH report:

"*In this specific test, observations on immobilization of the Chironomus riparius were made after 24 and 48 hours. The immobilised Chironomus riparius were counted and abnormal*

behaviour was noted at test start and every 24 hours thereafter. Water temperature, pH and dissolved oxygen were recorded throughout the exposure period. Chironomus riparius were not fed during the test period. Analytical determinations for total Pyrethrins concentration were made from samples taken from each replicate of each test item group at the start and end of the study. Mortality data as absolute numbers of immobile daphnids and as percent of exposed animals is shown below:"

• Section A.3.2.1.2:
As it is stated in this section, the tests were not performed with the test material FEK-99. The three acute immobilisation tests with *C. riparius* were performed for the chemical similarity report, using the three available sources.

• Section 4.1:
Thank you for this comment. The value corrected to 12ºC is 11.2 d. This should be amended in table 4.6 as well as in section 4.1 (last paragraph in "Fate and behaviour in aquatic compartment").

• Section A 6.1.3:
Thank you for this comment. The value corrected to 12 ºC is 11.2 d. This should be amended in section A.6.1.3. PBT Assessment.

• Appendix VII 2):
The classification was proposed according to the available studies under BPR (no other studies were available to be evaluated by this DS). Nevertheless, we added some studies that were included in the plant protection product dossier to such Appendix VII but did not change the initial proposal.

The BPR dossier refers to Chrysanthemum extract whereas the PPP dossier refers to Pyrethrins, hence this CLH report refers to the extract from hydrocarbon solvents (max. content of 78% pyrethrins, see comment 1). Actually, the endpoints from the studies, estimated in total pyrethrins, need to be converted from total pyrethrins to the extract, considering the APCP WG-III-2021 decision regarding the reference specification (see comment 1).

Nevertheless, being pyrethrins the active biocidal component assessed in the tests, and according to the approach 1S1A, we would accept the evaluation made by Italy under PPP.

Regarding the chronic classification, the study with *A. bahia* has some deficiencies regarding the analytical methods as stated in the DAR ("the expert concluded that the method of this study is not acceptable, is not fully validated - results are not in accordance with RD – two different reference materials were used - materials are not compliant with RD, the composition of batch remained uncharacterized"). Nevertheless, the study has been considered valid for the risk assessment in the RAR. Hence, the DS could consider the higher M factor for the chronic classification (M-Factor 100 for not readily biodegradable substances, based on *A. bahia* study in the interval 0.0001 < NOEC < 0.001 mg/L).

Regarding the acute classification, we are reluctant to accept the M factor of 1000, as it is based on a study with *Hyalella azteca*, and there is no OECD guideline approved for this species, whose behaviour is complicated, hence these studies are not usually considered valid for evaluation in the BPC WG or require an additional further assessment by the competent authorities' experts. Furthermore, there are some deficiencies stated in the RAR such as the

not acceptability of the analytical methods, the composition of batch remained uncharacterized, and the study is not accepted by method experts.

The DS could consider for classification the acute study with *M. bahia*, which was accepted in the RAR, and hence the M factor would be 100, same as in the actual proposal.

Considering all the above, and the changes in the reference specification from BPC APCP WG-III-2021 (see comment 1), please find here a comparative table with the environmental classification proposals, including a new proposal which has considered the comments here submitted:

	IT CLH proposal for Pyrethrins under PPP		ES CLH actual proposal for Chrysanthemum extract from hydrocarbon solvents		ES CLH new proposal for Chrysanthemum extract from hydrocarbon solvents after commenting period	
Acute	A1		A1		A1	
M factor	1000	Based on 0.76 µg total pyrethrins/L for *H. azteca**	100	Based on *C. riparius* 0.00311 mg total pyrethrins/L (equivalent to 0.0047 mg *Chrysantemun* extract from hydrocarbon solvents without solvent, where pyrethrins are at a concentration of 65.27%)	100	Based on *M. bahia* 0.0014 mg total pyrethrins/L (equivalent to 0.0018 mg/l of *Chrysanthemum* extract from hydrocarbon solvents, without solvent, where pyrethrins are at max. concentration of 78% in the composition of the plant extract)
Chronic	C1		C1		C1	
M factor	100	Based on *A. bahia* 0.00025 mg total pyrethrins/L	10	Based on *Daphnia magna* 0.00086 mg total pyrethrins/L (equivalent to 0.0013 mg *Chrysanthemum* extract from hydrocarbon solvents without solvent. Considering the substance as total pyrethrins the M factor would be 100 based on a NOEC = 0.00086 mg/L)	100	Based on *A. bahia* 0.00025 mg total pyrethrins/L (equivalent to 0.00032 mg *Chrysanthemum* extract from hydrocarbon solvents without solvent, where pyrethrins are at a max. concentration of 78% in the composition of the plant extract)

* Studies not submitted under BPR but considered under PPP for classification:

M. bahia	*Pyrethrum extract (FEK-99)*	*96h flow through*	*LC50 = 1.4 µg pyrethrins/L*
H. azteca	*Pyrethrum Stewardship Blend*	*96h flow through*	*LC50 = 0.76 µg pyrethrins/L*
A. bahia	*Pyrethrum Stewardship Blend*	*28 days, flow through*	*NOEC = 0.25 µg pyrethrins/L*

These values should be converted to *Chrysanthemum* extract considering the % of total pyrethrins in the extract itself. I.e.: M. bahia LC50 = 0.0018 mg C. extract HCS/L.

RAC's response

Thank you for the comments and the answers. Regarding the studies with A bahia and H Azteca, RAC has taken them into account and has discussed the validity of the studies in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2022	United Kingdom	Health and Safety Executive	National Authority	20

Comment received

Comments:
Long-term toxicity data are not available for the most sensitive fish species Oncorhynchus mykiss. Equally, at present reliable water phase dosed long-term toxicity data to for the acutely sensitive species Chrironomus riparius are not available. On this basis, the surrogate approach should be considered which would result in a more stringent M-factor of 100.

We note the Heintze, 2001 OECD 219 study with C. riparius is considered supporting information at present. Is there further information regarding analytical verification of the test substance in the water and sediment phases over the study available to consider if a long-term endpoint based mean measured water phase concentrations can be reliably determined?

Dossier Submitter's Response

We agree to apply a more stringent M-factor for C1 classification (please see comment 19).
We consider that the three trophic level chronic studies submitted are valid and enough for classification. Nevertheless, as there is a more stringent NOEC for other invertebrates' study, we agree to the M-factor of 100 for chronic classification (please see comment 19). This would cover the possible higher sensitivity of *O. mykiss*.

Regarding water/sediment, only the acute test with chironomids is used for classification, not the chronic one (supporting information).

FYI: some additional chronic tests with sediment organisms are being performed by the applicants under BPR.

RAC's response

RAC agrees that for the Heintze, 2001 OECD 219 study with C. riparius, a long-term endpoint based mean measured water phase concentrations cannot be reliably determined on the basis of the data presented in the CLH report.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2022	Netherlands		MemberState	21

Comment received

Environment – General comments

Test material
The ecotoxicity testing was performed using different pyrethrum extracts (or known pyrethrin metabolites) as test material. Can the dossier submitter explain how these extracts are representative for the Chrysanthemum cinerariaefolium extracts from supercritical CO2 and HCS? Is the relative abundance of the pyrethrin in the used extracts comparable to that of the supercritical CO2 or HCS extracts? A quantitative composition should be provided of the to be classified extracts as well as the extracts used in the

experiments.

Composition
In relations to the comment above, it is not clear how the content of total pyrethrins relates to the chrysanthemum extract without solvent and with solvent. There is no compositional overview of this. Reporting on this matter is confusing:

1.
In section A.3.3. (Overall summary of acute and chronic aquatic toxicity data and Comparison with the CLP criteria), the compositional fractions of the extract (without solvent) are presented as follows: 'Pyrethrin I: Pyrethrin 1 (min 418.9 g/kg), Cinerin 1 (min 46.0 g/kg), Jasmolin 1. (min 28.8 g/kg); Pyrethrin II: Pyrethrin 2 (min 285.5 g/kg), Cinerin 2 (min 41g/kg) and Jasmolin 2 (min 21.8g/kg). […] Further the substance contains other plant material (max 88.1 g/kg), BHT (max 69.4 g/kg), water (max 2.7 g/kg)..'

On the basis of this, the total pyrethrins in the extract would be at least 842 g/kg.

However, in section A.3.3.1, under the C. riparius bullet point, it is mentioned that the pyrethrins are at a concentration of 82.39% in the composition of the plant extract considered as the mixture. This seems to be in contrast with the aforementioned purity of 842 g/kg. This also affects the conversion of the ecotoxicological effect values. Using a purity of 84.20% (instead of 82.39%), the 21-d NOEC of D. magna of 0.00086 mg/L total pyrethrines would be equivalent to a maximum of 0.00102 mg/L Chrysanthemum cinerariaefolium extract from supercritical CO2, without solvent. A slight increase to the minimum total pyrethrins in the extract of 84.2 g/kg would further decrease the converted NOEC. It may therefore be possible that the NOEC would drop below 0.001 mg/L, which would trigger a higher M-factor.

2.
Furthermore, the lowest acute and chronic effect values for risk assessment are presented as follows:
EC50 = 5.20 µg total pyrethrins /L = 7.97 µg a.s./L considering the whole extract as the a.s.
And
NOEC (21 days) = 0.86 µg total pyrethrins/L = 1.32 µg a.s./L, considering the whole extract as the a.s.
In these scenario's the whole extract contains (5.20/7.97)*100% = ca. 65% pyrethrins. How does this relate to the previous?

3.
We further note that there may be a difference in the composition between the extracts obtained by supercritical CO2 and HCS. It appears that the supercritical CO2 extract contains '82.39%' whilst the HCS extract contains '65.27%' (only mentioned in the C. riparius bullet point of Section A.3.3.1. Short-term (acute) aquatic hazard in both reports). On the other hand, in Section A.3.3.2. Chronic/ long-term aquatic hazard (including information on bioaccumulation and degradation) of both the extraction reports, it is mentioned that the % pyrethrin 1 in the extract is 43.9%. Based on the previous, it is unclear whether there are relevant compositional differences between the two extractions for the environmental classifications. All of this hampers a proper evaluation.

In short
The dossier submitter is requested to present clear and concise information on the composition (individual and total pyrethrins; in extract; with and without solvent) for both extraction methods and the extracts used in the ecotoxicity tests. In light of this, the dossier submitter is requested to reassess the M-factor of the chronic classification, as pyrethrin concentrations clearly differ in the different extracts, this might affect the key values used for the proposed classification.

Environmental fate testing

The hazard assessment is currently based on all pyrethins, while the environmental fate assessment is based on only pyrethrin 1; as it is (volume-wise) the predominant component:
The fate and distribution in the environment was derived from studies on pyrethrin 1, since pyrethrin 1 represents the predominant analogue and a typical member (or paradigm) for the pyrethrum family. Therefore, it was regarded as feasible to make extrapolations from pyrethrin 1 to the active substance (Chrysanthemum cinerariaefolium extract from supercritical CO2). Hence, it was also considered to be justified to model the fate of total pyrethrins in the environment based on characteristics of pyrethrin 1.

However, the other constituents classified as Aquatic Chronic 1 (or higher) should also be considered relevant components. It seems that read-across is applied. The dossier submitter has not provided a a justification on how data on pyrethrin 1 can be considered relevant (and worst-case) for all the other relevant components. Therefore, the DS is requested to provide a read-across justification according to the relevant guidance.

Dossier Submitter's Response

Environment – General comments

Test material

The majority of the tests were performed with extracts from supercritical CO_2 or from hydrocarbon solvents. FEK-99 is a representative for hydrocarbon solvents extracts (there is a technical equivalence for these extracts). Please see comment 1 regarding how the extracts are obtained: it should be noted that indeed the two substances only differ in the extraction method. Irrespective of the extraction method, the concentration of pyrethrins is adjusted with the solvent leaving it in both cases at around 50%.

The results of the ecotoxicity tests were expressed as total pyrethrins (pyrethrins I and II) to provide comparable results. The reference specification has been amended after BPC APCP WG-III-2021. The new reference specification corresponds to a max. concentration of 78% total pyrethrins in the *Chrysanthemum* extract from hydrocarbon solvents and to a max. concentration of 90% in the extract from supercritical CO_2. The maximum % is used to convert the endpoints from total pyrethrin to the extract itself, not considering the solvent.

Composition

Please see comment 1.

The reference specification does not include the solvent, which is not considered as part of the active substance for classification purposes. Hence, the max. 78% content of pyrethrins in the plant extract from hydrocarbon solvents does not consider the solvent.

1. Regarding section A.3.3, this should be amended due to the reference specification changes after APCP WG-III-2021. Hence, the paragraph "Pyrethrin I: Pyrethrin 1 (min 418.9 g/kg), Cinerin 1 (min 46.0 g/kg), Jasmolin 1. (min 28.8 g/kg); Pyrethrin II: Pyrethrin 2 (min 285.5 g/kg), Cinerin 2 (min 41g/kg) and Jasmolin 2 (min 21.8g/kg). […] Further the substance contains other plant material (max 88.1 g/kg), BHT (max 69.4 g/kg), water (max 2.7 g/kg)." is obsolete and should be deleted.

The value to be considered in the *Chrysanthemum* extract from hydrocarbon solvents composition is max. 78% total pyrethrin and max. 90% in the extract from supercritical CO_2.

Nevertheless, and due to the more stringent studies, the M-factor has been proposed to be changed to 100 for chronic classification. Hence the uncertainties stated in this comment would be covered with this worst case (see comment 19).

2. The 65.27% was the obsolete reference specification for *Chrysanthemum* extract from hydrocarbon solvents (the value 82.39% was the obsolete specification for the other extract, *Chrysanthemum* extract from supercritical CO_2). We are sorry for not having included these changes before.

3. As mentioned in comment 1, both extracts will be standardized to around 50% total pyrethrin. The extract obtained from supercritical CO_2 provides a higher purity (max. 90%) whereas the extract obtained from hydrocarbon solvents provides a lower purity (max. 78%).

Please take into consideration that:
- The studies have been performed with different extracts from different sources from several applicants.
- This is a UVCB substance with a variability in its composition.
- The active substance is not handleable without the solvent, hence the studies had to be performed with the extracts containing the solvent.
- It has been decided in BPC-41 that the solvent should not be considered as part of the active substance, and this should apply to the classification as well.

The concise information on the composition is confidential, that is why the reference specification the DS has provided in the CLH dossier is only the maximum value of the total pyrethrin contained in the extracts.

This variability in the concentration has an impact; hence, we have proposed a more stringent M-factor for the chronic classification, based on a study submitted under PPP, which allows to cover the variability and uncertainties found (please see comment 19).

Environmental fate testing

The DS prepared a detailed document for the justification of the use of fate properties of pyrethrin 1 as representative for the 6 main constituents in the extract (the six components in pyrethrin I and II). In such document all 6 components fate and ecotoxicological properties are compared and the conclusion of pyrethrin 1 representativeness is supported. Although it was prepared for the risk evaluation under BPR and it includes further rationale which is not applicable to classification, this DS is willing to provide this document to the RAC Secretariat, if necessary.

The new proposed classification as Aquatic Chronic 1 with M-factor = 100 is the more stringent one, and it has been derived from studies with the extract containing all constituents, so the DS considers that the classification covers all the relevant components.
RAC's response

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	22
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2022	France		MemberState	23
Comment received				
p52 : Auto-ignition temperature: An auto-ignition temperature of 284 °C has been determined for the pure active substance (Siusiene, E. 2022). However, a DSC screening on pure active substance showed that degradation starts at a temperature of 149 °C. As a consequence, could you please clarify that the measured auto-ignition temperature may not correspond to the auto-ignition temperature of the substance, as it is degraded before ignition ?				
Dossier Submitter's Response				
DSC has been conducted to provide preliminary thermal stability information on a test substance to screen explosive or self-reactive properties. The onset temperature of energetic activity is indicated by examining any deviation in the sample heat flow from the baseline. DSC shows un upward deviation in the sample heat flow from the baseline indicating exothermic activity at the temperature of 149 ºC. A second upward deviation from the baseline indicating exothermic effect has been determined at the temperature of 253ºC. Subsequently, DSC shows a downward deviation indicating endothermic activity. The DSC was conducted in a gold (high pressure, sealed) crucible type in the following conditions: 20ºC to 500ºC at 4ºC/min. In the other hand, the autoignition temperature (AIT) of a substance is defined by the ASTM as "the minimum temperature at which autoignition occurs under the specified conditions of test". This definition highlights the non-fundamental nature of AIT, that is, the measured value depends on the conditions of the experiment. The test is conducted in accordance with the procedure described in EU Regulation 440/2008, test A.15. As determined by this method, the AIT is the lowest temperature at which the substance will produce hot flame ignition in air at atmospheric pressure without the aid of an external ignition source. The				

AIT changes significantly depending on many conditions (e.g. the volume of the vessel used is particularly important since lower autoignition temperatures will be achieved in larger vessels). Therefore, the AIT by a given method does not necessarily represent the minimum temperature at which a given material will self-ignite. Therefore, the conditions used to conduct the DSC screening and the AIT are very different and may not be comparable. In addition, the test substance is a UVCB substance with multitude of constituents, not only pyrethrins. It means that the energetic activity showed in the DSC and the measured autoignition temperature may be influenced by different constituents present in the same mixture.
RAC's response
Thank you for your comments and answer. RAC supports the conclusion based on the defined AIT.

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2022	Denmark		MemberState	24
Comment received				
-				
Dossier Submitter's Response				
RAC's response				

PUBLIC ATTACHMENTS
1. PJV comments_hydrocarbon solvent_non confidential.zip [Please refer to comment No. 5]
2. Pyrethrins_RAR_Volume 1-2_2022-01-18.pdf [Please refer to comment No. 3]
3. Chrysanthemum Cineranium extract HCS CLH-report commenting table_23.06.2022.pdf [Please refer to comment No. 2]

PUBLIC ATTACHMENTS (Dossier Submitter's response)
1. CLH Chrysanthemum extract Hydrocarbon solvent.docx [Please refer to response to comment No. 5]

CONFIDENTIAL ATTACHMENTS
1. PJV comments_hydrocarbon solvent_confidential.zip [Please refer to comment No. 5]
2. Pyrethrins_RAR_01_Volume 1_2022-01-18.pdf [Please refer to comment No. 3]