Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate;

1R-trans-Z-momfluorothrin

EC Number: Not assigned
CAS Number: 1065124-65-3

CLH-O-0000001412-86-71/F

Adopted

11 September 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1R-TRANS-Z-MOMFLUOROTHRIN

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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

Substance name: 1R-trans-Z-momfluorothrin
CAS number: 1065124-65-3
EC number: -
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2015	Germany		MemberState	1
Comment received				
DE agrees on classification as proposed by UK but additionally classification as Acute Tox 4, H332 and Carc 2 should be considered. Concerning environmental endpoints, we propose some clarifications in the CLH report.				
Dossier Submitter's Response				
Thank you for your comment. However, we do not agree that classification with Acute Tox 4: H332 and Carc 2; H351 is appropriate, full rationale for our proposal is contained in the CLH report. Clarifications regarding the environmental endpoints are provided in our response to comment number 6.				
RAC's response				
See response to comments nr. 4 (carcinogenicity), 5 (acute toxicity) and nr. 6 (environmental endpoints).				

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2015	France		MemberState	2
Comment received				
MS FR agrees for the classification proposal based on the data reported in the CLH report for human health hazards (Acute Tox 4: H302 and STOT-SE 2: H371) MS FR also agrees with classification proposal for Aquatic Acute 1: H400 (M=100) and Aquatic Chronic 1: H410 (M=100).				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.03.2015	United Kingdom	Sumitomo Chemical (UK) Plc	BehalfOfAnOrganisation	3
Comment received				
We agree with the proposed classification: - Acute Tox 4; H302- Harmful if swallowed				

- STOT-SE 2; H371 – May cause damage to the CNS
- Aquatic Acute 1: H400 – Very toxic to aquatic life (M = 100)
- Aquatic Chronic 1: H410 – Very toxic to aquatic life with long lasting effects (M = 100)

Additional comments to the CLH report can be found under 'Public attachment'.

Dossier Submitter's Response

Thank you for your comment on the proposed classification.

With regards to the 'public attachment' we thank you for providing the clarifications. We cannot amend the CLH report but have the following responses.

Comments on sections 1.3, 4.1.1, 4.1.2, 4.1.3, 4.9, 4.10.3 and 4.10.4 should be taken into account, but do not impact on the classification proposal.

5.1.2.3: Water-sediment simulation study
We agree the maximum CO_2 percentage in the [acid ^{14}C] 1R-trans-E-momfluorothrin isomer was 27.4% AR on day 59. This typo does not impact on the classification proposal.

5.4: Aquatic toxicity of degradants
The introductory text in section 5 of the CLH report notes that acute ecotoxicity testing for the degradants MFOA-D, MFOA and *t*-COOH-CA are available. However, the studies were not conducted to GLP and indicate the degradants to be significantly less toxic than the parent. On this basis and because momfluorothrin is considered not rapidly degradable, they were not used further and the CLH report focuses on the parent alone.

5.4.2.2: Long term toxicity to aquatic invertebrates
The CLH proposal is based on the lowest study NOEC of 0.0005 mg/l for dry weight (Fournier, 2012).

The text in section 5.4.2.2 did not consider the parental body length NOEC in detail. It noted that despite the statistically significant differences between the solvent control and treatments 0.0005, 0.0013 and 0.0093 mg/l, a clear dose-response was not observed as the intervening 0.0031 mg/l treatment was not statistically different to the solvent control. Footnote [d] to Table 37 also notes that the parental body length effects observed at the 0.0005 and 0.0013 mg/l treatment levels were determined to not be toxicant-related. Table 38 proposes the NOEC for this parameter to be 0.0031 mg/l (3.1 µg/l). The ensuing text only observed that should the statistical difference be valid for NOEC derivation, a resulting parental body length NOEC would, in any case, fall in the same CLH range of 0.0001 to 0.001 mg/l as the dry weight NOEC and not impact the proposal. On this basis the endpoint was not considered further for CLH.

Section 5.4.4: Other aquatic organisms (including sediment)
The cited Picard (2012) study is not an aquatic exposure study as treatments were prepared by adding the test material (with the aid of a solvent) to silica and the sediment substrate. The endpoints were quoted in mg a.s./kg. On this basis we do not feel it is appropriate to include the study in the CLH report.

RAC's response

RAC agrees with DS response. Thank you for the additional information which, however, doesn't change the classification proposal.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1R-TRANS-Z-MOMFLUOROTHRIN

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2015	Germany		MemberState	4
Comment received				
Pp 42 – 54: DE proposes classification Carc 2 (rather than non-classification) for the following reasons: - Clearly dose-related increases in hepatocellular adenoma and carcinoma in male and female rats - even maximal historical control data are exceeded, at least in male rats) - Observed hepatic-carcinogenic effects in animals must be regarded as relevant for humans as long as MoA cannot sufficiently rule out human relevance. There is some but not sufficient evidence that MoA might be less relevant for humans. The key experiment - stimulation of replicative DNA synthesis in vitro – is not convincing to conclude on human non-relevance (see Fig 9, in Annex I of CLH Report) as stimulation of replicative DNA synthesis was also not clearly demonstrated in rat hepatocytes (inhibitory effect from 100 µM onwards, effect of phenobarbital on increases on replicative DNA synthesis also not convincing). The results observed in vivo are not supported by the results observed in this in vitro experiment.				
Dossier Submitter's Response				
Thank you for your comments. We do not consider that classification for carcinogenicity is required based on all available data. Full rationale regarding our proposal has been provided in the CLH report.				
RAC's response				
Momfluorothrin is clearly carcinogenic in rats, for which CAR activation seems to be the most plausible mechanism. As to the relevance to humans of this MoA, the *in vitro* study with human hepatocytes has shown that despite CAR activation, and in contrast to rat hepatocytes, there was no cell proliferation upon momfluorothrin treatment. Results for PB were similar. It is true that *in vitro* the level of stimulation of cell proliferation was not that high for PB, but this seems to be consistent with the moderate increase in cell proliferation found for PB in rats *in vivo*. The reason for the inhibitory effect on cell proliferation at higher concentrations of momfluorothrin is not clear, but could for example be due to over-stimulation of the cells. It is also noted that no such inhibitory effect with increasing momfluorothrin doses was observed in rats *in vivo*. Based on all evidence presented, including the fact that for momfluorothrin the prerequisite for tumour formation, i.e. DNA replication, does not seem to occur in human hepatocytes following induction of human CAR, in contrast to rats, RAC is of the opinion that there is a qualitative difference between rats and humans. Due to this qualitative difference, the liver tumours as a result of CAR-activation by momfluorothrin are considered to be of little relevance to humans. Hence, RAC concludes that no classification is warranted for carcinogenicity.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2015	Germany		MemberState	5
Comment received				
Pp 20-21: Classification as Acute Tox 4; H332 should be considered additionally, because max. concentration achieved was 2 mg/L and 1 female animal died. Category 4 for dust/mist according to CLP is between >1 and ≤ 5 mg/L.				
Dossier Submitter's Response				
Thank you for your comment but we do not consider it appropriate to classify based on available data. Whilst there was 1 death in the study, classification is not considered				

appropriate because it was not possible to reach a higher concentration and the LD50 is consequently > 2mg/l. Full rationale for our proposal is contained in the CLH report.
RAC's response
RAC agrees with the DS that the available study does not allow classification, given that the LC_{50} value in both male and female rats is > 2.03 mg/L and higher concentrations could not be tested.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2015	Germany		MemberState	6
Comment received				
We agree to the environmental classification and labeling proposal. Additional comments: Section 5.1, Table 28, p.61: Please recalculate the hydrolysis half-lives by application of the recommended EU outdoor temperature of 285 K (TGD Part II on Risk Assessment Part II, Chapter 2.3.6.1). Please indicate the metabolites identified during the hydrolysis study and the aqueous photolysis of the parent as well as their quantified maximum percentages. Section 5.1, Table 28, p.61: Regarding results from the water/sediment study, please delete mineralisation data here as these are presented in more detail in table 32, p. 68. Please add temperature to DT 50 values quoted. Section 5.1.2, p. 63ff: Please add temperature to all DT 50 values cited in this chapter. Section 5.1.2, Table 30, p. 65: we propose to include the maximum %- recovery rates for major degradates. Section 5.1.3, p. 69: when quoting DT 50 values, please state corresponding temperature. We encourage to include an overview of DT50-values (or range) at 12°C for the degradates identified (cf. draft CAR (2013), Doc IIA, table 4.8) Section 5: Please provide a chapter on fate and behavior in atmosphere including results on indirect phototransformation in air.				
Dossier Submitter's Response				
Thank you for the comments. <u>Hydrolysis:</u> Converted hydrolysis half lives at pH 9 and 12 °C are presented in section 5.1.3 (DT_{50} 18.3 to 20.3 days). As hydrolysis is pH dependant (increasing hydrolysis with increasing pH), these values are considered to represent the most rapid hydrolysis at a higher environmentally relevant pH range. The CLH Report notes hydrolysis degradation products were 'Z-CMCA' and 'MFOA'. It also noted that Z-CMCA was the principal degradant in the acid label isomer with MFOA the principal degradant in the alcohol label isomer. For information only, the maximum % AR for both the acid and alcohol label are presented below across the experimental temperatures. The remaining AR comprised the parent momfluorothrin and combined unidentified components <2% AR. Such detail was not presented in the CLH report as momfluorothrin is considered not rapidly degradable (including hydrolysis) for the purpose of classification – therefore the maximum degradant percentages were not relevant. In addition, the parent is considered to be more toxic than degradation products and so this classification focuses on the parent substance alone.				

Maximum amount of transformation products

Label and Transformation product		Max. amount [% AR] of degradation product measured at individual pHs		
		pH 4	pH 7	pH 9
(alc-RTZ)	MFOA	-	d30, 40°C: 26.4 d30, 50°C: 58.6 d21, 60°C: 88.0	d21, 25°C: 87.6 d5, 40°C: 92.2 d2, 50°C: 96.2
(acid-RTZ)	Z-CMCA	-	d33, 40°C: 30.4 d33, 50°C: 66.1 d21, 60°C: 87.5	d21, 25°C: 86.0 d5, 40°C: 94.1 d2, 50°C: 94.0

Photolysis:
The CLH Report notes photolysis degradation products were 'CMCA' and 'MFOA'. It also noted that CMCA was the principal degradant in the acid label isomer with MFOA the principal degradant in the alcohol label isomer.

For the acid RTZ label, CMCA comprised 38.8% AR in light samples at d13 termination. The remaining AR related to the parent momfluorothrin and other degradants at <3.6%AR.

For the acid RTE label, CMCA comprised 30.9% AR in light samples at d13 termination. The remaining AR related to the parent momfluorothrin and other degradants at <3.4%AR.

For the alcohol RTZ label, MFOA comprised 26.6% AR in light samples at d13 termination. The remaining AR related to the parent momfluorothrin and other degradants at <3.9%AR.

Such detail was not presented in the CLH report as momfluorothrin is considered not rapidly degradable (including aquatic photolysis) for the purpose of classification – therefore the maximum degradant percentages were not relevant. In addition, the parent is considered to be more toxic than degradation products and so this classification focuses on the parent substance alone.

Water-sediment study:
The CLH report template includes a summary of relevant degradation information (i.e. Table 28). We feel that mineralisation data from the study is a key endpoint and therefore included it in the summary table. CLH Report edits are not part of the Response to Comments procedure and therefore we are unable to update the table.

Section 5.1.2.3 of the CLH Report states the study was run at 20 ±2 °C. The temperature range applies to the DT_{50} values included in Table 28.

We are unable to update the CLH Report at this stage so cannot add the temperature values adjacent to DT_{50} values. However, study temperature values are presented in the relevant sections.

The CLH report did not include DT_{50} values at 12 °C as at the higher study temperature of 20 °C, the substance did not meet the half-life criteria for rapidly degradable meaning DT_{50} values at 12 °C were unnecessary and would not alter the classification. We have not included DT_{50} values for degradants as the parent is not considered rapidly degradable and therefore the data are not required for classification.

Table 30 of the CLH Report presents identified degradants. While it does not include maximum % recovery rates for major degradants, this information is included in Table 31.

Fate and behaviour in atmosphere: Section 5.2.2 includes information indicating momfluorothrin is unlikely to partition to the atmosphere. Other than consideration of substances hazardous to the ozone layer, environmental classification does not include consideration of the air compartment. Therefore, we have not presented additional information.
RAC's response
RAC agrees with the DS response. Thank you for the comments which, however, don't change the classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
27.03.2015	Belgium		MemberState	7
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species (acute aquatic toxicity : Fish (Oncorhynchus mykiss) with 96hLC50=0.0012mg/l (mm), chronic aquatic toxicity : Invertebrates (Daphnia magna with 21dNOEC= 0.0005 mg/l), the fact that the substance is not rapidly degradable it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic Acute 1, H400 and Aquatic chronic 1, H410. In view of the proposed classification and toxicity band for acute toxicity between 0.001mg/l and 0.01 mg/l, an M-factor for acute toxicity of 100 could be assigned and an M-factor for chronic toxicity of 100 (not rapidly degradable substance and NOEC between 0.0001mg/l and 0.001mg/l) In conclusion : we agree with the proposed environmental classification by the UK CA. Some editorial or/and minor comments : Typo on p70 : 5.2.2 Volatilisation Vapour pressure should read : between 2.478 x 10-7 Pa and 4.702 x10-7 Pa at 20°C				
Dossier Submitter's Response				
We note BE's agreement with the proposed environmental classification. We also note the typographical error and agree the vapour pressure should be quoted as between 2.478 x 10^{-7} Pa and 4.702 x10^{-7} Pa at 20 °C.				
RAC's response				
Noted.				

ATTACHMENTS RECEIVED:

1. **Comments from Sumitomo Chemical (UK) Plc – Substance supplier of 1R-trans-Z-momfluorothrin –** please refer to comment 3