Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

transfluthrin (ISO); 2,3,5,6-tetrafluorobenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate

EC Number: 405-060-5
CAS Number: 118712-89-3

CLH-O-0000006955-61-01/F

Adopted

18 March 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TRANSFLUTHRIN (ISO); 2,3,5,6-TETRAFLUOROBENZYL (1R,3S)-3-(2,2-DICHLOROVINYL)-2,2-DIMETHYLCYCLOPROPANECARBOXYLATE

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: transfluthrin (ISO); 2,3,5,6-tetrafluorobenzyl (1R,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
EC number: 405-060-5
CAS number: 118712-89-3
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	1
Comment received				
Comment will be divided into several attachments ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-677979-01-1 Position Paper Carc classification Redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment M-677979-01-1 Position Paper Carc classification.pdf				
Dossier Submitter's Response				
See our response to comment 4.				
RAC's response				
Thank you for your comment. We will carefully review and consider your arguments in our analysis.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	2
Comment received				
Comments will be divided several submissions due to file size ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cover letter_Redacted				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Zip 2.7z
Dossier Submitter's Response
See our response to comment 4.
RAC's response
Thank you for your comment. We will carefully review and consider your arguments in our analysis.

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	3
Comment received				
Comment were divided into several attachments ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-540892-01-1_preparation_Redacted2.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment M-540892-01-1.zip				
Dossier Submitter's Response				
See our response to comment 4.				
RAC's response				
Thank you for your comment. We will carefully review and consider your arguments in our analysis.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	4
Comment received				
please refer to attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-677979-01-1 Position Paper Carc classification Redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment M-677979-01-1 Position Paper Carc classification.pdf				
Dossier Submitter's Response				
Thank you for your comments and the additional study plan. We would like to provide our response to the main arguments made against classification in the expert statements. Liver tumours in mice - One of the main arguments for non-human relevance is quantitative. It is argued an increase in liver adenomas was only seen in female mice because they received the highest dose, and the activation of CAR/PPARa genes is much lower in humans. However, the results of the in vitro assay show that there is a high level of variation between individuals in the effect of transfluthrin in mRNA transcription, particularly so in humans. This makes it very difficult to say that an effect is not relevant to humans on quantitative grounds. - There also remains the issue of the enzyme levels that decreased in an unexpected way both in mouse and human hepatocytes. That this has also been observed with				

some other pesticides does not make this finding irrelevant. In the human hepatocytes, the activation of BQ activity was the most consistent finding over the three donors of the effects investigated. This effect was also observed in mice, but the implications of this effect are not known.
- As stated in the CLH report, the lack of proliferative response in human hepatocytes is an indication the MOA might not be relevant for humans. However, the lack of response of the mouse hepatocytes on phenobarbital means there was effectively no positive control for either mouse or human hepatocytes. The response on EGF shows the cells were alive and capable of proliferation, but tells us little about their response to non-physiological substances via nuclear receptor activation.

In conclusion, we remain of the opinion that it is not sufficiently proven that the liver adenomas in female mice are not relevant to humans.

Regarding your question whether the new in vitro mechanistic study will be taken into account in the evaluation, this decision lies with ECHA and RAC.

Bladder tumours in rats
It is argued the urinary bladder tumours in rats are not relevant for humans, due to a combination of lower exposure, lack of formation of TFBA, and lower sensitivity of the urothelium. This argumentation is again mostly quantitative, which diminishes its strength in the context of classification and labelling. Moreover, the knowledge on the human metabolism and excretion of transfluthrin is very limited. The liverbead study found only low levels of TFBA formed by mouse and rat liverbeads, while the main metabolite was TFB alcohol in all species. This is a deviation from the in vivo studies, in which mainly TFBA was formed, which means that the relevance of the outcome of the human liverbeads is also highly questionable.

RAC's response

Thank you for your comment. We will carefully review and consider your arguments in our analysis.

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	5

Comment received

please refer to attachments

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cover letter_Redacted
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Zip 2.7z

Dossier Submitter's Response

See our response to comment 4.

RAC's response

Thank you for your comment. We will carefully review and consider your arguments in our analysis.

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	6
Comment received				
As explained in the cover letter in one of my previous submission a 3rd mechanistic study is on going and the study plan M-678078-01-1 is submitted. A 1st draft report is expected on Week 13 and we propose to submit the final report to ECHA in April/May 2020. ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-540892-01-1_preparation_Redacted2.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment M-540892-01-1.zip				
Dossier Submitter's Response				
See our response to comment 4.				
RAC's response				
Thank you for your comment. We will carefully review and consider your arguments in our analysis.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
15.01.2020	Denmark		MemberState	7
Comment received				
Addition of Acute tox 4, H302 is supported.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
15.01.2020	Denmark		MemberState	8
Comment received				
Removal of Skin Irrit. 2, H315 is supported.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	9
Comment received				
please refer to attachments				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cover letter_Redacted ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Zip 2.7z
Dossier Submitter's Response
Thank you for your comments and for sharing the study report of the new acute neurotoxicity study in rats. We agree with your position regarding the results of the new study, which show significant and severe signs of neurotoxicity at 125 mg/kg bw, with some symptoms reaching statistical significance at 100 mg/kg bw. As such, the outcome of this study increases the strength of evidence for classification. However, we do not agree with your argument that Cat 2 would be more appropriate, which is based on the occurrence of mortality and the absence of neurotoxic effects in the developmental neurotoxicity study. The potency of the substance is an important factor in the determination of the category of classification for STOT SE. The effects observed in the studies included in the CLH report as well as in the new study occur below the guidance value for STOT SE 1 of 300 mg/kg bw. The argument that you should not have a double classification for mortality would have been warranted if transfluthrin would be classified as Acute tox Cat 3, of which the boundary values are 50 and 300 mg/kg bw. However, the incidence of mortality after single exposure at doses below 300 mg/kg bw is too low to warrant classification for acute toxicity. For this reason Cat 4 is proposed for Acute oral toxicity. As neurotoxicity is a more sensitive endpoint than mortality, we remain of the opinion that classification as STOT SE 1 is warranted. It should also be noted that STOT SE Cat 2 does in fact overlap with Acute tox Cat 4. Only relatively mild effects were observed in the developmental neurotoxicity study despite a top dose of 534 mg/kg bw/d, which may be related to the use of dietary exposure instead of gavage. Regardless of this, the absence of effects in the neurotoxicity evaluation of the pups is not very surprising, as this evaluation was performed on PND 60, which is 39 days after the end of the exposure period. As neurotoxic effects were observed in multiple other studies, in our opinion this study is not sufficient to decide against classification.
RAC's response
Thank you for your comment. We will carefully review and consider your arguments in our analysis.

Date	Country	Organisation	Type of Organisation	Comment number
15.01.2020	Denmark		MemberState	10
Comment received				
Addition of STOT SE 1, H370 (causes damage to the nervous system) is supported.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2020	France	Bayer	Company-Manufacturer	11
Comment received				
The study report M-540892-01-1 is too large for submission via this website and will submitted via the webform "Submission of documents in relation to the Harmonised Classification and Labelling process" ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-540892-01-1_preparation_Redacted2.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment M-540892-01-1.zip				
Dossier Submitter's Response				
See our response to comment 9.				
RAC's response				
Thank you for your comment. We will carefully review and consider your arguments in our analysis.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
15.01.2020	Denmark		MemberState	12
Comment received				
Addition of STOT RE 2, H373 (kidneys) is supported.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	France		MemberState	13
Comment received				
Could you please detail the justification regarding the adaptive nature of the observed liver effects?				
Dossier Submitter's Response				
Thank you for your comment. The observed liver changes at dose levels below the classification limit for STOT RE 2 consisted mainly of increases in liver weight, liver enzyme induction and centrilobular hypertrophy. These are reversible effects that are induced by many substances as the liver increases its capacity to metabolise the substance. This is as such described in the CLP guidance: "In some cases the adaptive response may also be associated with pathological changes which reflect the normal response of the target tissue to substances: for example, liver hypertrophy in response to enzyme induction".				

It would have been a different matter if more severe histopathological effects would have been noted, such as those mentioned in the CLP regulation: *significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination.* *(e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity.* *(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver).* (g) *evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.* Hepatotoxicity of sufficient severity to fulfil the criteria for classification was observed in mice and dogs, but not at dose levels below the guidance value for STOT RE 2.
RAC's response
Thank you for your comment.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
05.02.2020	France		MemberState	14
Comment received				
We agree with the classification proposal. Please note that in the table 27 of the CLH report (summary of relevant information on chronic aquatic toxicity), the results for the growth inhibition test on algae is NOErC ≥ 57 µg/L instead of NOErC ≥ 557 µg/L.				
Dossier Submitter's Response				
Thank you for your response and support, as well as pointing out the typo.				
RAC's response				
Thank you for your comment. The support of DS proposal for classification of the substance as Aquatic Acute 1, M-factor=1000 and Aquatic Chronic 1, M-factor = 1000 is noted by RAC. RAC agrees. The typo is noted by RAC.				

PUBLIC ATTACHMENTS
1. M-540892-01-1_preparation_Redacted2.zip [Please refer to comment No. 3, 6, 11]
2. M-677979-01-1 Position Paper Carc classification Redacted.pdf [Please refer to comment No. 1, 4]
3. Cover letter_Redacted [Please refer to comment No. 2, 5, 9]

CONFIDENTIAL ATTACHMENTS
1. M-540892-01-1.zip [Please refer to comment No. 3, 6, 11]
2. M-677979-01-1 Position Paper Carc classification.pdf [Please refer to comment No. 1, 4]
3. Zip 2.7z [Please refer to comment No. 2, 5, 9]