Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

3,3'-dicyclohexyl-1,1'-methylenebis (4,1-phenylene)diurea

EC Number: 406-370-3
CAS Number: 58890-25-8

CLH-O-0000001412-86-87/F

Adopted

4 December 2015

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CLH-O-0000001412-86-87/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 (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 harmonized classification and labelling (CLH) of:

Chemical name: **3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea**

EC Number: **406-370-3**

CAS Number: **58890-25-8**

The proposal was submitted by **Germany** and received by the RAC on **1 April 2015.**

In this opinion, all classifications and labelling are given in accordance with the CLP Regulation; the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer provided.

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 **5 May 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 June 2015**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Tiina Santonen**

Co-Rapporteur, appointed by RAC: **Katalin Gruiz**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation; the comments received are compiled in Annex 2. The RAC opinion on the proposed harmonized classification and labelling was reached on **4 December 2015**.

The RAC opinion was adopted by **consensus.**

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

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	616-094-00-7	3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea	406-370-3	58890-25-8	Skin Sens. 1 Aquatic Chronic 4	H317 H413	GHS07 Wng	H317 H413			
Dossier submitters proposal	616-094-00-7	3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea	406-370-3	58890-25-8	**Remove** Skin Sens. 1 Aquatic Chronic 4	**Remove** H317 H413	**Remove** GHS07 Wng	**Remove** H317 H413			
RAC opinion	616-094-00-7	3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea	406-370-3	58890-25-8	Aquatic Chronic 4	H413		H413			
Resulting Annex VI entry if agreed by COM	616-094-00-7	3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea	406-370-3	58890-25-8	Aquatic Chronic 4	H413		H413			

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

In the CLH report submitted to ECHA on April 2015, the Dossier Submitter (DS) proposed no classification for 3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea (Complex soap TH 28) for skin sensitisation. For the sake of brevity, the substance is referred to as Complex soap TH 28 throughout this opinion.

According to the DS, no classification for skin sensitisation was justified by the negative outcome of a mouse Local Lymph Node Assay (LLNA), performed in accordance with OECD TG 429 using Complex soap TH 28 i.e. corresponding to the substance registered under REACH.

According to the DS, there were no other studies for skin sensitisation on Complex soap TH 28. Furthermore, the DS stated that the current classification of Complex soap TH 28 as Skin Sens. 1; H317 may have been based on its impurities in earlier batches of former notifications. These include e.g. a residual amine (details not available), which is a potent skin sensitizer and has a harmonized classification according to annex VI of CLP.

The DS concluded that no classification was applicable for Complex soap TH 28 registered under REACH, but in case of similar substances with other impurities (e.g. due to different synthesis conditions), the potential impact of the impurities on the classification with respect to sensitisation had to be considered separately.

Comments received during public consultation

One member state questioned whether the skin sensitisation data were sufficiently complete to remove the current classification as Skin Sens. 1; H317, and emphasized that there was no information on what basis the substance had initially been classified as Skin Sens. 1; H317. No further comments were received.

The rapporteurs received information that the current classification of Complex soap TH 28 as Skin Sens. 1; H317 was based on the outcome of a previous skin sensitisation test (Buehler test), which was not included in the CLH dossier. The substance 3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea (EC number 406-370-3) was previously notified under the NONS Regulation (*i.e*. the EU Dangerous Substances Directive) and this skin sensitisation test was included in the NONS dossier. However, the data presented on the study in the NONS dossier were sparse. No information was available on the study date, the composition of the tested material or details on testing conditions. Positive reactions were seen in 7/20 animals at the 2nd reading upon challenge, but not after rechallenge, thus the outcome of the test was considered ambiguous.

In addition to the composition presented by the DS, another composition containing 1-5% of an isocyanate, which is classified as Skin Sens. 1, is also registered under REACH.

Assessment and comparison with the classification criteria

Local Lymph Node Assay

Complex soap TH 28 was tested for skin sensitisation in a Local Lymph Node Assay (LLNA) performed according to OECD TG 429 and EU Method B.42 (Török-Bathó, 2009).

Study design

Before conducting the study, six different vehicles were tested in order to select the one most compatible for the testing of Complex soap TH 28. The tested vehicles included a) acetone: olive oil 4:1 (v/v) mixture (AOO), b) N,N-dimethylformamide, c) ethyl-methyl-ketone, d) dimethyl sulfoxide, e) propylene-glycol, and f) n-hexane: olive oil 4:1 (v/v) mixture (HOO). The acetone: olive oil 4:1 (v/v) mixture (AOO) was identified as the most suitable vehicle, with a maximum available test item concentration of 10% (w/v). The test item was insoluble in all other solvents. In addition, a preliminary irritation/toxicity test was performed with Complex soap TH 28 in CBA/J@Rj mice at concentrations of 10% and 5% in AOO. The applicability and biocompatibility of the test item on ears of animals was found to be acceptable up to the maximum available concentration of 10%.

The LLNA was performed using sixteen female CBA/J@Rj mice, randomly assigned into four groups, with four animals in each group. The study groups were treated with Complex soap TH 28 in AOO at concentrations of 10%, 5% and 2.5%. The control group was treated with pure vehicle (AOO). The study protocol included application of the test item solution on the dorsal surface of the ears of the animals (25 µL/ear) for three consecutive days (days 1, 2 and 3). There was no treatment on days 4, 5 and 6. On day 6, the cell proliferation in local lymph nodes was determined by measuring the incorporation of tritiated methyl thymidine (3HTdR). Stimulation index (SI) values were calculated by comparing the methyl thymidine incorporation values obtained in each test group with the mean values of the vehicle control group, as stipulated in the test protocol.

Results

The results of the latest reliability check (performed within an interval of no longer than six months), were used to demonstrate the appropriate performance of the assay in accordance with the OECD TG 429. In the reliability check, the positive control substance α-hexylcinnamaldehyde (HCA) was examined at a concentration of 25% in the relevant vehicle. The SI-value with HCA was 4.9, indicating a significant lymphoproliferative response. This confirms the validity of the LLNA in the test laboratory.

After application of the 10% and 5% test item (Complex soap TH 28) solutions on ears of animals, a precipitate on the treatment area was observed. No mortality, systemic clinical signs, treatment-related effects on body weight, irritation, or other local effects were observed during the study.

In the LLNA performed with Complex soap TH 28, the calculated SI-values were 0.7, 0.5 and 0.5 at treatment concentrations of 2.5%, 5%, and 10%, respectively (table below). Thus, no significant lymphoproliferative response was observed, as SI was not ≥ 3 at any of the tested concentrations. No dose-response relationship was observed. The final outcome was that the test results were negative for skin sensitisation.

No human data were available on skin sensitisation.

Table: LLNA results, Complex soap TH 28 tested in female CBA/J@Rj mice

Test concentration	Stimulation Index (SI)	Result
2.5% Complex soap TH 28	0.7	Negative (SI < 3)
5% Complex soap TH 28	0.5	Negative (SI < 3)
10% Complex soap TH 28	0.5	Negative (SI < 3)
25% HCA (positive control)	4.9	Positive (SI ≥ 3)

Comparison with CLP classification criteria for skin sensitisation

According to OECD TG 429, SI-values ≥ 3 indicate a significant lymphoproliferative response. In the CLP regulation, for Skin Sens. category 1, an SI value of three or more is considered a positive response in an LLNA. Furthermore, an EC3 value (the estimated concentration of a test substance needed to produce a SI of three) ≤ 2% indicates a sub-category 1A classification is warranted, and an EC3 value > 2% indicates a sub-category 1B.

In the LLNA, Complex soap TH 28 did not induce any significant lymphoproliferative response. At each test concentration, the SI was < 3, meaning that the classification criteria for classification as Skin Sens. 1 are not fulfilled. No classification is therefore warranted for skin sensitisation for the substance 3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea (Complex soap TH 28) on the basis of the LLNA.

Conclusions

From the information available, the current classification of Complex soap TH 28 was based on a Buehler test, showing equivocal results which could not be evaluated further due to the scarce information on the study. The recent LLNA performed with 3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea (Complex soap TH 28) was clearly negative. Although the highest tested dose was only 10% (maximum soluble concentration in all tested vehicles), RAC considers the test reliable. On the basis of weight of evidence RAC concludes that **no classification is warranted for skin sensitisation** for this substance.

In the case of 3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea with a composition containing impurities classified for skin sensitisation, the impact of such on the classification should be considered separately by the manufacturer/importer/formulator according to the cut-off limits defined in the CLP Regulation Article 2(7) " *'substance' means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition*" and Article 11 "*Where a substance contains another substance, itself classified as hazardous, whether in the form of an identified impurity, additive or individual constituent, this shall be taken into account for the purposes of classification, if the concentration of the identified impurity, additive or individual constituent is equal to, or greater than, the applicable cut- off value in accordance with paragraph 3*".

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier submitter's proposal

The DS proposed to remove the existing classification: Aquatic Chronic 4.

The proposed removal was based on the comparison of the criteria against the substance data:

- Complex soap TH 28 is not acutely toxic in the range of its water solubility;
- Data revealed no chronic toxic effects below 1 mg/L;
- Complex soap TH 28 is not readily degradable;
- Complex soap TH 28 has the potential for bioaccumulation (indicated by a log Kow of 6.9);
- Toxicity results indicated that Complex soap TH 28 does not fulfil the criteria for environmental hazards according to the CLP Regulation by considering the scientific evidence showing classification to be unnecessary with a chronic toxicity NOEC > 1 mg/L derived from an algae test.

The water solubility of Complex soap TH 28 (4.47 mg/L) was determined using the shake flask method (OECD TG 105). It should however be noted, that the method used is not substance specific (DOC) which analyses the substance as such as well as potential impurities. Thus the real water solubility might slightly be lower than the values obtained.

Comments received during public consultation

Two Member State Competent Authorities (MSCA) commented on the proposal and both of them disagreed with the recommended removal of the classification of Complex soap TH 28 as Aquatic Chronic 4.

In the response following public consultation the removal of the environmental classification as Chronic 4 was no longer supported by the DS.

Assessment and comparison with the classification criteria

Classification as Aquatic Chronic 4 ("safety net" classification according to the CLP Regulation, Annex I: 4.1.2.6. Table 4.1.0) is appropriate when data do not allow classification under Aquatic Acute 1 or Chronic 1–3, but still, there are some grounds for concern. Such concerns include poorly soluble substances for which no acute aquatic toxicity is recorded at levels up to the water solubility, and which are not rapidly degradable and have an experimentally determined BCF ≥ 500 (or, if absent, a log Kow ≥ 4), indicating a potential to bioaccumulate. Complex soap TH 28 fulfils these criteria. Currently only one chronic toxicity NOEC above 1 mg/L is reported for algae and unfortunately, no data on chronic toxicity to fish and invertebrates is available. However, the situation could change were suitable scientific evidence to be provided in the future; chronic toxicity **NOECs** > water solubility and > 1 mg/L, would be required, to indicate that classification was not necessary.

Key studies: relevant information on test methods and toxicity endpoints

Method	Results	Remarks
Biodegradation OECD TG 301 A – old version Ready Biodegradability – Modified AFNOR Test	**Readily biodegradable** Not readily biodegradable 48% after 28 day	3 (not reliable) Test material (EC name): 3,3'-dicyclohexyl-1,1'-methylenebis(4,1-phenylene)diurea
Bioaccumulation	**Potential for bioaccumulation** log Kow = 6.9	The high log Kow indicates potential for bioaccumulation. No experimental bioaccumulation data are available.
Short-term toxicity to fish OECD TG 203 – Fish, Acute Toxicity Test; EU Method C.1 – Acute toxicity for fish	LC_{50} (96 h) > 4.47 mg/L based on water solubility	2 (reliable with restriction – no analytical monitoring) *Danio rerio* (zebra fish)
Long-term toxicity to fish	No fish data	No available data
Short-term toxicity to aquatic invertebrates OECD TG 202 – *Daphnia* Acute Immobilisation Test; EU Method C.2 – Acute toxicity for *Daphnia.*	EC_{50} (48 h) > 4.47 mg/L based on water solubility	2 (reliable with restriction – no analytical monitoring) *Daphnia magna* (water flea)
Long-term toxicity to aquatic invertebrates	No invertebrate data	No available data
Growth inhibition on algae EU Method C.3 – Algal Inhibition test and OECD TG 201 – Alga, Growth Inhibition Test	**ErC_{50}** (72 h) > 100 mg/L test material > 4.47 mg/L based on water solubility	2 (reliable with restriction – no analytical monitoring) for both studies Results are based on growth rate, determined using the water accommodated fraction (WAF): *Pseudokirchneriella subcapitata* (freshwater algae) and *Desmodesmus subspicatus* (freshwater algae).

According to the guidance on the application of the CLP criteria (Annex I.3.2, June 2015, version 4.1) sufficient evidence should be provided that the NOEC or equivalent EC_x **for each taxonomic group** is greater than 1 mg/L or greater than the water solubility of the substance under consideration in order to remove or lower a long-term aquatic classification. In addition to all these considerations, the water solubility value of 4.47 mg/L is also uncertain.

Overall, the RAC is of the opinion that the information on chronic aquatic toxicity and environmental fate do not at this point in time support "no classification" of Complex soap TH 28 and therefore considers the **grounds for removal of the classification as Aquatic Chronic 4 are not adequate**.

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 by RAC (excluding confidential information).