Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

carboxin (ISO); 2-methyl-N-phenyl-5,6-dihydro-1,4-oxathiine-3-carboxamide; 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxanilide

EC Number: 226-031-1
CAS Number: 5234-68-4

CLH-O-0000001412-86-180/F

Adopted
5 December 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CARBOXIN (ISO); 2-METHYL-N-PHENYL-5,6-DIHYDRO-1,4-OXATHIINE-3-CARBOXAMIDE; 5,6-DIHYDRO-2-METHYL-1,4-OXATHIINE-3-CARBOXANILIDE

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.

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

Substance name: carboxin (ISO); 2-methyl-N-phenyl-5,6-dihydro-1,4-oxathiine-3-carboxamide; 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxanilide
EC number: 226-031-1
CAS number: 5234-68-4
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.02.2017	Germany		MemberState	1
Comment received				
The German CA generally agrees to the proposed classification of Carboxin (ISO). In part B, section 1.1, table 5 of the CLH report the molecular weight is given as "235.3". Please clarify what the corresponding unit is. In part B, section 1.2, table 6 of the CLH report the typical concentration of Carboxin is 98.7 %. This value is not in accordance with the typical concentration given in the IUCLID dossier. Please clarify which typical concentration is the relevant one.				
Dossier Submitter's Response				
Thank you for your comments. The molecular weight is 235.3 g/mol The minimum purity is 98.7%, the typical purity is given as 99.4%.				
RAC's response				
Thank you for comments.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2017	Spain		MemberState	2
Comment received				
p. 51 Summary and discussion of carcinogenicity				

The Spanish CA support the conclusion of the UK CLP Competent Authority that consider not necessary to classify carboxin for carcinogenicity.

An increased incidence of hepatocellular carcinoma (above the historical control data) was noted in male rats receiving 400 ppm of carboxin, raising concern for classification with Carc 2 in the EFSA conclusion. However, when considering the low incidence observed (8% vs 2% in controls), the sex-specificity of the response, the lack of statistical significance, the absence of a respective response in liver adenomas and more importantly the "excessive toxicity" reported at this dose in males (75% mortality, clinical signs of toxicity, significant effects on terminal body weights [mean decrease of 17.3%] and on body weight gain [reduction of 23.4%] and the severe nephrotoxicity for which classification with STOT-RE 2 has already been proposed), it is concluded that these liver tumours are of no relevance to human health and therefore it is not proposed to classify for carcinogenicity.

In mice, there was an increase in benign lung tumours in males in the 5000 ppm group (34% vs 17% in controls), which marginally exceeded the range of the laboratory HCD (31.1%). However the combined incidence of adenoma and carcinoma at 5000 ppm (34%) was within the laboratory HCD upper limit for combined adenoma and carcinoma in males (37%). It is well established that CD-1 mice have a high spontaneous incidence of lung tumours, as shown by the concurrent and historical control data. Therefore, it is concluded that the slight increase (compared to controls) in lung adenomas observed in males at 5000 ppm is unrelated to treatment with carboxin.

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Agree. Thank you for your comments.

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	3

Comment received

Page 47

If we consider:
- Males surviving to termination at 400 ppm (12 rats): 3 males (or 25% of the survivors) exhibited hepatocellular carcinoma (vs. 4% in the controls group).
- Males surviving to termination + unscheduled deaths at 400 ppm (50 rats) : 8% exhibited hepatocellular carcinoma vs. 2% (control group)

In both cases, there is an increased incidence of hepatic carcinoma in males at the top dose level.

Page 51 Parathyroid effects (adenoma and hyperplasia):
Taking into account both hyperplasia and adenoma, the high mortality at the top dose level which can impact the dose–response relationship and the fact that chronic renal failure can cause parathyroid hyperplasia, FR is of the opinion that parathyroid effects should not be considered as unrelated to treatment.

Page 51 Mouse study
There is an increased incidence of lung adenoma in high dose males (slightly above HCD).

In the absence of any proposed underlying mode of action of the liver tumours in rat and lung tumor in mice, the relevance of these effects for human health cannot be ruled out. ☐ For the above listed reasons, a classification as H351 – Cat. 2 seems warranted.
Dossier Submitter's Response
The report acknowledges that an increase in hepatocellular carcinoma was observed in males at the top dose of 400 ppm (8% vs 2% in concurrent controls, including those animals surviving to termination and the unscheduled deaths). However, it is concluded that the sex-specificity of the response, the lack of statistical significance, the absence of a respective response in liver adenomas and more importantly the excessive toxicity observed at this dose in males (i.e., 75% mortality, clinical signs of toxicity, significant effects on terminal body weights [mean decrease of 17.3%] and on body weight gain [reduction of 23.4%] and the severe nephrotoxicity for which classification with STOT-RE 2 has already been proposed), it can be concluded that the liver tumours are of no relevance to human health. The increased incidence of parathyroid adenomas in rats could be considered treatment-related for the reasons indicated by FR. However, given the benign nature of the finding which was just marginally above the laboratory HCD, classification for carcinogenicity on the basis of these findings is not justified. An increase in benign lung tumours is reported in male mice at the top dose of 5000 ppm (34% vs 17% in controls). This marginally exceeded the range of the laboratory HCD (31.1%). However the combined incidence of adenoma and carcinoma (34%) was within the laboratory HCD upper limit for combined adenoma and carcinoma in males (37%). It is well established that CD-1 mice have a high spontaneous incidence of lung tumours, as shown by the concurrent and historical control data. It is also noted that in the absence of any lung toxicity or other pre-neoplastic lesions and taking into account the sex-specificity of the response, the biological plausibility of this increase is doubtful. Therefore, it is concluded that the slight increase (compared to controls) in lung adenomas observed in males at the top dose of 5000 ppm is unrelated to treatment with carboxin. Overall, based on a critical evaluation of all the available data, we remain of the opinion that classification of carboxin for carcinogenicity is not justified.
RAC's response
We agree with the analysis of weight of evidence provided by Dossier Submitter with conclusion that classification of carboxin for carcinogenicity is not warranted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	4
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	5
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	6
Comment received				
No comment				
Dossier Submitter's Response				
Noted.				
RAC's response				
Thank you.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2017	Spain		MemberState	7
Comment received				
p. 25 Summary and discussion of skin sensitisation The Spanish CA supports the proposed classification of carboxin as a skin sensitiser, category 1B (H317: May cause an allergic skin reaction). Carboxin fulfils the criteria for classification in sub-category 1 B as a response of > 30% was observed at an intradermal induction dose > 1%.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for comments. In the current Guidance on the Application of CLP Criteria (point 3.4.2.2.2), it is noted that classification into sub-categories is only allowed if data are sufficient. Therefore, care should be taken when classifying substances into category 1B when category 1A cannot be excluded. In such cases, classification into category 1 should be considered. This is particularly important if only data are available from certain tests showing a high response after exposure to a high concentration but where lower concentrations which could show the presence of such effects at lower doses are absent. To be classified in sub-category 1B, a response of ≥ 30% must be observed at an intradermal induction dose of > 1% or a response of ≥ 30% but < 60% at an intradermal induction dose of >0.1% but ≤ 1% is required. Carboxin fulfils the criteria for classification in sub-category 1B as a response of > 30% was observed at an intradermal induction dose > 1%. However, since for carboxin data for lower concentrations are absent, category 1A cannot be excluded, therefore the substance warrants classification as Skin Sens. 1 without				

subcategorization.
Taking into account available data and these considerations, RAC is of the opinion that carboxin warrants classification as skin sensitiser Category 1; H317.

Date	Country	Organisation	Type of Organisation	Comment number
13.02.2017	Sweden		MemberState	8

Comment received

The classification proposal for skin sensitisation (Skin Sens 1B) is based on one GPMT where 37-56% of the animals had positive reactions at a 10% intra dermal induction dose. According to CLP section 3.4.2.2.3.3, Table 3.4.4 this fulfils the criteria for classification as Skin Sens. 1B (positive reactions in ≥30% of the test animals at >1% intra dermal induction dose). Category 1A can be excluded since it would require a larger proportion of animals to test positive at a lower intradermal induction dose.

Hence, based on the information given in the CLH report we agree with the proposed classification. However, the reporting of the results lacks in detail which makes it difficult to properly evaluate the findings and to assess the validity of the study.

In the report, the dossier submitter reports only the percentages of animals with positive responses. We suggest to include the scoring tables from the original study in the CLH-report, the number of animals assessed as having positive reactions at the readings at 24 and 48 hours, and a discussion concerning the two animals that died during the study. If the cause of death was an infection, the validity of the positive responses in the remaining animals could be questioned since they too could have been infected, but without displaying symptoms. It would also be helpful if the scoring/assessment of reactions in the negative control animals were included.

Dossier Submitter's Response

Thank you for your comments.

Additional information is provided here.

In the challenge group, discrete erythema (grade 1) was noted in 4 males and 3 females at the 24 hour observation and in 5 males and 5 females at the 48 hour observation.

The 2 deaths reported in the study (1 male at day 9 and 1 female at day 11) were attributed to stress and are not considered to affect the interpretation of the results.

No signs of erythema were observed in the negative control group at challenge (i.e., all scores were 0).

RAC's response

Thank you for comments.
In the current Guidance on the Application of CLP Criteria (point 3.4.2.2.2), it is noted that classification into sub-categories is only allowed if data are sufficient. Therefore, care should be taken when classifying substances into category 1B when category 1A cannot be excluded. In such cases, classification into category 1 should be considered. This is particularly important if only data are available from certain tests showing a high response after exposure to a high concentration but where lower concentrations which could show the presence of such effects at lower doses are absent.
To be classified in sub-category 1B, a response of ≥ 30% must be observed at an

intradermal induction dose of > 1% or a response of ≥ 30% but < 60% at an intradermal induction dose of >0.1% but ≤ 1% is required. Carboxin fulfils the criteria for classification in sub-category 1B as a response of > 30% was observed at an intradermal induction dose > 1%. However, since for carboxin data for lower concentrations are absent, category 1A cannot be excluded, therefore the substance warrants classification as Skin Sens. 1 without subcategorization. Taking into account available data and these considerations, RAC is of the opinion that carboxin warrants classification as skin sensitiser Category 1; H317.

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	9
Comment received				
Page 26: Classification proposal as Skin Sens. 1B, H317 is supported.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for comments. Please see response to Comment No 7 and 8.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2017	Spain		MemberState	10
Comment received				
p. 41 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE The Spanish CA considers that the proposed classification is warranted for carboxin as STOT-RE 2; H373 – May cause damage to the kidneys through prolonged or repeated exposure. In a number of short-term and chronic oral and dermal studies involving repeated dosing of carboxin, there was clear evidence of significant organ (kidney) toxicity at doses relevant for classification as STOT-RE 2 (i.e. based on guidance values of 10≤C≤100 mg/kg bw/day from a 90-day study in the rat). Effects in rats included chronic nephritis with associated lesions and chronic progressive nephropathy increasing in severity with dose. Kidney weight (absolute and relative) was increased and there were clinical chemistry and urinalysis parameter changes related to reduce kidney function. These effects were consistently observed across all rat studies (oral and dermal) and occurred in both male and females rats, with males appearing to be more sensitive.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	11
Comment received				
Page 42: ☐ STOT RE - As mentioned in the different rat studies, kidney effects are observed at low dose levels close to cat.1 threshold : - From 30 mg/kg bw/d, vacuolar swelling epithelial cell in the proximal tubule in the 28-d study (gavage) - From 10 mg/kg bw/d, clinical chemistry (increased plasmatic urea and creatinine), chronic nephritis, tubular cell degeneration in the first 90-d study (diet) - From 10.5 mg/kg bw/d (very close to the threshold): chronic progressive nephropathy in the other 90-d study (diet) - From 10 mg/kg bw/d, chronic nephritis in the 2-generation study - From 0.82 mg/kg bw/d fibrous osteodystropathy and parathyroid hyperplasia secondary effects linked to chronic altered renal function in the 2-y study ☐ Based on these results, we consider that a classification as STOT RE category 1 may be warranted.				
Dossier Submitter's Response				
As already described in the CLH report, some kidney effects were noted in subacute and subchronic studies (the studies generally used for STOT-RE classification) a doses below the guidance values for classification in Category 1. However, these effects were not considered to be so severe to justify classification in Category 1. Although kidney findings (fibrous osteodystropathy and parathyroid hyperplasia) were reported from a dose of 0.82 mg/kg bw/d in the 2-yr rat study, these were only minimally increased above controls. On this basis, these findings were not considered to be severe enough to justify classification in Category 1. Overall, the data more appropriately support classification in Category 2.				
RAC's response				
Thank you for your comments. We disagree with a proposal to classify carboxin as STOT RE category 1 . Taking into account all available data, RAC agrees that the effects observed in the 90-day oral studies in the most sensitive species (male rats) were observed at dose level of 10 and 10.5 mg/kg bw/day, which is borderline with the guidance value for STOT RE 1. However, RAC is of the opinion that the observed effects at this dose at this dose were mild and could be related to chronic progressive nephropathy which is a male rat-specific disease. Therefore, RAC agrees with the DS that carboxin warrants classification as STOT RE 2.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
13.02.2017	Germany		MemberState	12
Comment received				
The German CA generally agrees to the proposed classification of Carboxin (ISO).				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.02.2017	Sweden		MemberState	13

Comment received

The Swedish CA agrees with the proposal to classify carboxin as Aquatic Acute 1 (H400) with an M-factor of 1 and Aquatic Chronic 2 (H411).

Minor comments:
Page 8, section 1.2 "Harmonized classification and labelling proposal" under "Labelling" the hazard statements should be H400 – "Very toxic to aquatic life" and H411- "Toxic to aquatic life with long lasting effects".

Page 58, Table 19 "Summary of relevant information". We suggest to include more details (i.e. 0% degraded in 28 d) on the study results from the Ready biodegradation test according to OECD guideline 301 B.

Page 60, section 5.1.2.2. "Screening tests". Study 1(Van Dijk, 1989): We suggest to include a description of the methodology and to include a discussion of the results of the study to improve transparency and understanding.

Page 65, Table 22a. "Summary of relevant information on aquatic toxicity to fish". The reliability of the tests are missing in the report. We would also like to point out that the OECD guideline 204 (fish test with Cyprinus carpio) has been removed and the endpoint is therefore no longer considered valid.

Dossier Submitter's Response

Thank you for your comments

Page 8, section 1.2
As the proposal is Aquatic Acute 1 (H400) and Aquatic Chronic 2 (H411), we proposed H410 following Table 4.1.6-a in the Guidance on the Application of the CLP Criteria (Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures) Version 4.1, June 2015.

Page 58, Table 19
Further limited details are presented in section 5.1.2.2 of the CLH report. A similar level of detail is presented in the DAR (section B.8.4.3). We confirm that 5.9% biodegradation was observed by day 28.

Page 60, section 5.1.2.2.
Further details are presented in section 5.1.2.3 of the CLH report including details of the overall method, results and interpretation of results.

Page 65, Table 22a.
The data included in the CLH report were reviewed under Directive 91/414/EEC and considered valid unless otherwise noted. On this basis quoted ecotoxicity data are considered reliable for classification.

In section 5.4.1.1 of the CLH report we note the OECD 204 test guideline was removed by the OECD and consider the data as supporting information i.e. prolonged acute toxicity to fish data. In addition, we note that the study does not present a valid chronic NOEC for the

purpose of classification. Given this, a surrogate approach was considered for chronic toxicity to fish.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	France		MemberState	14
Comment received				
FR agrees with the classification for environmental hazards and with the acute M factor value proposed in the CLH report.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
09.02.2017	Belgium		MemberState	15
Comment received				
BE CA supports the classification for acute toxicity : Aquatic Acute 1, H400, M=1. We don't support, however, the chronic classification with Aquatic Chronic 2, H411 and are of the opinion that Carboxin should be classified as Aquatic Chronic 1, H410 with M=1 instead. The 3d NOEC for the substance carboxin was calculated from de growth inhibition on day 3 and the mean concentration of day 0 and day 5: - Taken the mean concentration of day 0 and day 5 doesn't reflect the correct concentration of day 3 - At this recalculated concentration of 0.107 mg/l, growth inhibition was 11.3%, thus rather a LOEL than a NOEC. As the recalculated concentration is close to the cut off of 0.1 mg/l and growth inhibition was seen at this concentration, the NOEC will be < 0.1 mg/l and thus it is more appropriate to classify the substance as Aquatic chronic 1, H410 with M=1.				
Dossier Submitter's Response				
Thank you for your comments. We are unclear what carboxin 3 day NOEC you are referring to. The Hughes, 1990 study is presented in the CLH report as a 5 day NOEC of 0.107 mg/l based on growth inhibition (13.1%) on day 5 and analytical measurement of carboxin on days 0 and 5. This 5 day NOEC of 0.107 mg/l (mean measured) reflects the nominal 0.125 mg/l treatment. At this treatment there was no statistically significant difference (Analysis of Variance and Dunnett's Test $p \leq 0.05$) in growth inhibition compared to the solvent control on day 5. Hence, this treatment was considered the study 5 day NOEC. There was no statistical comparison of growth inhibition (11.3%) on day 3 and a 3 day NOEC was not determined. While we note the nominal 0.125 mg/l (0.107 mg/l mean measured carboxin) treatment				

was observed to have 11.3% and 13.1% growth inhibition on days 3 and 5, we feel the statistical basis for the NOEC is valid for classification. In addition, we note the controls appear to be valid at day 5. While we agree the resulting 5 day NOEC of 0.107 mg/ is close to the 0.1 mg/l cut off, it *is* >0.1 mg/l and within the range 0.1 to 1 mg/l resulting in the Aquatic Chronic 2 proposal. There are two additional valid chronic NOECs also in the 0.1 to 1 mg/l range which support the Aquatic Chronic 2 classification proposal.
RAC's response
Thanks to the BE CA to identify this issue. RAC also has reassessed the meassuered results applying the Williams test and also found the lowest test concentration to be significantly different to the solvent control. Consequently the lowest test concentration is a LOEC and the NOEC is smaller. The EC_{10} at 96h should be used for classification.