Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

(3a*S*,5*S*,6*R*,7a*R*,7b*S*,9a*S*,10*R*,12a*S*,12b*S*)-10-[(2*S*,3*R*,4*R*,5*R*)-3,4-dihydroxy-5,6-dimethylheptan-2-yl]-5,6-dihydroxy-7a,9a-dimethylhexadecahydro-3*H*-benzo[c]indeno[5,4-e]oxepin-3-one; 24-epibrassinolide

EC Number: -
CAS Number: 78821-43-9

CLH-O-0000006728-62-01/F

Adopted

5 December 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON (3AS,5S,6R,7AR,7BS,9AS,10R,12AS,12BS)-10-[(2S,3R,4R,5R)-3,4-DIHYDROXY-5,6-DIMETHYLHEPTAN-2-YL]-5,6-DIHYDROXY-7A,9A-DIMETHYLHEXADECAHYDRO-3H-BENZO[C]INDENO[5,4-E]OXEPIN-3-ONE; 24-EPIBRASSINOLIDE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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.

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

Substance name: (3aS,5S,6R,7aR,7bS,9aS,10R,12aS,12bS)-10-[(2S,3R,4R,5R)-3,4-dihydroxy-5,6-dimethylheptan-2-yl]-5,6-dihydroxy-7a,9a-dimethylhexadecahydro-3H-benzo[c]indeno[5,4-e]oxepin-3-one; 24-epibrassinolide
EC number: -
CAS number: 78821-43-9
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Germany		MemberState	1
Comment received				
The submitted CLH report is part of the DAR on 24-Epibrassinolide (combined template for both procedures). Comments of the DE-CA on this DAR are provided within a Confidential Annex to this comment. We agree that according to the available information no classification is currently proposed for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, skin corro-sion/irritation, serious eye damage/eye irritation, skin sensitization, specific target organ toxicity – single exposure and specific target organ toxicity – repeated exposure. However, it is concluded that the data basis on some important toxicological end points in the PPP application is insufficient. A final assessment of the impact on human health and the resulting classification and labelling is thus currently not recommended and the request of additional data within the PPP procedure is recommended. No OECD test guideline compliant studies as required according to Commission Regulation (EU) No 283/2013 were submitted to different toxicological endpoints. This was justified by the applicant and the RMS by the presence of brassinosteroids in plants and because the literature review did not raise concerns regarding potential effects. However, the literature review was not very helpful in the assessment of 24-Epibrassinolid because only 8 publications with only few supplementary toxicological				

information were included in the DAR. Therefore, the reference that no concerns were found in the literature is not a sufficient justification that the required toxicological studies were not submitted. Also the presence in plants is not considered to be general evidence that an impact on hu-man and animal health can be excluded.

In Volume 1, Table 2.10.2.2 the data on all toxicological endpoints without respiratory sensi-tisation and aspiration hazard are described as "conclusive but not sufficient for classifica-tion". However, as also discussed in the attached Confidential Annex (commenting table on the DAR), this conclusion is not supported. Further toxicological information is considered necessary for a reliable conclusion on classification and labelling. In the Peer Review under Regulation (EC) 1107/2009 Germany has proposed to request at least further studies on in vivo genotoxicity and in vitro studies on endocrine disruption.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Commenting_table_template_New_DAR_format_24-Epibrassinolid_BfR.doc

Dossier Submitter's Response

For this substance, no complete data package according to Regulation (EU) 283/2013 has been submitted. This is considered acceptable as the substance occurs naturally in food of plant origin, and there is continuous lifetime exposure to phytosterols including 24-epibrassinolide via the diet.
It is agreed that information in public literature on 24-epibrassinolide is scarce. In contrast to that, a wealth of literature on phytosterols and –stanols is available. Presentation of data available on various phytosterols and –stanols, cholesterol, and phytoestrogens is considered to be clearly outside the boundaries of this specific assessment.
Due to lack of data indicating any effects, no classification for carcinogenicity, adverse effects on sexual function and fertility, development, or lactation was proposed in in the assessment (see
In Table 2.10.2.2, a selection has to be made from the following entries:

- *data lacking;*
- *data inconclusive;*
- *data conclusive but not sufficient for classification;*
- *hazard class not assessed in this dossier;*
- *harmonised classification proposed;*
- *hazard class not applicable (e.g. if the substance is not in the applicable physical state for the hazard class in question).*

"Data conclusive but not sufficient for classification" was selected for **carcinogenicity** to reflect the fact that although there is continuous lifetime exposure to 24-epibrassinolide via food, no indications for carcinogenicity could be retrieved from literature. This might be inappropriate and changed to "data lacking" if considered to better reflect the situation.
For the hazard classes **germ cell mutagenicity** and **reproductive toxicity**, data is available. Although it is not a compltet data package according to Regulation (EU) 283/2013, the available data does not justify a proposal for classification and labelling. Therefore, for these hazard classes, the selected entries seem appropriate.
Since **endocrine disruption** is not a hazard class according to Regulation (EU) 1272/2008, this topic should be discussed during approval of 24-epibrassinolide according to regulation (EU) 1107/2009.

RAC's response

Thank you very much for your comment. RAC will assess the available information noting the lack of data for certain hazards.

Date	Country	Organisation	Type of Organisation	Comment number
14.03.2019	Germany	Suntton GmbH, Member of Suntton companies	Company-Manufacturer	2

Comment received

(1) CLH Report chapter 1.5.1, page 12 to 14, Application rate per treatment

Applicant's comment:

Please correct the application rate in column 12. A concentration of 1.5 mg a.s. / hL is not given in the GAP. The maximum rate is 0.1% (see below) which is equal to 0.4 L product / 4 hL water. With a concentration of 0.1 g a.s. / L product, the highest concentration of the active substance is 10 mg a.s. / hL. Therefore, please correct the application rates in column 12 and 14 as described in the attachment.

The following attachment is provided with this comment: Comments on CLH dossier-24 Epibrassinolide.pdf

(2) CLH Report, chapter 2.2.2, page 22, persistence of foaming

Applicant's comment:

The maximum concentration according to the GAP is NOT 0.25%. The product is diluted in varying ratios depending on the crop canopy size (1:1000 – 1:3000, see last column in the GAP). The maximum concentration according to the GAP is 0.4 L product / 400 L water (0.1%; corresponding to a maximum active substance concentration of 10 mg / hl water). The persistent foaming test by Gao, J. (2016), Report No: NC-2015-034 (219-001), CP 2.8.2/01 was therefore conducted at the highest intended application rate according to the GAP (0.1%). Thus, the study is acceptable and there is no data gap.

(3) CLH Report, chapter 2.9.3, page 51, Summary of effects on Arthropods (Table 30)

Applicant's comment:

Based on the comment provided in the attachment, the reproduction ER50 for T. pyri is > 3500 g a.s./ha. Thus, the concluding remark that chronic risk can't be fully excluded should be corrected. Acceptable risk to NTA was demonstrated.

The following attachment is provided with this comment: Comments on CLH dossier-24 Epibrassinolide.pdf

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on CLH dossier-24 Epibrassinolide.pdf

Dossier Submitter's Response

(3) Comment regarding NTA (Table 30):
Agree, ER50 was corrected to > 3500 mL product/ha in Table 30.

RAC's response
Thank you very much for your comment. RAC notes that this information is not relevant for setting a proposal of classification.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Germany		MemberState	3
Comment received				
We agree with the proposal of classification for environmental hazards as Aquatic Chronic 4; H413. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Commenting_table_template_New_DAR_format_24-Epibrassinolid_BfR.doc				
Dossier Submitter's Response				
Noted, thank you for the agreement.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	United Kingdom		MemberState	4
Comment received				
24-epibrassinolide (EC: N/A; CAS: 78821-43-9) Environmental classification: The DAR states that 'adverse effects to algae posed by 24-Epibrassinolide are considered unlikely' and that the data waiver to not conduct toxicity to algae / aquatic plants is acceptable. This statement appears to contradict the CLH proposal for Aquatic Chronic 4 which is based on a concern for algal toxicity in the absence of experimental ErC50/NOErC data. We also note the EFSA peer review process for 24-Epibrassinolide is not yet concluded and further information on algal/plant effects may yet be available or forthcoming by the time this CLH Report is considered by the RAC. We consider that the Aquatic Chronic 4 classification may be appropriate for some substances where a specific concern (for example, a particular mode of action) is evident but data on it are lacking and we would welcome further consideration of this by the RAC and guidance on this topic from ECHA. In the case of 24-Epibrassinolide, the concern needs to be clarified before the application of Chronic 4 can be considered.				
Dossier Submitter's Response				
The waiver for algae and macrophytes in Vol. 3 CA B9 B.9.2.6/ B.9.2.7 is accepted in the view of considering a low **risk** under environmental conditions. The proposal for a classification as "aquatic chronic 4" (safety net) is based considering the potential **hazard** under tier 1 standard laboratory studies (due to possible effects on growth under semi-static exposure laboratory conditions). Such potential hazard effects under tier 1 standard laboratory study conditions can't be fully excluded since no studies are presented and the active substance is considered as not readily biodegradable. For a detailed justification of the proposal please refer to Vol. 1 2.9.2.4.2 (please also consider footnote 1 on page 50).				

RAC's response
24-Epibrassinolide is a phytohormone which affects the growth and development of plants and algae. Literature shows that at low concentrations phytohormones promote algae growth (i.e.:Mekhalfi et al 2012; Salama et al 2014, Tate et al 2012; Czerpak et al 2012). However, at higher concentrations phytohormones produce and inhibitory effect of algae growth (i.e.: Talarek-Karwel et al 2018; Czerpak et al 2012; Tate et al 2012) showing that the effect of these hormones is concentration dependant. According to the CLP regulation a 'safety net' classification (referred to as category Chronic 4) can be used when the data available do not allow classification under the formal criteria for acute 1 or chronic 1 to 3 but there are nevertheless some grounds for concern. Since no standard laboratory experiements are available for algae and macrophytes, potential effects due to the mode of action of the substance cannot be excluded, the substance is not rapidly degradable and has low solubility RAC considers the the "safety net" hazard class Aquatic Chronic 4; H413 appropiate for this substance.

PUBLIC ATTACHMENTS
1. Comments on CLH dossier-24 Epibrassinolide.pdf [Please refer to comment No. 2]

CONFIDENTIAL ATTACHMENTS
1. Commenting_table_template_New_DAR_format_24-Epibrassinolid_BfR.doc [Please refer to comment No. 1, 3]