Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Triflusulfuron-methyl; methyl 2-({[4-(dimethylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl]carbamoyl}sulfamoyl)-3-methylbenzoate

EC number: N/A
CAS number: 126535-15-7

CLH-O-0000001709-67-02/A2

Adopted

5 December 2013

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPSAL ON TRIFLUSULFURON-METHYL; METHYL 2-({[4-(DIMETHYLAMINO)-6-(2,2,2-TRI FLUOROETHOXY)-1,3,5-TRIAZIN-2-YL]CARBAMOYL} SULFAMOYL)-3-METHYLBENZOATE

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.

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Substance name: triflusulfuron-methyl; methyl 2-({[4-(dimethylamino)-6-(2,2,2-tri fluoroethoxy)-1,3,5-triazin-2-yl]carbamoyl} sulfamoyl)-3-methylbenzoate
EC number: -
CAS number: 126535-15-7
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2013	Netherlands		MemberState	1
Comment received				
On page 14 it is stated that: "Note: DAR refers to triflusulfuron. However, all of the data evaluated refer to triflusulfuron-methyl. Therefore CLH Report & dossier is presented for triflusulfuron-methyl. No data allows to draw a conclusion on triflusulfuron." As triflusulfuron-methyl is a variant of triflusulfuron, different variants might have different toxicological profiles (as also pointed at by EFSA in their peer review of triflusulfuron). We therefore agree that the classification proposal should be on triflusulfuron-methyl and not on triflusulfuron.				
Dossier Submitter's Response				
noted				
RAC's response				
RAC agrees that the classification proposal should be on triflusulfuron-methyl and not on triflusulfuron.				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2013	Germany		MemberState	2
Comment received				
The German CA supports the proposed classification as Carc. Cat. 3; R40 and Category 2–H351 of triflusulfuron-methyl according to 67/548/EEC or CLP regulation criteria, as well as the classification and labeling as N; R50/53 (DSD) and H400, H410 (CLP regulation). We support the M-factors and concentration limits, too.				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2013	Netherlands		MemberState	3
Comment received				
Based on the provided data, we agree that the observed neoplastic effects in liver are not considered relevant for human health risk. The effects were observed in a single species (i.e. mouse) and a single sex (males). The hepatic tumors were benign in nature and no effects on hepatic cell proliferation was observed. Furthermore, in comparison with historical controls the incidences of hepatic adenomas were not statistically significant increased. Based on the provided data, we agree that a potential relevance of the observed neoplastic effects on testes to human health cannot be excluded. We also agree that the mechanism responsible for the carcinogenic effects in testis is non-genotoxic. The available data suggest that the mechanism inducing Leydig cell tumours is aromatase inhibition. There is not sufficient evidence that this mechanism of action is not relevant in humans. The effects were however observed in a single species (i.e. rat). We therefore agree with the proposed classification of Carc. 2/H351 (CLP) and Carc. cat. 3/R40 (DSD).				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2013	Germany		MemberState	4
Comment received				
The argumentation of the dossier submitter can be followed to propose classification Carc. Cat. 3; R40 and Category 2– H351 according to 67/548/EEC or CLP regulation criteria, respectively, based on the increased incidence of Leydig cell hyperplasia and adenomas in a single study in rat.				
Dossier Submitter's Response				
noted				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2013	Denmark	DEPA	National Authority	5
(*ECHA note: The comment below was submitted as a separate attachment)* Proposed classification: R40: (Carc. Cat 3): Limited evidence of a carcinogenic effect H351/ (Carc.2): Limited evidence of carcinogenicity effects				

Based on the increased incidence of Leydig cell hyperplasia and adenomas at high doses in one specie which was considered as relevant to humans, a classification with Carc.Cat.3/ R40 and Carc.2/H351 (CLP) is proposed. **DK supports the proposed classification.** *--- End of attachment ---*
Dossier Submitter's Response
noted
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2013	United States	E.I. du Pont de Nemours and Company	Company-Manufacturer	6
Industry disagrees with the proposal to classify Triflusulfuron methyl as a Cat 2 Carcinogen (H351: Suspected of causing cancer) on the basis of the following points: Based on the biological and functional differences between rat and human Leydig cells and the absence of a plausible causal association for Leydig cell tumor induction in humans from epidemiological studies, the overall weight of evidence strongly indicates that rat Leydig cell tumors are most probably not predictive of a cancer hazard to man and have negligible relevance for human safety assessment. The toxicological database for triflusulfuron methyl, the considerable amount of published data on rat Leydig cell tumor formation, as well as the comprehensive epidemiological and clinical database indicate that: • The mode of action for experimental Leydig cell tumor formation has been identified in studies conducted with triflusulfuron methyl both in vivo and in vitro. Triflusulfuron methyl is a weak aromatase inhibitor. • The relevance for humans in terms of hazard assessment is negligible • The only tumor response across the entire toxicological database occurred in aged male rats which are known to be especially susceptible to this tumor type. • A clear threshold has been established for the formation of Leydig cell adenomas and associated hyperplasia due to triflusulfuron methyl treatment. (*ECHA note: The attachment "Comments on Proposed Classification of Triflusulfuron Methyl (126535-15-7)" is being provided as a separate document to this table)*				
Dossier Submitter's Response				
The Company has submitted a "position paper" on the relevance to humans, arguing that rats Leydig cells have higher number of receptors; with different responsiveness compared to human Cells, based on literature data (no new study was submitted). The weight of evidence is that Rats Leydig cells could be more sensitive to stimulation, involving a supplementary hyperplasia at high dose level. But these effects are secondary to the aromatase inhibition, even if rats are a little more sensitive to up and down regulation, there is not sufficient evidence that this mechanism of action is not relevant in humans. Moreover, as already discussed in the CLH report in *4.10.5 Comparison with criteria*				

"according to a specialized expert working group (see the Draft summary record of the meeting of Ispra, January 22_23 2004, ECBI/08/04 Rev 2, April 2004), substances causing Leydig cell tumours in rats by perturbating the HPT axis should be classified in Carcinogen Category 3, unless the mechanism can be proven not to be relevant for human Leydig cell carcinogenesis. Among the currently identified non-genotoxic mechanisms of rodent Leydig cell tumorigenesis (see review in Cook et al., *Critical Reviews in Toxicology*, 1999, 29(2), 169-261), only dopamine and GnRH agonist mediated-effects are not considered relevant for humans." Therefore, as the mechanism of action of Triflusulfuron-methyl on Leydig cells was likely mediated by aromatase inhibition, the compound should be classified as a Cat 2 H351 classification.
RAC's response
RAC agrees with the DS

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2013	Netherlands		MemberState	7
Comment received				
Fertility effects: In the rat 2-generation study, no substance-related effects on reproductive organs and parameters of reproduction were observed. In one of the available 90-day rat studies (Biegel, 1993), effects such as testicular atrophy/degeneration and oligospermia, and decreases in testicular weights (absolute) were observed. These effects were however seen only at the highest dose level tested (15000 ppm, 965 mg/kg bw/day), which is above the cut-off level for classification for STOT-RE. Effects such as decreased body weight (gain), decreased food consumption and food efficiency were also observed at this dose level and below (2000 and 10000 ppm corresponding to 127 and 646 mg/kg bw/day). In a previous 14-day rat study (no full data shown), no effects on testes were observed (dose level of 1500 mg/kg bw/day). In addition, a second rat 90-day study did not reveal fertility effects. The observed effects on testis in the rat 90-day study of Biegel (1993) are therefore considered not relevant for classification. In a 90-day mouse study, no effects relevant for classification for fertility effects were observed. In a 90-day dog study (Atkinson, 1991), small epididymis was observed in the high dose group (8000 ppm corresponding to 268 mg/kg bw/day) with effects such as aspermatogenesis (4000 and 8000 ppm, corresponding to 146 and 268 mg/kg bw/day). Furthermore, effects such as reduced testis weight and small testis were observed at 146 and 268 mg/kg bw/day with vacuolization of germinal epithelium and decreased thickness of the seminiferous tubules. In addition, in the 1-year dog study (Auletta, 1993), no effects on testis were observed at dose levels up to 3500 ppm (111.8 mg/kg bw/day). It can be concluded that testes effects are only observed at very high doses, that are not relevant for classification. Furthermore, C&L Guidance paragraph 3.7.2.3.1 states, "Toxicological effects, including marked effects, observed in a standard repeat dose study could be considered valid for the pre-mating phase for adult females and the pre- and postmating phase for adult males. However in case of contradictions between the standard repeat dose studies and reproductive studies, the result from the latter should be considered more relevant." We agree that, based on the data available, classification for fertility effects is not necessary.				

Dossier Submitter's Response
noted
RAC's response
Noted

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2013	Germany		MemberState	8
Comment received				
No classification is proposed				
Dossier Submitter's Response				
Germany agrees with Dossier submitter concerning the absence of genotoxic classification.				
RAC's response				
Agreed.				

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2013	Netherlands		MemberState	9
Comment received				
In the rat 2-generation study, no developmental effects were observed. In the rat developmental study, statistically significant increases in the number of foetuses with variations were observed at 350 and 1000 mg/kg bw/day compared to the concurrent controls. Furthermore, the number of fetoeses with malformations was statistically significant increased at a dose-level of 1000 mg/kg bw/day. These foetal effects were observed at dose levels at which also reduced maternal body weight (gain) and reduced maternal food intake (during early phase of dosing) were observed. Furthermore, the observed foetal effects were observed within historical control incidences. They are therefore not considered relevant for classification. In the rabbit developmental study high incidences of abortions of 50% and 60% (8/16 dams and 12/20 dams) were observed at the dose levels of 270 and 800 mg/kg bw/day respectively. At these dose levels also maternal toxicity was observed. The observed abortions at 800 mg/kg bw/day are not considered relevant for classification, given the excessive mortality rate in the dams (9/20; 45%). This is also considered to be the case for the dose levels of 270 mg/kg bw/day. At this dose levels also clear maternal toxicity can be observed. Mortality at this dose level is however much lower (mortality in 2/20 dams, 10%) than in the high-dose group, which might therefore be considered a borderline case. No significant test substance-related effects on fetuses were observed, though the number of fetuses/litters was drastically reduced due to abortions and mortality. Triflusulfuron-methyl belongs to the triazinyl sulfonylurea herbicides. Evaluation of the current classification of other substances belonging to this group did not reveal a potential group-related developmental or overall reproductive effect. Based on all the available data, we agree that classification for developmental toxicity is not necessary For effects via lactation, no data are available. Overall, we agree that triflusulfuron-methyl should not be classified for reproductive toxicity.				

Dossier Submitter's Response
noted
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2013	Germany		MemberState	10
Comment received				
No classification is proposed				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2013	Germany		MemberState	11
Comment received				
No classification is proposed				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2013	Netherlands		MemberState	12
Comment received				
We agree that triflusulfuron is not rapidly or readily degradable in the environment and that triflusulfuron is considered to have a low bioaccumulation potential (logKow < 3 at environmentally relevant pH, highest measured log Kow 2.3 at pH 5). We note that the results of the Lemna gibba studies are based on a 14-day exposure period. As non-exponential growth of the control cultures throughout the study can influence the results of the studies, we recommend that the results of the 14-day studies be checked to ensure that the control cultures were in exponential growth during the whole study period. If they are not, we suggest recalculating the results based on 7-day exposure as is recommended in the current OECD guideline 221.				

The results of the Sloman study in Lemna gibba are reported as nominal concentrations although the measured test concentrations were less than 80% of nominal. As a result, the reported EC50 is higher than the highest measured tested concentration. We recommend recalculating the results of this study using mean measured concentrations.

The key study used for the Aquatic Acute classification is Sloman (EC50 based on growth rate) although in the study of Hughes and Williams a lower EC50 (basis unspecified), was obtained. However, the study of Hughes and Williams was used as the key study for Aquatic Chronic classification using a NOEC with an undefined basis. Based on the CLP (note 2 to table 4.1.0), results using growth rate should be used unless the basis for the results is not specified in which case the lowest values should be used. Following this reasoning, the study of Hughes and Williams has the lowest EC50 and NOEC values and should therefore be used for classification. Based on the presented information, using the Hughes and Williams study as key study will not change the proposed classification or M-factors. However, after the results of the Sloman study have been reconsidered and recalculated to 7-day exposure periods and measured concentrations, it would be prudent to check which study, Sloman or Hughes & Williams, is more appropriate as the basis for classification.

Dossier Submitter's Response

Degradation: noted.

The toxicity values reported in the CLH report are those validated during the peer-review for the inclusion of the substance in the Annex I of the directive 91/414/EEC. It is considered more appropriate to keep the same values between both dossiers.

The lowest 14-d EC50 of 0.00282 mg/L from the Hughes and Williams study could be used for the acute classification instead of the ErC50 from the Sloman study. Indeed, no EC50 based on growth rate is specified in the Hughes and Williams study.

RAC's response

RAC generally agees with the concerns, which have been addressed in the opinion:
For the two 14-day Lemna studies 7-day values have been recalculated and nominal concentrations were corrected to initial measures concentrations. According to the text of the CLH report (section 5.4.3, p. 57), the unspecified EC50 value is indeed an ErC50 value. All recalculated and corrected ecotoxicological results have been reconsidered and based on this new data basis a new key study is proposed for classification of the long-term aquatic hazards.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2013	Finland		MemberState	13

Comment received

We support the proposed classification for environmental hazards for Triflusulfuron-methyl:

Aquatic Acute 1 – H400
Aquatic Chronic 1 – H410
M-factor (acute): 100
M-factor (chronic): 10

Degradation:

We agree with the conclusions that Triflusulfuron-methyl is not rapidly degradable and not

readily biodegradable.

Concerning the metabolites formed in the hydrolysis study several percentage values are included in the CLH report (page 77). It could be specified to which parameter these values are referring to (the sum of the percentages of the two metabolites at pH 5 is nearly 200%).

The guidelines, study references and test durations of the water/sediment and soil simulation tests are not included in the report and could be specified. It could also be clarified whether the water sediment simulation tests were done in aerobic or anaerobic conditions. On page 80 a soil photolysis study is mentioned. It is unclear whether this is the same study that is mentioned on page 78 (a reference could be given).

Bioaccumulation potential:

We agree with the conclusion that Triflusulfuron-methyl does not have potential for bioaccumulation based on the comparison of the reported experimental log Kow values to the log Kow cut-off values (CLP or DSD).

Dossier Submitter's Response

For the results of the hydrolysis study, the sum of each metabolite is higher than 100% because the substance is clived in each metabolite and both metabolites are radiolabeled.

For the water/sediment study, the reference of the study is "Hawkins D.R., Kirkpatrick D., Dean G.M., Mellor S.J. (1993). Degradability and fate of DPX-66037 in the water/sediment system. Report HRC/DPT 279/921671 and DuPont AMR-2399-92". This study was performed in aerobic condition during 100 days and under the BBA guideline (Guidelines for the official testing of plant protection products part IV, 5.1)

The indication for the soil photolysis in page 80 is a summary of the results from the study described in page 78.

For other points of the comment: Noted.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2013	Belgium		MemberState	14

Comment received

Based on the results of the acute and chronic aquatic toxicity test on the most sensitive species (Lemna gibba with 14dEC50 = 0.00282mg/l and a 14dNOErC= 0.00127mg/l) the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic Acute 1, H400 and Aquatic chronic 1,H410.

In view of the proposed classification and toxicity band for acute toxicity between 0.001 and 0.01 mg/l, an M-factor for acute toxicity of 100 could be assigned, and an M-factor for chronic toxicity of 10 (not rapidly degradable substance and toxicity band between 0.001 and 0.01 mg/l).

Based on the classification and labelling criteria in accordance with dir. 67/548/EEC,

Triflusulforon-methyl should be classified as N, R50/53 with SCL : N; R50-53 Cn ≥0.25% N; R51-53 0.025%≤C<0.25% R52-53 0.0025%≤C<0.025% In conclusion : we agree with the proposed environmental classification (based on CLP criteria) by the French MSCA.
Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2013	Spain		MemberState	15
Comment received				
We are in agreement with the UK comments in order to use the lower Lemna NOEC value instead the value used on the French proposal, although this aspect do not change the final environmental classification.				
Dossier Submitter's Response				
We are in agreement with the comment. The lowest EC50 of 0.00282 mg/L could be used for the acute classification as no EC50 based on growth rate is specified in this study.				
RAC's response				
Noted and addressed in the opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
02.05.2013	United Kingdom		MemberState	16
Comment received				
The environmental acute and chronic classifications are based on a Lemna gibba ErC50 of 0.0035 mg/L and NOEC of 0.00127 mg/L. This Lemna 14d ErC50 is based on 'healthy frond count', the EC50 from the second 14d Lemna study is however lower at 0.00282 mg/L. Although this is not specified as an ErC50, reference to the second study summary reports that 'Effects on growth rate were assessed through the number of fronds'. Therefore, in the absence of information to the contrary, it could be assumed that this EC50 is also a comparable rate-based endpoint. It is proposed therefore that the most sensitive acute classification endpoint is 0.00282 mg/L for Lemna. This does not affect the proposed classification or M-factors (or SCLs) however.				
Dossier Submitter's Response				
We are in agreement with the comment. The lowest EC50 of 0.00282 mg/L could be used for the acute classification as no EC50 based on growth rate is specified in this study.				
RAC's response				
Noted and addressed in ODD. See also response to comment 12.				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2013	Germany		MemberState	17

Comment received

The use of data from aquatic plant tests instead of algae tests is usual for classification and labeling purposes. As a general remark we suggest to use for classification and labeling of acute effects of the substance EC50 values at day 7 (if available) instead of data at day 14 from aquatic plant toxicity tests.

page 86: Hughes, J.S. and Williams, T.L. (1993a)
This study with Pseudokirchneriella subcapitata was run over 5 days (120 hours). In the raw data it is obviously that the growth of algae after day 4 was limited. We would therefore prefer to use new calculated EbC50 (96 hours) of 0.0351 mg/L for classification and labeling. The relevant NOEC (96 hours) is 0.018 mg/L. The correct NOEC (120 hours) is 0.018 mg/L, instead of 0.0036 mg/L reported in the study. This new calculation was done by Probit-Analysis with the available raw data from the study.

page 87: Sloman, T.L. (1999b)
This study with the duckweed Lemna gibba was run over a period of 14 days. The ErC50 (14d) is 0.0035 mg/L (nominal) and the NOEC (14d) is 0.0015 mg/L (nominal) related to healthy frond count. The initial (0 hours) measured test concentrations were only 71 -73 %. We would therefore suggest to correct these data to initial measured concentrations to ErC50 (14d) of 0.00256 mg/L (initial measured) and the NOErC (14d) of 0.0011 mg/L (initial measured) related to healthy frond count and to EbC50(14 d) of 0.00321 mg/L (initial measured) and NOEbC (14d) of 0.00146 mg/L (initial measured). For classification and labeling of the acute hazard we suggest to use the new calculated ErC50(7d) of 0.002 mg/L (initial measured). This new calculation was done by Probit-Analysis with the available raw data from the study.

page 87: Hughes, J.S. and Williams, T.L. (1993b)
This study with the duckweed Lemna gibba was run over a period of 14 days. The ErC50 (14d) is 0.00282 mg/L (nominal) and the NOEC(14d) is 0.00127 mg/L (nominal) related to healthy frond count. For classification of the acute risk we suggest to use new calculated ErC50 (7d) of 0.00269 mg/L (nominal). This new calculation was done by Probit-Analysis with the available raw data from the study.

Page 88 ff: Comparison with criteria for environmental hazards
Please correct the data in table 21 and the relevant data for classification and labeling according the suggested corrected ErC50 and NOEC values of the 3 above mentioned tests. The acute and chronic M-factors of 100 and 10 are the same, because the new relevant values ErC50 (7d) of 0.002 mg/L and NOEC (14d) of 0.0011 mg/L (initial measured) for Lemna gibba are in the same range as the relevant values cited in the CLH-report for Lemna gibba (ErC50 (14d) of 0.0035 mg/L and NOEC (14d) of 0.00127 mg/L).

Dossier Submitter's Response

The toxicity values reported in the CLH report are those validated during the peer-review for the inclusion of the substance in the Annex I of the directive 91/414/EEC. It is considered more appropriate to keep the same values between both dossiers.

RAC's response

Noted and addressed in the opinion. See also response to comment 12.

ATTACHMENTS RECEIVED

1. **Triflusulfuron methyl** – Comments, (Filename: triflusulfuron echa comments), submitted on 08.05.2013 by DEPA (ECHA note: Attachment copied under the section Carcinogenicity)
2. **Comments on Proposed Classification of Triflusulfuron Methyl (126535-15-7),** (Filename: Industry Response to CLH Proposal for triflusulfuron methyl), submitted on 09.05.2013 by E.I. du Pont de Nemours and Company