Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

thiencarbazone-methyl (ISO); methyl 4-[(4,5-dihydro-3-methoxy-4-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)carbonylsulfamoyl]-5-methylthiophene-3-carboxylate

EC Number: -
CAS Number: 317815-83-1

CLH-O-0000001412-86-244/F

Adopted

30 November 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON THIENCARBAZONE-METHYL (ISO); METHYL 4-[(4,5-DIHYDRO-3-METHOXY-4-METHYL-5-OXO-1*H*-1,2,4-TRIAZOL-1-YL)CARBONYLSULFAMOYL]-5-METHYLTHIOPHENE-3-CARBOXYLATE

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.

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Substance name: thiencarbazone-methyl (ISO); methyl 4-[(4,5-dihydro-3-methoxy-4-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)carbonylsulfamoyl]-5-methylthiophene-3-carboxylate
EC number: -
CAS number: 317815-83-1
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	1
Comment received				
BECA thanks UK CA for this proposal for classification.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Germany		MemberState	2
Comment received				
We agree with the proposal of classification for environmental hazards as Aquatic acute 1 (H400) and Aquatic chronic 1 (H410) and the acute/chronic M-factor of 1000. Substance ID: In section 1.2 of Part B of the CLH report it is stated that the impurities are provided in the confidential annex of the report. However, no information regarding the present impurities is included in the confidential annex.				
Dossier Submitter's Response				
Thank you for your supportive comment. A number of process impurities are found in TCM. None are considered to impact on the classification proposed. Details of the impurities in TCM do not appear in the confidential				

Annex as stated in the CLH. Unfortunately this text should have been deleted. They are, however, included in the IUCLID, as stated in both the text and Table 6.
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	3
Comment received				
BECA agrees with the justification given by the DS and support their decision to not classify thiencarbazone-methyl, particularly given that the induction of tumours caused by crystal formation in the bladder is not a relevant carcinogenic mechanism in humans, as mentioned in the ECHA guidance on the Application of the CLP Criteria.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment. RAC agrees to not classify thiencarbazone-methyl for carcinogenicity, because the incidence of tumours in mice was very low and occurred only at the top dose. It is noted that the reference given in the ECHA Guidance on the Application of the CLP Criteria on the human relevance of urinary bladder tumours caused by crystals in the bladder is IARC (1999) Scientific Publications No. 147 Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis, in which it is actually stated that "*although there are quantitative differences in the carcinogenic response to calculi between species, the effect is not species-specific.*" This point has been highlighted to the ECHA secretariat and the text in the ECHA Guidance will be reviewed and revised during the next update of the Guidance.				

Date	Country	Organisation	Type of Organisation	Comment number
28.12.2017	Spain		MemberState	4
Comment received				
4.9. Carcinogenicity Low incidences of benign and malignant tumours of the transitional epithelium (urinary bladder and prostatic urethra) were observed in the mouse carcinogenicity study in both sexes at the top dose level of 4000 ppm (which exceeded the Maximum Tolerated Dose). The key events in mode of action for the induction of urinary tract tumours in mice were the exceeding of the urinary concentration necessary for formation of thiencarbazone-methyl crystals, the formation of uroliths, the chronic mechanical irritation of the urinary tract urothelium leading to regenerative hyperplasia, and ultimately the induction of tumours. The same events did not occur in the rat carcinogenicity study because the threshold concentration of thiencarbazone- methyl necessary to produce uroliths was not reached. The induction of rodent tumours caused by crystal formation in the bladder is cited specifically in the ECHA Guidance on the Application of the CLP Criteria as an example of a mechanism not relevant for humans. The apparent disparity in susceptibility between laboratory animals and humans to irritation-induced bladder tumours is considered, in part, due to postural and anatomic differences in the orientation of the urinary bladder in				

biped humans compared to quadruped rodents. Unlike the rat and mouse, it appears that the anatomic orientation of the urinary bladder in humans favours clearance of potentially irritating urinary solids The Spanish CA agrees with the dossier submitter that the findings in mice are not considered to be relevant to humans and therefore no classification for carcinogenicity is needed.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Thank you. RAC concludes that the MTD was not exceeded in either sex, since systemic toxicity was low as judged by low or no effect on body weight and by lack of specific adverse effects in internal organs other than urogenital system. No increased number of animals at high dose was found dead as compared to the concurrent controls. However, the top dose used in the study was considered sufficiently high by RAC as indicated by the number of unscheduled deaths of males due to ulcerative skin lesions in the anogenital region leading to killing for humane reasons. However, RAC agrees to not classify thiencarbazone-methyl for carcinogenicity, because the incidence of tumours in mice was very low and occurred only at the top dose. It is noted that the reference given in ECHA Guidance on the Application of the CLP Criteria on the human relevance of urinary bladder tumours caused by crystals in the bladder is IARC (1999) Scientific Publications No. 147 Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis, in which it is actually stated that "*although there are quantitative differences in the carcinogenic response to calculi between species, the effect is not species-specific.*" This point has been highlighted to the ECHA secretariat and the text in the ECHA Guidance will be reviewed and revised during the next update of the Guidance.

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Denmark		MemberState	5
Comment received				
This is an example of a mechanical effect eliciting the tumors. The mechanism is without relevance to humans (IARC 1999). No classification is warranted.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment. Please see the RAC's responses to comments 3 and 4.				

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Germany		MemberState	6
Comment received				
In the methods column of table 20 on page 45, four doses are given in ppm, namely 0, 500, 2500 and 5000 ppm, but five "one-year doses" are given in mg/kg bw/d, namely 0, 10.6, 27.2, 136.4 and 268.6 mg/kg bw/d for males and 0, 13.2, 35.8, 176.7 and 366.6 mg/kg bw/d for females. Please correct or identify and explain the extra dose.				
Dossier Submitter's Response				
Thank you for your comment.				

In the main carcinogenicity study in rats, animals (60/sex/dose) were dosed with 0, 500, 2500 or 5000 ppm for two years (equivalent to 0, 22.8/29.9, 115.2/152.9 and 234.0/313.4 mg/kg bw/day in males/females). Satellite groups of 10/sex/dose were dosed with 0, 200, 500, 2500 or 5000 ppm for a treatment period of 1 year (equivalent to 0, 10.6/13.2, 27.2/35.8, 136.4/176.7 and 268.6/366.6 mg/kg bw/day in males/females). Therefore, an extra dose of 200 ppm (10.6/13.2 mg/kg bw/day) was used for the satellite group of rats.
RAC's response
Thank you for your comment.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	7
Comment received				
No classification is supported considering 7 in vitro studies provided by the DS and one in vivo are negative and therefore there is no concern about germ cell mutagenicity.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agree. Thank you for your comment.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	8
Comment received				
FERTILITY In light of the observed effects appearing at relatively high dose, without a dose-dependent relationship, such as spermless males (1, 0, 5 and 3 at 0, 500, 2500 and 10 000 ppm, respectively) and the associated decrease in the insemination index (96, 100, 92 and 80 % at 0, 500, 2500 and 10000 ppm, respectively) as well as in the number of F1 pups (249, 282, 220 and 217 at 0, 500, 2500 and 10 000 ppm, respectively), we agree there is no evidence for a concern on fertility. DEVELOPMENT In the rat, skeletal variations (delayed/absent ossification) observed at high dose (1000 mg/kg bw/d) and reduced pup body weight mostly reflect maternal toxicity and are not estimated to highlight a concern. In the rabbit study, effects related to maternal toxicity were noted at the highest dose (increase in the number of runts with 34.8, 58.3, 9.5 and 23.0 % and lower pup weight with 36.7±5.9, 32.5±6.5, 34.7±6.2 and 32.2±7.1 g at 0, 50, 125 and 500 mg/kg bw/d, respectively). BECA is of the opinion that these data are not sufficient to require a classification.				
Dossier Submitter's Response				
Thank you for your support.				

RAC's response
Thank you for your comment. RAC agrees that no classification is warranted for reproductive toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Denmark		MemberState	9

Comment received

Care should be given to interpretation of the significance of abnormal penis in the 18 month mice study together with the spermless males (F0) in the rat multigeneration study.
There is some inconsistency in the indicated dose levels on page 56 below table 23.

Dossier Submitter's Response

The finding of abnormal penis in the 18-month carcinogenicity study in mice was not associated with any intrinsic histopathological findings, but was associated with chronic ulcerative dermatitis and/or an abscess in the preputial gland in the majority of cases at the microscopic examination.

In the multigenerational study in rats, a number of F_0 males were found to have no sperm.

Dose (ppm)	0	500	2500	10000
No. of F_0 males with no sperm (corresponds to female without implantations)	1	0	5	3
Insemination index (%)	96	100	92	80

The finding was seen in the absence of a dose response and was not statistically significant. There were no biologically relevant effects on sperm parameters (epididymal sperm count, sperm motility and morphology and testicular spermatids counts). This finding was not observed in F_1 males and is considered unrelated to treatment.

The DS does not believe that the finding of abnormal penis in mice, associated with ulcerative dermatitis is related to the finding of no sperm in F_0 male rats.

In the final sentence of the second paragraph on page 56 there is a typographical error where the dose level reads "1000 ppm" instead of 10000 ppm.

RAC's response

Thank you for your comment. RAC has carefully assessed the studies in the RAC opinion.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	10
Comment received				
According to the available data, BECA acknowledges that no classification is warranted as LD50 for all routes are superior to guidance values requiring a classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agree. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	11
Comment received				
BECA agrees with the DS that no classification is required.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agree. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	12
Comment received				
BECA agrees with the DS that no classification is required.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agree. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	13
Comment received				
BECA agrees with the DS that no classification is required.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agree. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	14
Comment received				
BECA agrees with the DS that no classification is required.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agree. Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	15
Comment received				
BECA is of the opinion that kidney and urinary tract are the target organs of thiencarbazone-methyl as it is clearly showed across studies with consistency in effects affecting different species and both sexes. However, effects are appearing at doses outside the guidance values (mostly at very high doses) and, as clearly mentioned by the DS, relevance to humans may be very poor considering quadrupeds are differently affected by calculi: their position may easily maintain of the calculi in the bladder, for example, and therefore induce irritation/hyperplasia. This lessen the concern. For these reasons, we support UK CA.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment. RAC agrees that no classification is warranted for specific target organ toxicity.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
08.01.2018	France		MemberState	16
Comment received				
We agree with the classification and M factors (acute and chronic) proposals.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Belgium		MemberState	17
Comment received				
BE CA supports the proposed environmental classification as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410 but does not agree with the proposed M-factors.				

Aquatic acute toxicity:
Normally exposure via the water phase is considered for classification and labelling purposes and studies that use spiked water test design could be taken into account. The key study proposed for aquatic toxicity with Myriophyllum spicatum is however an aquatic/sediment study and no mention is made in the CLH report of the spiking of the water. Therefore, exposure via the sediment (root uptake) cannot be excluded. Furthermore, degradation studies demonstrate rapid partitioning from water to sediment. BE CA is of the opinion that this study should be considered not adequate for aquatic classification. A sediment-free Myriophyllum spicatum toxicity test (OECD 238) however can be considered appropriate for aquatic classification purposes.

In that respect, the lowest aquatic toxicity value is the 7dErC50=0.00131mg/L resulting from a growth inhibition study with Lemna gibba performed according to OECD TG 221, which is a sediment free study. The M-factor should be 10 instead of 1000.

Aquatic chronic toxicity:
The same remark as above can be made for the proposed key chronic study (with Potamogeton pectinatus) which is also an aquatic/sediment study where the water phase was not spiked.
The Lemna gibba 7dNOErC of 0.00021 mg/l (Kern ME and Lam CV, 2006b) should than be considered as the lowest aquatic Chronic toxicity value to be used, resulting in an M-factor of 100 instead of 1000.

Dossier Submitter's Response

Thank you for your comments. We recognise that the two studies mentioned on *Myriophyllum* and *Potamogeton* are in some ways not standard for hazard classification, however given the significantly lower acute and chronic endpoints determined from them we felt they should be considered.

In both studies the substance was applied by spiking the water phase, not the sediment. Although there was degradation or dissipation to sediment, this was not as rapid as might have been predicted from the phys/chem and environmental fate data.

In the *Myriophyllum* study (Christ & Lam, 2007b), the Day 11 measured concentrations in the water phase ranged from 84% to 115% of nominal and the Day 14 measured concentrations ranged from 61% to 85% of nominal. The majority of exposure during this period would have been via the water phase, or indeed the sediment pore water (concentrations in which are normally modelled to be similar to that in overlying water). The proportion of uptake from direct contact of roots with the substance adsorbed to sediment particles is unknown but we expect it to be relatively low in comparison with water phase uptake. The subsequent recalculation (Bruns & Solga, 2013) did also determine a growth rate E_rC_{50} based on mean measured concentrations in the water phase over the whole 14-day exposure period.

Similarly in the study on *Potamogeton* (Hoberg, 2007), the mean measured concentrations in the water phase over the 14 days initial exposure period were <0.016 (control), 0.075, 0.26, 0.95, 3.1 and 10 µg a.s./L. These range from 75 to 86% of the nominals - so again not a substantial decline. The 14-day NOE_rC was also based on the mean measured concentrations in the water phase.

On the basis that these are not standard studies (or species), we proposed in the CLH Report (Section 5.6) that reliance on their endpoints for classification purposes be discussed by the RAC. Our initial feeling is that because exposure over the duration of these studies seems to be predominantly via the water phase, they could be relied on and used. However, we do recognise that there is some uncertainty over the use of studies involving sediment generally. Generic questions over the use of sediment studies - and which endpoints from them could potentially be used under which circumstances, may benefit from further consideration by the RAC and updated guidance on CLP.
RAC's response
RAC agrees with the DS's answer. Further details can be found in the Opinion Document.

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Denmark		MemberState	18
Comment received				
Agree with the proposal.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2018	Germany		MemberState	19
Comment received				
Page 105, chapter 5.6 conclusion on classification and labelling for environmental hazards We support the proposal to consider the lowest reliable and most sensitive acute and chronic endpoints for aquatic plants (Myriophyllum spicatum and Potamogeton pectinatus) although these are not standard species, because Thiencarbazone-methyl is an herbicide.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
29.12.2017	Finland		MemberState	20
Comment received				
FI CA supports the conclusions that thiencarbazone-methyl (ISO) is neither rapidly degradable or potentially bioaccumulative. Acute toxicity values for aquatic macrophytes are well below ≤ 1 mg/l and chronic toxicity values for aquatic macrophytes are well below ≤ 0,1 mg/l. Thus FI CA supports the proposed hazard classification Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. The lowest acute toxicity ErC50 value of 0,00094 mg/l for Myriophyllum spicatum and the lowest chronic toxicity NOErC value of 0,000075 mg/l for Potamogeton pectinatus were				

from non-standard studies. Myriophyllum spicatum study was conducted prior to the validation of the specific Myriophyllum spicatum test guideline. However, the test conditions were similar to the current validated OECD test guideline 239.

There was some variety in water temperature (18 - 27 °C) in the Potamogeton pectinatus study (Hoberg 2007). With the lack of any validation criteria for this non-standard test, is there any information available on how the variety in water temperature was explained and have it possibly affected the Potamogeton pectinatus growth?

Based on classification criteria FI CA supports the proposed environmental classification Aquatic Acute 1, H400 with M-factor of 1000 and Aquatic Chronic 1, H410 with M-factor of 1000 for thiencarbazone-methyl.

Dossier Submitter's Response

Thank you for your comment and agreement on the M-factors.

In relation to the study on *Potamogeton* (Hoberg, 2007), we recognise that this is not a standard study for classification purposes and there was some variation reported in water temperature. We have consulted the study report again and for the test on *Potamogeton*, the water temperature was continuously monitored and minimum/maximum temperatures were recorded daily. The temperature probe was located in the *Elodea* control replicate A for the *Elodea* and concurrent *Potamogeton* tests. It is key to note that the protocol required that the temperature of test solutions be maintained at ambient greenhouse temperatures, typically between 15 to 35 °C, i.e. this reflected normal diurnal variation in external temperatures and the test was not conducted under controlled or constant environment conditions. In this respect, the 18 - 27 °C variation did not deviate from that intended.

It is presumed that all control and treatment replicates, in both *Elodea* and concurrent *Potamogeton* tests, experienced very similar changes in growth conditions. Growth in the *Potamogeton* controls was acceptable and consistent over the 14 days - and growth in the treatment groups was compared directly with that in the controls under this same variation in environmental conditions. Using this direct comparison between treatments and controls, a well-defined concentration-response in shoot length and growth rate was observed in the *Potamogeton* test during the initial 14-day exposure period (see Table 45 in CLH Report). Standard deviations between replicates in controls and all treatment groups were also small. We therefore feel that the variations in growth observed can be directly related to exposure to the test substance rather than to any undue variation in growth conditions.

RAC's response

Noted. RAC agrees to the DS conclusion on the effect of temperature variation.