Committee for Risk Assessment

RAC

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

5 December 2019

CLH-O-0000006717-65-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **carbendazim (ISO); methyl benzimidazol-2-ylcarbamate**

EC Number: **234-232-0**

CAS Number: **10605-21-7**

The proposal was submitted by **Germany** and received by RAC on **15 November 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **21 January 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 March 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

Co-Rapporteur, appointed by RAC: **Ignacio de la Flor Tejero**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **5 December 2019** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	613-048-00-8	carbendazim (ISO); methyl benzimidazol-2-ylcarbamate	234-232-0	10605-21-7	Muta. 1B Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	H340 H360FD H400 H410	GHS08 GHS09 Dgr	H340 H360FD H410			
Dossier submitters proposal	613-048-00-8	carbendazim (ISO); methyl benzimidazol-2-ylcarbamate	234-232-0	10605-21-7	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Skin Sens. 1	**Retain** H400 H410	**Retain** GHS09 **Add** GHS07	**Retain** H410 **Add** H317		**Add** M=10 M=10	
RAC opinion	613-048-00-8	carbendazim (ISO); methyl benzimidazol-2-ylcarbamate	234-232-0	10605-21-7	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Skin Sens. 1	**Retain** H400 H410	**Retain** GHS09 **Add** GHS07	**Retain** H410 **Add** H317		**Add** M=10 M=10	
Resulting Annex VI entry if agreed by COM	613-048-00-8	carbendazim (ISO); methyl benzimidazol-2-ylcarbamate	234-232-0	10605-21-7	Muta. 1B Repr. 1B Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H340 H360FD H317 H400 H410	GHS07 GHS08 GHS09 Dgr	H340 H360FD H317 H410		M=10 M=10	

GROUNDS FOR ADOPTION OF THE OPINION

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) proposed no classification of carbendazim for physical hazards on the basis of the following data:

Property and Method	Results	Remarks	Reference
Explosives screening procedures in Appendix 6 of the UN-MTC, Table A6.1	Examination of the structure indicates that there are no chemical groups associated with explosive properties. Not explosive	Statement: Based on the theoretical assessment of the chemical structure	Reisinger, 2008
Flammability (solids) Method: Hoechst internal Directives of 1973-10-01 similar to EEC A.10	Not highly flammable	Evaluation: Class 3 (topical burning or glowing without diffusion) Details concerning the used methods and the purity of the tested material is not available	Albrecht and Lehr, 1975
Self-ignition temperature Hoechst internal Directives of 1973-10-01 similar to EEC A.16	No spontaneous ignition up to 400°C	-	Albrecht and Lehr, 1975
Oxidising properties (solids)	Not oxidising	Statement: Based on the theoretical assessment of the chemical structure	Maier and Rexer, 1990
Self-reactive substances	Not self-reactive properties	Statement: Based on the theoretical assessment of the chemical structure	
Pyrophoric solids	Not pyrophoric properties	Statement: Based on experience in manufacturing and handling	

Comments received during public consultation

There were no comments provided.

Assessment and comparison with the classification criteria

Explosives

According to Annex I: 2.1.4.3 of the CLP Regulation a substance is not classified as explosive when there are no chemical groups associated with explosive properties present in the molecule. Taking into account that carbendazim does not contain chemical groups associated with explosive properties it does not warrant classification as an explosive substance.

Flammable solids

Carbendazim was considered as 'not highly flammable' in an experimental study (Albrecht and Lehr, 1975) similar to A.10. Although, the hazard class should be assessed in accordance with

the test method described in Part III, sub-section 33.2.1, of the UN RTDG, Manual of Tests and Criteria: powdered, granular or pasty substances shall be classified as readily combustible solids when the time of burning of one or more of the test runs, is less than 45 seconds or the rate of burning is more than 2.2 mm/s.

However, according to chapter R.7.1.10.3 of Guidance on Information Requirements and Chemical Safety Assessment (R.7a): *If available data from an A.10 test method indicate that a classification as a flammable solid does not apply (result: not highly flammable), no more testing is necessary. However, if the A.10 test method has come to the conclusion 'highly flammable', it will be necessary to also determine the influence of the wetted zone as described in the UN Test N.1.* Since the result of test method similar to A.10 performed with carbendazim was 'not highly flammable' the classification as flammable solids is not warranted.

Self-reactive substances

The classification procedures for self-reactive substances and mixtures need not be applied in accordance with section 2.8.4.2 of Annex I to CLP Regulation if there are no chemical groups present in the molecule associated with explosive or self-reactive properties. Examples of such groups are given in Tables A6.1 and A6.2 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria.

Taking into account that carbendazim does not contain chemical groups associated with explosive and self-reactive properties it does not warrant classification as a self-reactive substance.

Pyrophoric solids

In accordance with section 2.10.4 of Annex I to CLP Regulation, the classification procedure for pyrophoric solids needs not to be applied when experience in manufacture or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)).

Carbendazim is known to be stable in contact with air at room temperature for prolonged periods of time (days) and hence, it does not warrant classification as a pyrophoric solid.

Self-heating substances

No spontaneous ignition up to 400°C was reported in the experimental study (Albrecht and Lehr, 1975) carried out according to a method similar to EEC A.16. The hazard class should be assessed using method N.4 in Part III of the UN RTDG manual of test and procedure, where the substance is heated up to 140°C. If the result of this test is negative no further test is necessary. There is a difference in volume-to-surface ratio (5:1) in the tested sample between the N.4 test (100 mm sample cube) and the A.16 test (20 mm sample cube), and increased volume-to-surface ratio leads to less efficient removal of heat from the centre of the sample. Diversely, in method A.16 the substance is heated up to 400°C. RAC considers that the difference in sample size is compensated by the difference in temperature between the two methods.

Furthermore, according to chapter R.7.1.10.7 of Guidance on Information Requirements and Chemical Safety Assessment (R.7a): *the study (N.4) does not need to be conducted for solids if preliminary results exclude self-heating of the substance up to 400°C and if available data from a test according to method A.16 indicate that a classification as a self-heating substance does not apply, no more testing is necessary. Only in case of positive result with A.16 test method, the appropriate UN test method is required to confirm classification.*

Overall, as carbendazim did not ignite up to 400°C, it does not warrant classification as a self-heating substance.

Substances which in contact with water emit flammable gases

In accordance with section 2.12.4 of Annex I to CLP Regulation, the classification procedure for this class need not be applied if:

a) the chemical structure of the substance or mixture does not contain metals or metalloids; or
b) experience in production or handling shows that the substance or mixture does not react with water, e.g. the substance is manufactured with water or washed with water; or
c) the substance or mixture is known to be soluble in water to form a stable mixture.

Carbendazim fulfils all of the above criteria, therefore it does not warrant classification as a substance which emits flammable gases in contact with water.

Organic peroxides

The substance does not contain peroxide groups, and therefore classification is not warranted.

Oxidising solids

For organic substances or mixtures the classification procedure for this class shall not apply in accordance with section 2.14.4 of Annex I to CLP Regulation, if:

a) the substance or mixture does not contain oxygen, fluorine or chlorine; or
b) the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

Carbendazim fulfils criterion (b), above, therefore it does not warrant classification as an oxidising solid.

In conclusion, RAC supports the proposal of the DS for **no classification of carbendazim as regards physical hazards**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS proposed to classify carbendazim as a skin sensitiser in category 1 without subcategorization on the basis of the results of two guideline and GLP compliant tests (positive Guinea Pig Maximisation Test (GPMT) and negative Buehler assay in guinea pigs). In a third test (primary skin irritation and sensitisation test), no animals showed a dermal reaction. However this test did not comply with recognised test guidelines and the DS considered the study not applicable for comparison with the CLP criteria.

Comments received during public consultation

One Member State Competent Authority (MSCA) agreed with the DS with classification of carbendazim as Skin Sens. 1, H317, based on the positive, reliable, GPMT. Although, MSCA asked for confirmation that the concentration of tested item used for each inducing exposure was the maximum concentration leading to mild to moderate skin irritation and that the concentration

used for the challenge exposure corresponded to the highest non-irritant dose, in accordance with the OECD TG 406.

According to DS' response, the concentrations used for both induction and challenge had been selected on the basis of a preliminary test on which no further details had been given in the original study report (Anonymous, 1997). However, it had been stated that the 5% carbendazim applied intradermally 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 had been described as the "maximum practical concentration that could be prepared and dosed topically and did not give rise to irritation effects". There was no further proof of these statements but, in principle, the previous information was confirmed by the findings in the main study. Slight irritation had been reported to have occurred, as expected, after intradermal induction. In fact, slight erythema had been seen after topical application but it could be also due to the vehicle Alembicol D. In the control animals which had been exposed to carbendazim only during challenge, no dermal reactions had been noted.

Assessment and comparison with the classification criteria

Summary of the main findings reported in the CLH report on animal skin sensitisation studies with carbendazim:

<table>
<tr><th>Study</th><th>Dose level</th><th>Results</th><th>Reference</th></tr>
<tr>
<td>GPMT
OECD TG 406

Dunkin Hartley guinea pig

10 males/ treatment group

5 males/ control group

GLP</td>
<td>Carbendazim (purity 99.5%)

Induction: (day 0) intradermal injection - 5% w/v (day 7) topical application - 62.5% w/v

Challenge: (day 21) - 62.5% w/v and 31.25% w/v

Vehicle: Alembicol D
Adjuvant: 50% FCA in water

Positive control: yes</td>
<td>Responses at 24, 48, and 72h after path removal

<table>
<tr><td>Responses at</td><td>24h</td><td>48h</td><td>72h</td></tr>
<tr><td colspan="4">Challenge 62.5%</td></tr>
<tr><td>treated</td><td>1/10</td><td>4/10</td><td>3/10</td></tr>
<tr><td>control</td><td>0/5</td><td>0/5</td><td>0/5</td></tr>
<tr><td colspan="4">Challenge 31.25%</td></tr>
<tr><td>treated</td><td>0/10</td><td>3/10</td><td>3/10</td></tr>
<tr><td>control</td><td>0/5</td><td>0/5</td><td>0/5</td></tr>
</table>

Conclusion: positive</td>
<td>Anonymous, 1997</td>
</tr>
<tr>
<td>Buehler assay

OECD TG 406

Pirbright-White guinea pig

20 females/ treatment group

10 females/ control group

GLP

Deviations: 9 inductions, challenge treatment was conducted on day 37 instead of day 27-29</td>
<td>Carbendazim (purity 99.4%)

9 induction applications - day 1, 3, 5, 8, 10, 12, 15, 18, 19
Challenge – day 37

Induction and challenge: 50% w/v

Vehicle: petrolatum

No positive control</td>
<td>No skin sensitising effects at 24 and 48 h after patch removal.

Conclusion: negative</td>
<td>Anonymous, 1987</td>
</tr>
</table>

Primary skin irritation and sensitization test on guinea pigs Non- Guideline, 10 males/treated and control group **Disregarded study** due to the following deficiencies of the method: test was performed with 10 instead 20 animals, no local irritation was created with sodium lauryl sulphate, challenge was performed after 2 weeks instead of 3 or 4 weeks, no information on the sensitivity and reliability of the experimental technique	Carbendazim (purity 98%) Induction: 4 intradermal inductions, one each week over a period of 3 weeks Concentration: 1% w/v Vehicle for induction: dimethyl phthalate Challenge: after 2 weeks rest Concentration: 4 and 40% w/v (topical) Vehicle for challenge: Acetone No positive control	No skin sensitising effects Conclusion: negative	Anonymous, 1976

Since the Buehler test is considered less sensitive and both, the Buehler test as well as the non-guideline study, present limitations in the study design, classification of carbendazim is proposed based on the positive GPMT.

In one reliable GPMT study according to OECD TG 406, skin reactions indicative of sensitisation were observed in 4 out of 10 treated animals (40%) after intradermal induction with 5% of carbendazim in Alembicol D (Anonymous, 1997). Therefore, RAC considers that the CLP criteria for classification as a Cat. 1B skin sensitiser (positive response in ≥ 30% of animals at > 1% intradermal induction dose in GPMT) have been met. It is very unlikely that at lower concentrations the criteria for Cat. 1A (≥ 30% response at ≤ 0.1% intradermal induction dose, or ≥ 60% response at 0.1-1% intradermal induction) would be met, given the fairly low response rate at 5%. However, lower concentrations have not been tested and therefore, Cat. 1A cannot be totally excluded in line with the CLP regulation. In conclusion, RAC supports the DS' proposal for **classification of carbendazim as skin sensitizer in category 1 (Skin Sens. 1; H317 - May cause an allergic skin reaction)**, without a subcategory.

Specific concentration limit

Carbendazim has, based on existing data, a weak potency of skin sensitisation, therefore, the generic concentration limit should be applied.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Degradation

Hydrolysis

In the hydrolysis study included in the dossier, rates were calculated for temperatures of 50°C and 60°C to be later extrapolated to 25°C and 12ºC. The Arrhenius equation was used for this extrapolation.

At 12ºC, carbendazim was found to be stable at pH 5 and 7 (>2 years). The mean half-live at pH 9 was around 153 days. 2-Aminobenzimidazole (2-AB) was determined as significant hydrolysis product and amounted for approximately 30% of the parent compound.

Ready biodegradability

A study on the ready biodegradability of carbendazim was performed according to OECD TG 301B. The CO_2 evolution measured after 4, 7, 14 and 28 days was less than 20% of the theoretical CO_2 content. Carbendazim is therefore considered not readily biodegradable by the Dossier Submitter.

Photochemical degradation

In the available study, carbendazim was demonstrated to be photolytically stable over the period of 166 hours corresponding to 35 sunny days under natural conditions at 52° Northern latitude in June. No transformation products were identified. The study was not conducted under environmentally relevant conditions (sterile, pH = 5). Thus, the extrapolation of the degradation rate constant from laboratory tests to natural water is limited.

Water/sediment degradation data

The dissipation of ^{14}C-Carbendazim was studied in two water/sediment systems (Bickenbach, Unter Widdersheim) incubated under aerobic conditions in the dark at 20 ±2°C over a period of 149 days (Guideline: SETAC Europe (1995): Procedures for assessing the environmental fate and ecotoxicity of pesticides).

DT_{50} values of 15.1 days (Bickenbach) and 76.8 days (Unter Widdersheim) were calculated for the total system, corresponding to 28.6 and 142.6 days, respectively, when converted to an average EU outdoor temperature of 12°C. Mineralisation amounted to 23.0 and 6.0% $^{14}CO_2$ after 149 days.

Throughout the study, several metabolites were identified in the water, sediment and whole system, some of them were not identified. With regard to the total system, no metabolite was detected above 10% of applied radioactivity.

Conclusion on degradation

Carbendazim is hydrolytically stable at pH 5 and 7. The Hydrolysis half-life at pH 9 exceeds 16 days (~ 153 days). The substance is not readily biodegradable. Half-lives derived from studies in water-sediment and soil were higher than 16 days (at 12°C) and mineralization was far below 70%. 2-AB (2-amino-benzimidazole, CAS Number 934-32-7) was detected as significant hydrolysis product and relevant metabolite (> 10%) during degradation in soil (= 10%). Based on the available information, the DS considered carbendazim as not rapidly degradable, for classification purposes.

Bioaccumulation

In anonymous (1984a), bioconcentration was determined in a flow-through test on Bluegill sunfish (*Lepomis macrochirus*) with two concentrations of radiolabelled carbendazim (0.018 and 0.17 mg/L) based on EPA Guidelines. The results were similar at the two exposure concentrations with maximum BCFs of 27 and 23 L/kg at the low and high exposures, respectively. It remains unclear if steady state was reached, since after a plateau between 14 and 21d, concentrations in fish increased again at day 28. The study was considered as acceptable with a reliability of 2. The BCF for fish does not exceed the trigger value of 500 L/kg and therefore indicates a low potential for bioaccumulation, for classification purposes.

The estimated log k_{ow} for carbendazim according to OECD TG 107 was estimated to be 1.5. According to CLP, a log $K_{ow} \geq 4$ is used to indicate a potential for bioaccumulation, therefore the log K_{ow} also indicates a low potential for bioaccumulation for carbendazim.

Aquatic toxicity

Acute toxicity

The next table shows information available for acute toxicity. Only valid studies are included here, supporting data included in the CLH dossier is not presented. All studies conducted with technical grade carbendazim (> 90%).

Method	Species	Results	Remarks	Reference
OECD TG 203	*Cyprinus carpio*	LC_{50} (96 h) = 0.44 mg/L nominal	Static	Anonymous, 1988a CLH_11_5_A7_4_1_1_1
OECD TG 203	*Oncorhynchus mykiss*	LC_{50} (96 h) = 0.83 mg/L mean measured	static	Anonymous, 1988b CLH_11_5_A7_4_1_1_2
OECD TG 204	*Oncorhynchus mykiss*	LC_{50} (96 h) > 0.56 mg/L nominal	Flow-through	Anonymous, 1989 A40788CLH_11_6_A7_4_3_1_1
ASTM	***Ictalurus punctatus***	**LC_{50} (96 h) = 0.019 mg/L nominal**	**static**	**Palawski, 1986 CLH_11_5_A7_4_1_1_3 Key study**
ASTM	*Oncorhynchus mykiss*	LC_{50} (96 h) = 0.87 mg/L nominal	static	Palawski, 1986 CLH_11_5_A7_4_1_1_3
ASTM	*Lepomis macrochirus*	LC_{50} (96 h) > 3.2 mg/L nominal	static	Palawski, 1986 CLH_11_5_A7_4_1_1_3
OECD TG 202	*Daphnia magna*	EC_{50} (48 h) = 0.15 mg/L nominal	static	Fischer, 1988 CLH_11_5_A7_4_1_2_1
OECD TG 201	*Desmodesmus subspicatus*	E_rC_{50} (72 h) > 8 mg/L nom. conc., max. water solubility	static	Heusel, 1991 CLH_11_5_A7_4_1_3_2

Two studies on acute toxicity of carbendazim in fish (Anonymous, 1988a,b) and a prolonged study in accordance with OECD TG 204 (Anonymous, 1989) have been evaluated in detail.

In Anonymous (1988a), *Cyprinus carpio* (Mirror carp) was exposed to carbendazim (99.4 %) OECD TG 203. Ten fish per tested concentration with an age of 11 – 13 month (3.4 – 4.2 cm length and a weight of 1.7 – 3.2 g) were exposed to nominal concentrations of 0.018, 0.032, 0.056, 0.10, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 mg carbendazim/L. The LC_{50} was 0.44 (0.33 – 0.58) mg/L. The validity criteria according to OECD TG 203 were met. The study was considered by the DS as acceptable with a reliability of 1.

In Anonymous (1988b), *Oncorhynchus mykiss* (Rainbow trout) was exposed to nominal concentrations of 0.32, 0.56, 1.0, 1.8, 3.2, 5.6, 10 mg/L in a first test (a) and in a second test (b), with 0.010, 0.018, 0.032, 0.056, 0.10 and 0.18 mg/L of carbendazim 99.4 %, both with

acetone as solvent for a duration of 96h (0.1 mL acetone/L). The test substance precipitated in the test media at concentration levels of 0.32 mg/L and higher, therefore the results refer to mean measured concentrations of the test substance with an LC_{50} (96h) = 0.83 mg/L calculated (with a 95 % confidence interval of 0.55 – 1.97 mg/L). The study fulfils the validity criteria according to OECD TG 203 and a reliability of 1 was given.

In Palawski (1986), carbendazim toxicity was assessed for three different fish species, *Oncorhynchus mykiss*, *Ictalurus punctatus* (Channel catfish) and *Lepomis macrochirus* (Bluegill) with 10 fish per test concentration and 96h of duration. Furthermore, additional test series were performed to determine effects of temperature, pH, water hardness and effects on early life stages on *O. mykiss* and *I. punctatus*. The study followed a static test design, analytical monitoring of test substance was not performed, and results for controls and data on validity of the test were not reported. However, the non-GLP study was performed according to an ASTM guideline. The study revealed for *I. punctatus* a LC_{50} (96h) of 0.019 mg/L (95 % confidence limit = 0.013 – 0.027 mg/L), for *O. mykiss* a LC_{50} (96h) of 0.87 mg/L (95 % confidence limit = 0.63 – 1.19 mg/L) and for *L. macrochirus* a LC_{50} (96h) > 3.2 mg/L, based on nominal concentrations of carbendazim. The study was considered by the DS as acceptable with a reliability of 2. As this study provided the lowest acute effect value for carbendazim for fish with 96h LC_{50} = 0.019 mg/L (nom.) for *I. punctatus*, this study was chosen as a key study.

Anonymous (1989) represents a prolonged study according to OECD TG 204 and was further prolonged to cover a period of 21 days. In the test no mortalities occurred up to the highest tested concentration within the first 96 h, consequently a LC_{50} > 0.56 mg/L can be derived from this study.

For aquatic invertebrates, Fischer (1988) assessed the toxicity of carbendazim to *Daphnia magna* in a static-acute toxicity test according to OECD TG 202 and following GLP. Four tests (test A, B, C, D) with two different vehicles (HCL and acetone) and with different series of test substance concentrations were performed. Test A had a concentration range from 0.1 to 1 000 mg/L with HCL as a vehicle. In Test B and C, the concentration ranged from 0.001 to 10 mg/L, using acetone as a vehicle. In Test D, test b was replicated using HCl as a vehicle. Out of these, test series 'D' was considered relevant for EC_{50} derivation. An EC_{50} = 0.15 mg/L was obtained based on nominal concentrations (concentrations within the HCL system remain within ± 20 of nominal).

Acute toxicity to algae (Heusel, 1991), was assessed based on a study without chemical analysis of test substance concentration. The study was performed with *Desmodesmus subspicatus* (formerly *Scenedesmus subspicatus*) following OECD TG 201 and in accordance with GLP. Cell growth was monitored at 24, 48 and 72 h. A high concentration range was covered (nom. 1.0, 1.8, 3.2, 5.6, 10,18, 32, 56, 100, 180, 320, 560 and 1000 mg/L), with the higher concentrations exceeding the maximum solubility of 8 mg/L in water, leading to a visible precipitate of the test substance. The highest concentration without precipitate, 10 mg/L, showed no effects on the test organism. Hence, it can be concluded that EC_{50} values are higher than the water solubility limit of carbendazim, E_rC_{50} > 8 mg/L. The study was considered as acceptable and reliable for aquatic hazard assessment.

Chronic toxicity

The next table shows information available for chronic toxicity. Only valid studies are included here, supporting data included in the CLH dossier is not presented here. All studies conducted with technical grade carbendazim (> 90%).

Method	Species	Results	Remarks	Reference
OECD TG 210	*Oncorhynchus mykiss*	NOEC (79 d) = 0.011 mg/L mean measured	flow-through	Anonymous, 1993 CLH_11_6_A7_4_3_2_1
OECD TG 202	*Daphnia magna*	NOEC (21 d) ≥ 0.01 mg/L nominal	semi-static	Fischer, 1988 CLH_11_6_A7_4_3_4_1
OECD TG 202	***Daphnia magna***	**NOEC (21 d) = 0.0015 mg/L mean measured**	**semi-static**	**Kelly et al. 1997 CLH_11_6_A7_4_3_4_2 Key study**
OECD TG 201	*Desmodesmus subspicatus*	NOE_rC (72 h) = 8 mg/L nom. conc., max. water solubility	static	Heusel, 1991 CLH_11_5_A7_4_1_3_2

Anonymous (1993) investigated long term toxicity to *O. mykiss* according to OECD TG 210 and GLP. Measured concentrations were within a range of 80 – 120 % of nominal concentrations, however test results have been recalculated on the basis of mean measured concentrations (0.00046, 0.0014, 0.0042, 0.011, 0.034, and 0.92 mg/L). Embryo survival, hatching data and larval mortality were recorded daily, length and weight of fish were measured at the end of the test. Based on embryo mortality after 79d, a NOEC of 0.011 mg/L and a LOEC of 0.034 mg/L were derived. The study was considered acceptable, reliability 2, due to the technical problems in the last week of the test.

A semi-static reproduction study with *Daphnia magna* (Fisher, 1988) was performed following OECD TG 202 and GLP. Daphnia were exposed to nominal concentrations of 0.001, 0.0018, 0.0032, 0.0056 and 0.01 mg/L and a solvent control was performed with each 10 animals per vessel and 4 replicates for 21d. Numbers of immobile parental animals and offspring as well as the development of embryos was determined three times a week. A reliability of 2 was given for this study since measured concentrations exceeded in most cases nominal concentrations (116 – 180 %). Due to the lack of effects observed and because for the highest concentration only a slight exceedance of nominal concentration was measured, a recalculation to mean measured concentrations was not considered necessary. A NOEC of ≥ 0.01 mg/L was derived from this study.

The reproduction study with *D. magna* (Kelly *et al*. 1997) was performed in accordance with mean measured concentrations were within a range of 81 to 106 % of nominal: 0.0015, 0.0046, 0.015, 0.045 and 0.19 mg/L. After 21 days a NOEC = 0.0015 mg/L for reproduction was derived, based on mean measured concentrations. The study was considered valid, reliability 1.

In Heusel (1991) (see study summary above), a NOEC = 8 mg/L was obtained for *D. subspicatus.*

DS conclusion on classification

Adequate acute toxicity data are available for all three trophic levels (fish, crustacean, algae/aquatic plants). The fish species *Ictalurus punctatus* LC_{50} = 0.019 mg/L (nominal concentration) was the most acutely sensitive species tested. Based on this value, the DS proposed classification as Aquatic Acute 1 (H400), M = 10 (considering 0.01 mg/L < LC_{50} ≤ 0.1 mg/L).

Carbendazim is considered as not rapidly degradable and has a low potential for bioaccumulation. Adequate chronic toxicity data are available for all three trophic levels (fish, crustacean, algae/aquatic plants). In the available data, invertebrates represent the most sensitive trophic level for chronic toxicity and a NOEC of 0.0015 mg/L for Daphnia magna was considered for classification.

Based on this value, the DS proposed classification as Aquatic Chronic 1, H410, with M = 10 (considering 0.001 mg/L < NOEC < 0.01 mg/L for non-rapidly degradable substances).

Comments received during public consultation

Two MSCAs commented on the CLH proposal. One MS agreed with the proposed classification. The other MS asked for further information to clarify the relevance and reliability of the Palawski (1986) and the use of *Ictalarus punctatus* data for acute classification. In addition, it asked for further clarification on the use of yolk sac fry data for classification.

The DS submitter provided further information on the study (see RCOM) and concluded that it is valid. Furthermore, it indicated within the same study there are further results for *O. mykiss* which perfectly match 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 Anonymous, 1984, vs. 96 h LC_{50} = 0.83 mg/L in Anonymous, 1988b).

In relation to the yolk sac fry data, the DS does not consider these results relevant for classification.

Assessment and comparison with the classification criteria

Rapid degradability

RAC agrees with the DS and considers the carbendazim to be **not rapidly degradable:** carbendazim is hydrolytically stable at pH 5 and 7. Hydrolysis half-life at pH 9 exceeds 16 days (~ 153 days). The substance is not readily biodegradable. In all simulation studies (water-sediment and soil), DT_{50} values were higher than 16 days (at 12 °C) and mineralisation did not reach 70 % within 28 days.

Bioaccumulation

RAC agrees with the DS and considers carbendazim as **non bioaccumulative**. The measured BCF_{fish} value of 27 L/kg does not exceed the trigger value of 500 L/kg and the measured log k_{ow} = 1.5 does not exceed the trigger value of 4.

Aquatic toxicity

RAC analysed the Palawski (1986) study (also published as Palawski and Knowles, 1986) and recognises that relevant data for its reliability assessment is missing, i.e.: Tested concentrations and control data were not provided and validity criteria cannot be checked.

Despite these shortcomings, RAC agrees with the DS and accepts the endpoint LC_{50} = 0.019mg/L for acute classification and considers the following regarding the acute data for the yolk sac fry endpoints:

- Although the data is not ideal, the acute endpoint is obtained following a standard test (ASTM) comparable to OECD TG 203. Aspects known for RAC such as fish size (1.2 g), temperature (22 ºC), feeding regime (no food was provided 24 hours before the test started and during the test), number of fish (10), observations (done every 24h) and water hardness are all within Guideline Requirements.
- The results presented within the study are plausible, in fact the results for *O. mykiss*, 96h LC_{50} = 0.87 mg/L, are in good agreement with the corresponding study by Fisher (1988), which provides 96h LC_{50} = 0.83 mg/L for the same species.
- 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 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 OECD TG 203 under REACH, although it can be used in a weight of evidence approach.

For acute aquatic classification RAC agrees with the DS and considers that adequate acute toxicity data are available for all three trophic levels (fish, crustacean, algae/aquatic plants).

Fish *Ictalurus punctatus* LC_{50} (96h) = 0.019 mg/L

Invertebrates *Daphnia magna*: EC_{50} (48h) = 0.15 mg/L

Algae *D. subspicatus* EC_{50} (72h) > 8 mg/L

The most sensitive species tested in the aquatic compartment is *Ictalurus punctatus* LC_{50} = 0.019 mg/L (nominal concentration). Based on this and considering that 0.01 mg/L < LC_{50} ≤ 0.1 mg/L, the substance fulfils the criterion for Acute classification and warrants classification **Aquatic Acute 1 (H400)**, **M = 10**.

For chronic aquatic classification RAC agrees with the DS and considers that adequate chronic toxicity data are available for all three trophic levels (fish, crustacean, algae/aquatic plants):

Fish, *O. mykiss* NOEC (79d) = 0.011 mg/L

Invertebrates*, Daphnia magna* NOEC (21d) = 0.0015 mg/L

Algae, *D. subspicatus* NOE_rC (72h) = 8 mg/L.

Hence, according to the classification criteria the classification for the long term aquatic hazards the substance being not rapidly degradable and with a NOEC of 0.0015 mg/L for *Daphnia magna* (0.001 mg/L < NOEC < 0.01 mg/L), carbendazim warrants classification as **Aquatic chronic 1 (H410), M = 10.**

It should be noted that on the basis of acute test results *O. mykiss* does not represent the most sensitive fish species under acute testing, as *I. punctatus* gives more conservative results. As only long-term data for *O. mykiss* are available, the hazard assessment cannot cover chronic data for the most acutely sensitive fish species. Using the acute data for *I. punctatus* in the surrogate approach, the same classification as that using the chronic invertebrate data (as proposed above) would be obtained.

Additional references

Palawski D.U., and Knowles C.O., 1986. Toxicological studies of Benomyl and Carbendazim in rainbow trout, channel catfish and bluegills. Environmental Toxicology and Chemistry, Vol. 5, pp. 1039-1046, 1986

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).