Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

N,N-DIMETHYLACETAMIDE (DMAC)

EC number: 204-826-4
CAS number: 127-19-5

CLH-O-0000004716-69-03/F

Adopted

12 September 2014

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

12 September 2014

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 harmonised classification and labelling (CLH) of:

Chemical name: **N,N-DIMETHYLACETAMIDE (DMAC)**

EC number: **204-826-4**

CAS number: **127-19-5**

The proposal was submitted by **The Netherlands** and received by the RAC on **28 November 2013.** All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS); the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer given.

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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 **13 December 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **27 January 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Christine Bjørge**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **12 September 2014** and the comments received are compiled in Annex 2.

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

OPINION OF THE RAC

The RAC adopted the opinion on **N,N-DIMETHYLACETAMIDE (DMAC)** that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					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	616-011-00-4	*N,N*-dimethylacetamide	204-826-4	127-19-5	Repr. 1B Acute Tox. 4 * Acute Tox. 4 *	H360D *** H332 H312	GHS08 GHS07 Dgr	H360D *** H332 H312		Repr. 1B; H360D: C ≥ 5 %
Dossier submitters proposal	616-011-00-4	*N,N*-dimethylacetamide	204-826-4	127-19-5						Removal of SCL for Repr. 1B
RAC opinion					n.a.	n.a.	n.a.	n.a.	n.a.	Removal of SCL for Repr. 1B
Resulting Annex VI entry if agreed by COM					Repr. 1B Acute Tox. 4 * Acute Tox. 4 *	H360D *** H332 H312	GHS08 GHS07 Dgr	H360D *** H332 H312		

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

Currently, DMAC is classified as Repr. 1B: H360: C≥ 5% under CLP and the Member State Committee has agreed on its identification as a Substance of Very High Concern. As a consequence, the DS proposes to review the specific concentration limits (SCL) for this substance.

According to the CLP Regulation, the GCL for Repr. 1B is ≥ 0.3%. The current criteria for setting SCLs are described in the 'Guidance on the Application of the CLP Criteria' (see sections 3.7.2.4.5, 3.7.2.5.5 and 3.7.2.5.6): the criteria include the potency group (defined based on the lower ED_{10}) and the presence of modifying factors.

In a number of studies in rats and rabbits, the lowest ED_{10}-value for effects warranting classification was 217 mg/kg bw/day. This ED_{10}-value corresponds to the medium potency group (4 mg/kg bw/day < ED_{10}-value < 400 mg/kg bw/day). Modifying factors were taken into account for a change in the potency group. However, no change was proposed because although DMAC produced severe effects, its ED_{10}-value was not close to the threshold for the high potency group (4 mg/kg bw/day).

The DS therefore proposed to remove the existing SCL (C ≥ 5.0%) for DMAC, in which case, the GCL of 0.3% would apply.

Comments received during public consultation

Two MSCA agreed on the proposed removal of SCL for DMAC. One MSCA commented on the derivation of the ED_{10}-values by the DS, which were the basis for the proposal for the SCL removal.

Assessment and comparison with the classification criteria

N,N-Dimethylacetamide (DMAC) has a harmonised classification for developmental toxicity as Repr. 1B; H360D with an SCL of 5.0%. According to the data on developmental effects following exposure to DMAC included by the DS in the CLH report, and based on the CLP guidance (Version 4 November 2013) for setting the SCL, the SCL of 5.0% should be removed and the GCL of 0.3% for substances classified in Repr. 1B should be applied.

Twelve reproductive toxicity studies were included by the DS in the CLH report for the assessment of removal of the SCL at 5.0%; seven in rats, two in mice and three in rabbits following oral or inhalation exposure. Three reproductive toxicity studies with dermal exposure to DMAC were also mentioned by the DS in the CLH report; two in rats and one in rabbits. However, the dermal studies were performed by a particular laboratory, considered by the DS to be known to have provided fraudulent reports to sponsors during the 1970's. These studies where therefore not assessed by the DS due to the absence of an independent verification of the study reports. Since RAC was unable to investigate this further, the studies were not taken into account in the substance evaluation.

Seven of the twelve studies were selected for deriving the ED_{10} values. According to the CLP Guidance, the ED_{10} value is the lowest dose which induces effects which fulfil the criteria for classification of reproductive toxicity with an incidence or magnitude of 10% after correcting for the spontaneous incidence. In the dose-response modelling used for deriving the ED_{10} values, the DS analysed studies together where the same test species and similar experimental setups were used. The DS explained that the advantage of pooling is that it gives a more precise end result, since it is based on more information. Pooling of data was performed for two rat and two rabbit developmental toxicity studies.

RAC supported the DS in the selection of the reproductive toxicity studies as well as the pooling of relevant studies used to derive ED_{10} values for DMAC. The studies selected were: one mouse oral single dose study with exposure to DMAC on gestation day 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 (BASF, 1975), one mouse (BASF, 1976a, 1976b), two rat (Johanssen et al., 1987 and Haskell Lab, 1997) and two rabbit (BASF, 1974 and Merkel and Zeller, 1980) oral developmental toxicity studies according to OECD TG 414, and one inhalation rabbit developmental toxicity study according to OECD TG 414 (Okuda et al., 2006). These study reports included sufficient information to derive ED_{10} values according to the requirements in the CLP Guidance for setting SCLs (section 3.7.2.5). The developmental effects used to derive ED_{10} values and which fulfilled the criteria for classification for developmental toxicity were malformations (in the head, whole body, heart, vessels and skeleton and cleft palate, fused ribs and microphtalmia).

There were two main reasons for not including the other developmental toxicity studies with oral or inhalation exposure to DMAC in the ED_{10} analysis. The first is that developmental effects were not shown in these studies which fulfilled the criteria for classification. The second that there was incomplete reporting of the studies, and therefore no ED_{10} values could be derived. According to the Guidance for setting SCLs (section 3.7.2.5.3.1), "For both developmental effects and on sexual function and fertility, the lowest ED_{10} for the effect(s) that fulfils the criteria for classification in the different studies, is then used as the ED_{10} that determine the potency of that substance."

RAC supported the DS in the selection of methods use to derive ED_{10} values, using the bench mark dose software (PROAST) and calculation by linear interpolation. Both methods are described in the CLP Guidance for setting SCL (section 3.7.2.5.3). In the benchmark approach, a dose-response model is fitted to the data, and this model is used for estimating the dose at a certain level of response. The use of the bench-mark dose software is considered to result in a more precise estimate of the $ED_{10,}$ because all data from the dose-response curve are used. Below are the estimated ED_{10} values from the selected studies, calculated both by the bench mark dose software (PROAST) and linear calculation with the LOAEL values given in the brackets.

- 597/596 (600) mg/kg bw/day (sum of visceral and skeletal malformations in mouse by oral route; BASF, 1975),
- 844/597 (1200) mg/kg bw/day (cleft palate in mouse by oral route; BASF 1976a and 1976b)
- 484/463 (400) mg/kg bw/day (fused ribs in mouse by oral route; BASF 1976a and 1976b)
- 358/400 (400) mg/kg bw/day (sum of malformations in head, whole body, heart, vessels and skeleton in rats by oral route; Johanssen et al., 1987)
- 332/264 (400) mg/kg bw/day (malformations in heart and great vessels in rats by oral route; Johanssen et al., 1987)
- 217/185 (400) mg/kg bw/day (sum of malformations in head, whole body, heart, vessels and skeleton in rats by oral route; pooled from both Johanssen et al., 1987 and Haskell Lab 1997 when derived by PROAST and from Haskell Lab only for linear interpolation)
- 244/194 (400) mg/kg bw/day (heart and great vessels malformations; pooled from both Johanssen et al., 1987 and Haskell Lab 1997 when derived by PROAST and from Haskell Lab only for linear interpolation)
- 284/239 (282 in both studies) mg/kg bw/day (sum of malformations, cleft palate, fused ribs and microphtalmia in rabbits by the oral route; pooled from both BASF, 1974 and Merkel and Zeller, 1980 when derived by PROAST and from Merkel and Zeller study only for linear interpolation)
- 387/413 (287) mg/kg bw/day (total heart/great vessel malformations in rats by inhalation; Okuda et al., 2006)

From the ED_{10} values derived by PROAST and with calculation by linear interpolation it can be seen that the ED_{10} values are in the same range for both methods used and that malformations were reported in the same organs in several of the selected studies. According to the CLP Guidance, the lowest ED_{10} value of all the selected studies for effects warranting classification determines for the overall ED_{10} of the substance. RAC agreed that for DMAC this was the ED_{10} values of 217 mg/kg bw/day (derived by PROAST for the sum of malformations in the oral developmental toxicity study

in rats using pooled samples from Haskell Lab, 1997 and Johanssen et al., 1987) and 185 mg/kg bw/day (derived by linear interpolation from the Haskell Lab, 1997 study).

The ED_{10} values derived for DMAC by the DS and agreed by RAC corresponded to the medium potency group (i.e. 4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day).

According to the CLP Guidance for setting SCLs (section 3.7.2.5.5) modifying factors should also be considered when deriving a SCL. The modifying factors include type and severity of the effect observed, data availability (e.g. limitations in the database), dose-response relationship, mode or mechanism of action, toxicokinetics and bioaccumulation of substances. These modifying factors are used to account for case-specific data situations which indicate that the potency group for a substance as obtained by the preliminary assessment should be changed. The modifying factors were assessed for DMAC as follows:

Type and severity of the effect:

The type of effects observed in reproductive toxicity studies following exposure to DMAC included severe malformations in three species (rat, mouse and rabbit) and were considered as severe. However, the ED_{10} was not close to the threshold dose for a higher potency group (not close to 4 mg/kg bw/day). Therefore, this does not change the potency group.

Data availability:

The available data for DMAC was considered more than adequate compared to the REACH requirements and does not justify adaptation of the potency group.

Dose-response relationship:

DMAC showed a steep dose-response relationship and no adaptation of the potency group was considered necessary.

Mode or mechanism of action:

No conclusive information was available on the mode or mechanism of action of DMAC for the induction of malformations. Therefore adaptation of the potency group was not necessary.

Toxicokinetics:

There were no data available that indicate that DMAC data from animals would not be relevant for humans and no adaption to the potency group is needed.

Bio-accumulation of substance:

DMAC was not considered to be a bio-accumulating substance from the data available in the CLH dossier and from the registration dossier.

Conclusion on modifying factors:

Based on the available data, RAC considered that no modifying factors were considered necessary that can affect the potency of DMAC. Therefore, DMAC is considered a medium potency reproductive toxicant.

RAC agreed that the data for setting concentration limits (CL) for developmental toxicity for DMAC clearly shows that DMAC corresponds to the medium potency group (i.e. 4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day; CLP Guidance table 3.7.2-d) and according to CLP Guidance (table 3.7.2-e) a CL of 0.3% should be applied for DMAC.

Since DMAC is classified according to CLP as Repr. 1B, the CL of 0.3% is the same as the GCL for Repr. 1B substances. RAC considers therefore that the current SCL of 5% should be removed and the GCL should be applied for DMAC.

ANNEXES:

Annex 1 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 rapporteurs' comments (excl. confidential information).