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-methylbenzyl (1*RS*,3*RS*)-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate; Tefluthrin (ISO)

EC number: -
CAS number: 79538-32-2

CLH-O-0000001412-86-61/F

Adopted

05 June 2015

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 attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). 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.

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Substance name: Tefluthrin (ISO); 2,3,5,6-tetrafluoro-4-methylbenzyl (1*RS*,3*RS*)-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate

CAS number: 79538-32-2

EC number: -

Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2014	Netherlands		MemberState	1
Comment received				
NL CA comments for Environmental Hazard only. Agreed with a minor comment. P126. Refers to the long term aquatic toxicity US EPA guideline and that it is similar to the OECD 202. This should probably be the OECD 211 as the 202 is a short term test				
Dossier Submitter's Response				
Thank you for your comments and agreement with environmental classification and labelling. For clarification: the OECD guideline 211 for long term aquatic toxicity for invertebrates (daphnia magna reproduction test) was adopted september 1998, the former OECD guideline 202/part II for reproduction test of Daphnia sp. was adopted since april 1984.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2014	France		MemberState	2
Comment received				
Page58: as regards health hazards, FR agrees with the classification proposal: Acute Tox 2; H310 Acute Tox 1; H330 Acute Tox 2; H300 STOT RE 1; H372 (nervous system) FR agrees with the classification proposal for environmental hazards and FR agrees with the				

acute and chronic M factors.
Dossier Submitter's Response
Thanks to France
RAC's response
Noted, thank you for the comment

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2014	United Kingdom	Syngenta	BehalfOfAnOrganisation	3
Comment received				
We disagree with the proposal for STOT-RE, as we believe that the effects on which this is proposed to be based are more appropriately covered by an acute toxicity classification.				
Dossier Submitter's Response				
Thank you for the comment. Please refer to comment 9.				
RAC's response				
Thank you for the comment. Please refer to comment 11.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2014	France		MemberState	4
Comment received				
Page 60-FR: It is concluded that: "There was a positive trend of neoplastic findings in liver, lung, harderian gland and pituitary gland. However, these findings are not considered to be an evidence of carcinogenic activity of tefluthrin since the observed incidences were mainly within historical control data." However, at the top dose the incidence of liver adenoma in females and the incidence of lung adenocarcinoma in males were outside the HCD range. Could you further argue on the non carcinogenic potential of tefluthrin in this study?				
Dossier Submitter's Response				
In female mice the incidence of liver adenoma was increased, but without a potential to progress to malignant tumours, because liver carcinoma were definitely not increased. The increased incidence of lung adenocarcinoma in male mice was not significant: the incidences in both control groups were 0/50 and 2/50 [2/100]; at 25 ppm 0/50, at 100 ppm 1/49 and at 400 ppm 3/100. Furthermore, no influence on the incidence of lung adenoma was observed. Based on these facts no carcinogenic potential of tefluthrin was considered in mice.				
RAC's response				
Thank you for the comment. RAC supports the explanation by the DS.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2014	Belgium		MemberState	5
Comment received				
Acute tox by oral route: the both studies in rats and in mice show clear clinical toxicity and mortality occurs both in males and females within the 14 days observation period. The estimaded LD50 value is within the range of Cat.2 and therefore the classification proposal				

for acute tox by oral route is supported. Acute tox by dermal route: the lowest LD50 value in the rat study is within the cat.2, we therefore support the DS'proposal. Acute tox by inhalation route: the lowest four-hour median lethal concentration of tefluthrin fulfils the criteria for cat.1 and again the classification proposal is supported.
Dossier Submitter's Response
Thanks to Belgium
RAC's response
Noted, thank you for the comment

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2014	France		MemberState	6
Comment received				
Page 23-24-FR: In table 18 and table 19 could you please report the tested doses in ascending order, for a better readability.				
Dossier Submitter's Response				
Thank you for the comment. However, these tables were excerpted from the original study report.				
RAC's response				
Thank you for the comment.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2014	Belgium		MemberState	7
Comment received				
Eye irritation: We question the validity of the test presented in the dossier. According to the guidance, the evaluation criteria on the eye are severity of the damage and reversibility within the observation time of 21 days . the Southwood study doesn't seem to be relevant for the assessement of eye irritation. Besides no information are provided related to the assessment of the animal up to 4 days and 17 days.				
Dossier Submitter's Response				
In this study from 1987 ocular reaction was planned to examine up to 17 days after instillation. Four out of the six animals showing paraesthesia were distressed and killed for human reasons. According to the study report all signs of irritation observed in these two surviving animals disappeared after three days (one male) and after nine days (one male). The final irritation assessment was therefore based on the limited data on animals killed on day 1 and two surviving animals.				
RAC's response				
Thank you for the comment. RAC supports the comment from the DS. Please see the ODD for further details.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2014	Belgium		MemberState	8

Comment received
STOT SE: STOT SE is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture. As the same effects (neurotoxicity) are already covered by the classification Acute Tox (via three routes), we support the DS' proposal not to propose classification with STOT SE.
Dossier Submitter's Response
Thanks to Belgium
RAC's response
Noted, thank you for the comment

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2014	Belgium		MemberState	9
Comment received				
STOT RE: the evidences presented in the dossier are considered weak to support the classification STOT RE1 (neurotox). In the 90-d study in dogs, whole body tremor is only seen in one female at day 4 at 1.5 mg /kg bw/day and was full recovery within one hour and was not observed again in this animal. No histological effects are reported and no other effects were observed (clinical, ophthalmological findings or haematological parameters). In the 1-year dogs study, ataxia and tremors were seen in 9/12 dogs in the first week but no histological findings were reported. We recognize that the dogs are more sensitive than the rats. However there is no dose-related effects and the neurotoxic effects are only observed at the beginning of the study. We question the evidences proposed by the DS in order to support STOT RE1 and we considered them as no sufficient for the classification.				
Dossier Submitter's Response				
Thank you for the comment. However, discussion of repeated dose toxicity findings relevant for classification as STOT RE has already been provided under section 4.7.2 of the CLH report. Furthermore consideration for classification due to neurotoxic effects after repeated administration was also recommended by the PRAPeR expert meeting.				
RAC's response				
Thank you for the comment. Please refer to comment 11.				

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2014	Spain		MemberState	10
Comment received				
STOT RE 1 (p. 35-46) The Spanish CA agrees with the German proposal of classification for tefluthrin as STOT-RE 1; H372 (nervous system) taking into account the overt signs of neurotoxicity after oral repeated exposure in dogs (tremor, ataxia) at 1.5 mg/kg bw/day in the 90-day study and at 2.0 mg/kg bw/day in the first weeks of a one-year study. The Spanish CA regards that this proposal is also supported by the neurotoxic effects observed in both developmental toxicity studies. In the developmental study in rat (Killick, 1986) at 7.5 mg/kg bw/day there were mortality in 7 animals and clinical signs associated with maternal toxicity such as abnormal gait, uncoordinated limb movements, involuntary spasms, hypersensitivity to noise, piloerection and subdued behaviour. In the developmental study in rabbit (Killick, 1985) at the dose of 12 mg/kg bw/day body tremors were observed in 6 animals. The Spanish CA				

also notes the effects seen in the early part of the pre-mating period in the 3-generation study in rats (Wickramaratne, 1987) at 250 ppm (splayed gait, abnormal or high stepping gait and shaking; Table 59 of the proposal). Furthermore, the Spanish CA also regards dermal exposure as a relevant route of exposition for STOT-RE 1 along with oral exposure. This is supported by the results obtained in the 21-day repeated dermal study in rats. According to the proposal, clinical observations in this study included a dose-related incidence of upward or downward curvature of the spine, tip-toe gait, splayed gait and bizarre behaviour at 50 mg/kg bw/day. Some of these effects were also observed at 1 and 0.1 mg/kg bw/day (Table 38 of the proposal). In the proposal these signs were considered to be indicative of paresthesia rather than systemic toxicity. During the Peer Review of the EFSA this issue was discussed [PRAPeR Expert Meeting 76 (31 May -04 June 2010)]. The EFSA finally decided not to regard these effects for systemic toxicity and established a NOAEL in this study of 50 mg/kg bw/day and a LOAEL for local effects (based on signs indicative of paresthesia and skin irritation) of 0.1 mg/kg bw/day (EFSA Journal 2010;8(12):1709). However, the Spanish CA has some remarks. -Paresthesia is a temporary burning, stinging, itching and tingling of the skin and it is a well known effect that happens after dermal exposure in pyrethroids. In our opinion there is not clear and univocal evidence that clinical signs observed in the 21-day repeated dermal dose toxicity study (upward curvature of spine, splayed gait, tip toe gait, bizarre behaviour) at 50 mg/mg kg/bw and also in a less extent at lower doses are related to paresthesia. -In the acute dermal toxicity study (LD50 of 177 mg/kg bw) some of these effects such as splayed gait or upward and/or downward curvature of the spine were observed at doses 50 and 100 mg/kg bw. In this case they were regarded as a sign of motor incoordination. In the discussion of STOT (p.25) it is stated that "after single dermal exposure to tefluthrin clinical signs of neuromuscular incoordination were observed in some animals at 100 mg/kg bw (males) and 50 mg/kg bw (females), dose levels below the calculated LD50 value of 177 mg/kg bw/ (e.g. upward curvature of spine, splayed gait, tip toe gait)". -The cut-off value for STOT-RE 1 after dermal exposure (21 days) is extrapolated to 85.7 mg/kg bw/day according to Haber´s rule. Besides the LD50 after single dermal exposure is 177 mg/kg in rats. Therefore, taking into account that these effects occurred below the cut-off value for STOT-RE 1 and considering that there is a reasonable doubt whether these effects are indicative of paresthesia (local effect) or neurobehavioural effects associated to neurotoxicity (systemic toxicity), the Spanish CA considers dermal exposure as a relevant route for STOT-RE 1. Tefluthrin should be classified as: STOT RE 1 (H372): Causes damage to nervous system through prolonged or repeated oral and dermal exposure. Considerations of STOT-RE after inhalation exposure (p. 42) In chapter 4.7.1.2., the Spanish CA also regards that it is not necessary to perform short term inhalation toxicity studies but it is not in agreement with the given reasons focused on the Plant Protection Products Regulation. The objective of this CLH proposal is to set the classification of the active substance tefluthrin (which is a solid), not the classification of a product containing this substance. In our opinion there is no need of a repeated dose inhalation study taking into account the high inhalation toxicity of tefluthrin after single exposure with a classification H330 – Category 1 (limits for classification (dust or mist): (0-0.05] mg/l). Any possible effect is covered with this severe classification.
Dossier Submitter's Response
Thanks to Spain for the detailed comment. As already mentioned by Spain this was discussed in detail at the PRAPeR expert meeting with a different conclusion. In the end, RAC has to decide.
RAC's response
Thank you for the comment.

RAC agrees with the conclusion from the PRAPeR Expert Meeting, that it is unlikely that observed effects (curvature of the spine, curvature of the spine) in the 21-days dermal study in rats is due to a neurotoxic effect (systemic effects). It is more likely that the effects were secondary to pareshesia (local effect). When taking the low dermal absorption value into account along with an oral rat NOAEL (11.6 mg/kg bw/day; 90-days Pinto, 2002) that is much lower than the expected systemic dose in the 21-day dermal study, it is unlikely that the observed effects were due to systemic exposure.

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2014	United Kingdom	Syngenta	BehalfOfAnOrganisation	11

Comment received

A STOT-RE classification is not required for tefluthrin, as the signs of neurotoxicity seen very soon after dosing are indicative of interference with voltage gated sodium channels, an effect which is completely reversible, does not get worse on repeated exposure, and which is thus more appropriately covered by the proposed acute classifications. Tefluthrin does not cause any toxicological effects which could be considered "severe" or "significant" according to the CLP guidance.

ECHA comment: The comment below was provided in an attached document " Comments on the EChA Annex VI Report (Proposal for Harmonised Classification & Labelling) submitted by Germany July 2014".

Germany are proposing a Category 1 STOT-RE classification, H372, based on *"the overt signs of neurotoxicity in dogs (tremor, ataxia) at 1.5 and 2.0 mg/kg bw/d"* in the 90 day & 1 year dog studies.

Syngenta do not believe a Category 1 STOT-RE classification is warranted, for the following reason:

The main toxicological endpoint of tefluthrin in all species is clinical signs of neurotoxicity. This is not unexpected, given the insecticidal mode of action of pyrethroids in interfering with voltage gated sodium channels. The effect is generally seen within a few hours of dosing, and recovers rapidly; thus when seen in repeat dose studies, this response is effectively a regular acute toxicity. It does not get worse on repeat daily dosing, in fact the opposite is seen. This effect is transient and reversible, and a manifestation of acute toxicity, for which classifications of H300, H310 and H330 (Fatal via oral, dermal or inhalation routes), are being proposed.

This position is supported by the following statement from the CLP guidance:
"According to CLP Annex I, 3.9.1.1, specific toxic effects covered by other hazard classes are not included in STOT-RE. STOT-RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class."

The guidance also states that *"STOT-RE is assigned on the basis of findings of "significant" or "severe" toxicity. In this context "significant" means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. "Severe" effects are generally more profound or serious than "significant" effects and are of a considerably adverse nature which significantly impact on health. Both factors have to be evaluated by weight of evidence and expert judgement."*

The effects in the repeat dose tefluthrin studies are assessed against these criteria:

- In the 90 day rat study, there was a reduction in bodyweight gain at 31.8mg/kg/day. There were no effects indicative of significant or severe toxicity.
- In the 90 day dog study, a single transient episode of tremors was seen in a single dog on day 4 of the study, following 4 daily doses of 1.5mg/kg/day. This observation was not repeated, and in particular did not get worse on repeated dosing. This single episode is considered to be an acute effect more appropriately covered by the relevant acute toxicity classifications. A single transient episode of tremors is also not considered to represent "significant" or "severe" toxicity within the context of STOT-RE classification.

- In the 1 year dog study, one animal died at 2mg/kg/day, however this was considered unlikely to be treatment related, as there were no signs of toxicity preceding this isolated death.
- In the 1 year dog study, transient tremors and ataxia were seen at 2mg/kg/day, generally during the first few weeks of the study; again, these are considered a reflection of acute toxicity. Given the transient and reversible nature of this effect, it is not considered to represent "significant" or "severe" toxicity.
- None of the studies show any consistent histopathological effects.

Conclusion

A STOT-RE classification is not required for tefluthrin, as the signs of neurotoxicity seen very soon after dosing are indicative of interference with voltage gated sodium channels, an effect which is completely reversible, does not get worse on repeated exposure, and which is thus more appropriately covered by the proposed acute classifications. Tefluthrin does not cause any toxicological effects which could be considered "severe" or "significant" according to the CLP guidance.

Dossier Submitter's Response

Thank you for the comment. Please refer to comment 9.

RAC's response

Thank you for the comment.
Neurotoxicological findings are seen soon after dosing at doses signicantly below the calculated LD50 values. The findings are in more cases seen not only in the beginning of the testing period but also in the middle and end of the testing period (Stonard, 1-year study in dogs 1986; Stonard et al, 2-year toxicity/oncogenicity study in rats 1986; Pinto, 13-week neurotoxicity study in rats 2002). This together with the observation that "*There was an increase in the incidence and severity as the study progressed for the ataxia, increased activity, upward curvature of the spine and reduced splay reflex*" (Pinto, 2002) indicates that the low dosage neurotoxicological findings are repeated exposure effects.
A LOAEL of 26.6 mg/kg bw/day in the 13 weeks oral neurotox rat study (Pinto, 2002) would lead to a STOT RE 2 classification. However, dogs were more sensitive to Tefluthrin than rats, leading to a STOT RE 1 classification.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2014	Belgium		MemberState	12

Comment received

Results on acute aquatic toxicity show that fish (Oncorhynchus mykiss) and invertebrates (Mysidopsis bahia) are the most sensitive species when exposed to Tefluthrin with an LC50 in the same order of magnitude, resp. 0.00006 mg/l and 0.000053 mg/l. Based on these results it is justified to classify the substance as Aquatic Acute 1, H400 and to attribute a M-factor of 10 000 (0.00001mg/l<LC50≤0.0001mg/l).

In chronic studies the lowest NOECs are obtained for fish (Pimehales promelas) and invertebrates (Daphnia magna). Both NOECS are in the same order of magnitude resp. 0.00000397 and 0.00000792mg/l. Based on the result of the chronic toxicity test on the most sensitive species, the fact that the substance is not rapidly degradable it is justified to classify, following the classification criteria of regulation 1272/2008, as Aquatic chronic 1, H410 . In view of the proposed classification and toxicity band for chronic toxicity between 0.000001 mg/l and 0.00001mg/l, an M-factor for chronic toxicity of 10 000 should be assigned.

In conclusion : we agree with the proposed environmental classification by BAuA.

ANNEX 2 - COMMENTS AND response to comments on CLH proposal on Tefluthrin (ISO)

Some editorial or/and minor comments : Please provide in the CLH report also a short summary on the environmental distribution (adsorption/desorption, volatilisation) of the substance.
Dossier Submitter's Response
Thank you for your comments and agreement with environmental classification and labelling.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
25.09.2014	France		MemberState	13
Comment received				
FR agrees with the classification proposal and with the acute and chronic M factors.				
Dossier Submitter's Response				
Thank you for your agreement with environmental classification and labelling.				
RAC's response				
Noted.				

ATTACHMENTS:

1. **Comments on the EChA Annex VI Report (Proposal for Harmonised Classification & Labelling) submitted by Germany July 2014** – submitted by Syngenta on 25 September 2014 [Please refer to comment 11].