Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Carbendazim (ISO); methyl benzimidazol-2-ylcarbamate

EC Number: 234-232-0
CAS Number: 10605-21-7

CLH-O-0000006717-65-01/F

Adopted

5 December 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CARBENDAZIM (ISO); METHYL BENZIMIDAZOL-2-YLCARBAMATE

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: carbendazim (ISO); methyl benzimidazol-2-ylcarbamate
EC number: 234-232-0
CAS number: 10605-21-7
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	1
Comment received				
FR: p. 2: Table 3: Impurities: According to the EFSA conclusion on the RAR of the active substance (EFSA Journal 2010; 8(5):1598), there are both relevant impurities: AHP at 0.005 % and DAP at 0.006 %.				
Dossier Submitter's Response				
Thank you for comment. We agree, AHP and DAP are relevant impurities according to the EFSA conclusion. However, they are also relevant impurities according to the BPC opinion, where 2,3-diaminophenazine (DAP): ≤0.00023 % w/w and 3-amino-2-hydroxyphenazine (AHP): ≤0.00003 % w/w are stated as relevant.				
RAC's response				
Thank you for information.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	2
Comment received				
FR: Skin sensitization P14-10.6.1 Based on the positive, reliable, guinea pig maximisation test compliant with OCDE guideline N° TG 406, the carbendazim (iso), methyl benzimidazol-2-yl carbamate can be classified as a skin sensitizer H317 cat 1 (Guidance CLP 3.4.2.2.4). Could you please confirm that the concentration of tested item used for each inducing exposure is the maximum concentration leading to mild to moderate skin irritation and that the concentration used for the challenge exposure corresponds to the highest non-				

irritant dose, in accordance with the OCDE guideline N°TG 406?

Providing confirmation of this, we agree with the H317 cat 1 classification proposal in this CLH report.

Dossier Submitter's Response

The original study report by Coleman (1997) was checked once more. It is explained there that the concentrations used for both induction and challenge had been selected on the basis of a preliminary test on which no further details are given. However, it is stated that the 5 % carbendazim as intradermally applied for induction was "the highest concentration that caused irritation but did not adversely affect the animals". The 62.5 % concentration used for topical induction and challenge is described as the "maximum practical concentration that could be prepared and dosed topically and did not give rise to irritation effects". There is no further proof of these statements but, in principle, the previous information was confirmed by the findings in the main study. Slight irritation was reported to have occurred, as expected, after intradermal induction. In fact, slight erythema was seen after topical application but could be also due to the vehicle Alemicol D. In the control animals which were exposed to carbendazim during challenge, but not induced before, no dermal reactions were noted. On balance, there is no reason to doubt the concentration selection and we still regard the study and its results as valid.

RAC's response

Thank you for the question which allowed DS to provide additional information related to the concentration selection for the induction and challenge exposure.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France		MemberState	3
Comment received				
FR: Thank you for this very clear document. We agree with the Aquatic Acute 1 (H400 ; M-factor=10) and Aquatic Chronic 1 (H410; M-factor=10) classification proposal.				
Dossier Submitter's Response				
Thank you very much for your support.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	United Kingdom		MemberState	4
Comment received				
Carbendazim (EC: 234-232-0; CAS: 10605-21-7) Ecotoxicity endpoints: We think information is required to clarify the relevance and reliability of some acute toxicity to fish endpoint. Acute toxicity to Ictalurus punctatus [Report A30119, xxxx, 1984]: The non-GLP study followed an ASTM guideline using a static test system and Ictalurus punctatus (Channel catfish). There are no details for the exposure concentration range, test system media, validity criteria, treatment preparation or test item stability over study period. In addition, in the CLH report for thiophanate –methyl CAS: 23564-05-8				

(carbendazim is a degradant of thiophanate-methyl) it was noted that control raw data are missing. We consider further information is required to consider these issues and the overall validity of the study which is currently considered Reliability 2. This is important as the endpoint is presented as the most sensitive acute endpoint for classification and results in a lower M-factor than using other acute endpoints. Please can you provide further details to support the reliability of the study endpoint?

We note that the CLH proposal for thiophanate-methyl CAS: 23564-05-8, included yok-sac fry endpoints [Reference: xxxx (1984) Toxicological Studies of benanyl and carbendazim in fish following ASTM guidelines.] Please can you consider if this information is relevant for hazard classification.

Dossier Submitter's Response

Fish toxicity, Report A30119, CLH_11_5_A7_4_1_1_3 from 1984:

Further information on fish study: Standard reconstituted dilution water (pH 7.4, water hardness 40-48 mg/L as $CaCO_3$) was used as testing medium and was formulated in accordance with ASTM, 1980. Test concentrations according to a logarithmic progression were used; however chosen concentrations are not stated in the study report. Stock solutions of test substances (technical grade, 99 %) were prepared in acetone. 10 fish per jar in 15 L of dilution water were exposed for each concentration step. Acclimatisation to testing conditions and dilution water was performed over a three-day period and fish were placed in test chambers 24 h prior to exposure. No feeding was performed during acclimation or substance exposure period. Tests with *O. mykiss* have been performed at 12 °C and with *I. punctatus* and *L. macrochirus* at 22 °C. During the exposure period, fish were observed and dead fish removed at 24 h intervals. In addition to standardised testing four additional tests were performed to determine the (acute) effects of temperature, pH, water hardness and exposure of early life stage fish (*O. mykiss* and *I. punctatus*). We would consider test conditions and method also to be in line with OECD TG 203. All tests were performed with benomyl and carbendazim as its transformation product. However, no further information on test concentrations or control treatments are provided in the test report (representing a master thesis). In addition, no data with regard to validity criteria are included.

The test series with variations in temperature showed similar results to the acute test according to guideline test conditions, LC_{50} = 32 µg/L (95 % c.i.: 23--44 µg/L) for *I. punctatus*, furthermore sensitivity was reduced at lower temperatures. Different pH values during the test lead to similar results (*I. punctatus*: LC_{50} = 23 µg/L at pH 6.5, 14 µg/L at pH 7.5 and 23 µg/L at pH 8.5). With soft and hard water, LC_{50} = 18 and 24 µg/L were reported for *I. punctatus*. Similar results were demonstrated for *O. mykiss*.

Taking into account the year the study was performed, the level of documentation is in line with common practice at this time and we do not consider this as a major issue to reject this study. Furthermore, the test was performed multiple times with slight variations and the results support each other. Indeed the study reports significantly lower effect values for *I. punctatus* than for *O. mykiss*. However, this does not seem related to the test system, as within the same study the presented results for *O. mykiss* are perfectly matching the results from a GLP-study according to OECD TG 203 from 1988, which was considered as valid (96 h LC_{50} = 0.87 mg/L in CLH_11_5_A7_4_1_1_3, 1984, vs. 96 h LC_{50} = 0.83 mg/L in CLH_11_5_A7_4_1_1_1, 1988).

yok-sac fry endpoints, Report A30119, CLH_11_5_A7_4_1_1_3 from 1984:

The results with regard to yok-sac fry endpoints are presented within the same study as the acute effects to three fish species (master thesis from 1984, Report A30119, CLH_11_5_A7_4_1_1_3): With *O. mykiss* and *I. punctatus* acute testing (96 h) with different early life stages have been performed (yolk-sac fry, swim-up fry, 0.2 g fry). Early life stages showed indeed higher sensitivity towards carbendazim (yolk-sac fry LC_{50} = 7 µg/L (95 % c.i. 6-9 µg/L), swim-up fry LC_{50} = 12 µg/L (95 % c.i. 9-15 µg/L) and 0.2 g fry LC_{50} = 10 µg/L (95 % c.i. 8-13 µg/L)). However, this study does only cover short-term toxicity (96 h and LC_{50} values only), whereas an early life stage study according to OECD TG 210 would cover at least 14-32 days and results should be expressed as NOEC, EC_{10} or EC_{20}. Based on the age of the tested fish this study therefore is neither in line with conditions for acute fish testing (e.g. OECD TG 202), nor with chronic fish testing (e.g. OECD TG 210). Apart from the shorter time, this study is similar to OECD TG 212, which is considered mostly as a screening study, and if considered as a screening study, the results would in our opinion not justify further long-term testing. Therefore we do not consider these results as relevant or sufficient for hazard classification.

RAC's response

RAC analysed the data presented in the Palawski and Knowles study and considered the following regarding the LC_{50} = 0.019 mg/L and the yolk sac fry endpoints:

- RAC agrees with the DS and accepts the endpoint LC_{50} = 0.019 mg/L. Although the data is not ideal the endpoint is obtained following a standard test comparable to OECD TG 203.
- RAC considers the yolk sac fry test more comparable with OECD TG 236 Fish Embryo Acute Toxicity (FET). However, with the data available it is difficult to assess the embryo test adequacy. In addition, FET was designed for *Danio rerio* and would need to be adapted for *I. punctatus*. In the *I. punctatus* test, exposure time, life stage, temperature, etc., might not be the adequate.
- FET has uncertainties related to its predictive capacity and its applicability in the regulatory context as a substitute of standard tests. For many chemicals, FET sensitivity is lower than the OECD TG 203 although the reasons why this occurs are unknown. A limit number (thiophanate-methyl among them) exhibited a higher toxicity in FET with an FET/AFT LC_{50} ratio < 0.1. These may represent substances with a mode of action specific for embryonic development. Yet the reasons are unknown. In addition, there are still uncertainties in relation to its applicability domain, etc.
- For the above reasons it is not recommended to use it as a direct "one-to-one" replacement for the OECD TG 203 and thus to be used alone to meet the information requirements under REACH. It can be used in a weight of evidence approach.

In conclusion RAC agrees in using the *I. punctatus* LC_{50} =0.019mg/L but disregards in this case the use of embryo data.