**Committee for Risk Assessment**

**RAC**

# Opinion

proposing harmonised classification and labelling
at EU level of
**1-methyl-2-pyrrolidone (NMP)**

**EC number: 212-828-1**
**CAS number: 872-50-4**

CLH-O-0000004066-78-03/F

**Adopted**

**6 June 2014**

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06 June 2014

CLH-O-0000004066-78-03/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 harmonised classification and labelling (CLH) of:

**Chemicals name: 1-methyl-2-pyrrolidone (NMP)**

**EC number: 212-828-1**

**CAS number: 872-50-4**

The proposal was submitted by **The Netherlands** and received by the RAC on **13 August 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 **27 August 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **11 October 2013**.

### 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 **06 June 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 **1-methyl-2-pyrrolidone (NMP)** 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 | 606-021-00-7 | *N*-methyl-2-pyrrolidone; 1-methyl-2-pyrrolidone | 212-828-1 | 872-50-4 | Repr. 1B<br>Eye Irrit. 2<br>STOT SE 3<br>Skin Irrit. 2 | H360D***<br>H319<br>H335<br>H315 | GHS08<br>GHS07<br>Dgr | H360D***<br>H319<br>H335<br>H315 | | Repr. 1B;<br>H360D: C ≥ 5 %<br>STOT SE 3;<br>H335: C ≥ 10 % |
| Dossier submitters proposal | 606-021-00-7 | *N*-methyl-2-pyrrolidone; 1-methyl-2-pyrrolidone | 212-828-1 | 872-50-4 | | | | | | Removal of SCL for Repr. 1B |
| RAC opinion | 606-021-00-7 | *N-methyl-2-pyrrolidone; 1-methyl-2-pyrrolidone* | 212-828-1 | 872-50-4 | | | | | | Removal of SCL for Repr. 1B |
| Resulting Annex VI entry if agreed by COM | 606-021-00-7 | *N*-methyl-2-pyrrolidone; 1-methyl-2-pyrrolidone | 212-828-1 | 872-50-4 | Repr. 1B<br>STOT SE 3<br>Skin Irrit. 2<br>Eye Irrit. 2 | H360D***<br>H335<br>H315<br>H319 | GHS08<br>GHS07<br>Dgr | H360D***<br>H335<br>H315<br>H319 | | STOT SE 3;<br>H335: C ≥ 10 % |

# SCIENTIFIC GROUNDS FOR THE OPINION

## HUMAN HEALTH HAZARD ASSESSMENT

## RAC evaluation of reproductive toxicity

### Summary of the Dossier submitter's proposal

The substance has an entry in Annex VI of the CLP Regulation including Repr. 1B H360D with a specific concentration level (SCL) of 5%. The proposal of The Netherlands is to remove this SCL. The basis for the proposal is that the current guidance on setting SCLs is not deemed to support an SCl greater than the general concentration limit (GCL).

Data is presented from 16 studies in rats and rabbits for oral, dermal and inhalation routes. The $ED_{10}$ (bench mark dose) in these studies ranges from 225 to 626 mg/kg bw/day. As the cut-off for low potency reprotoxicants in the CLP guidance is 400 mg/kg bw/day, the DS argues that the criteria for setting a higher SCL are not fulfilled.

### Comments received during public consultation

Comments were received from seven MS, all in support of the proposal. During public consultation a new study (Sitarek et al, 2012) was submitted The study was summarised and discussed by the dossier submitter in the RCOM document.

### Assessment and comparison with the classification criteria

#### *Comparison with the criteria*

1-Methyl-2-pyrrolidone (NMP) has a harmonised classification for developmental toxicity as Repr. 1B; H360D with a SCL of 5%. According to the data on developmental effects following exposure to NMP included in the CLH report by the DS, and based on an analysis of this data according to the guidance for setting SCLs in the CLP Guidance (November 2013) the SCL which is currently set at 5.0% should be deleted.

Sixteen reproductive toxicity studies were included in the CLH report by the DS, thirteen in rats and three in rabbits and these involved oral, inhalation and dermal exposure. Three of these studies were selected for deriving $ED_{10}$ values. The $ED_{10}$ value was also derived by the DS (as reported in the RCOM) from a study submitted during the public consultation (Sitarek et al., 2012). The $ED_{10}$ value, according to the CLP Guidance, is the lowest dose which induces reproductive toxic effects which fulfil the criteria for classification of reproductive toxicity with an incidence or magnitude of 10% after correction of the spontaneous incidence.

RAC agrees with the DS on the reproductive toxicity studies selected for analysis. The key studies selected were a rat and rabbit developmental toxicity study and a rat 2-generation study, all involving oral administration. A second 2-generation study was also evaluated by the DS, but this study was not included in the analysis since similar results were observed to those in the first 2-generation study. These study reports included sufficient information to derive $ED_{10}$ values according to the requirements in the CLP Guidance for setting SCL (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 post-implantation losses, effects on the cardiovascular system and foetal mortality. There were two main reasons for not including the other developmental toxicity studies with oral, inhalation or dermal exposure to NMP in the $ED_{10}$ analysis. (1) developmental effects were not shown in these studies that fulfil the criteria for classification, and (2) developmental effects occurred at higher doses than in the studies included for deriving $ED_{10}$ values. According to the Guidance for setting SCL, 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 agreed with the DS in the selection of the methods use to derive the required $ED_{10}$ values, i.e. the benchmark dose software (PROAST) and calculation by linear interpolation. Both methods are described in the Guidance for setting the 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 particular 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. The estimated $ED_{10}$ values from the three selected key studies both calculated by the bench mark dose software (PROAST) and by linear interpolation are given below.

The $ED_{10}$ values for the most severe developmental effects from the key studies selected by the DS derived by bench mark dose software were 520 mg/kg bw/day (post-implantation loss, Saillenfait AM et al., 2001, 2002), 225 mg/kg bw/day (post-implantation loss, IRDC, 1991) and 263 mg/kg bw/day (complete litters lost at the end of the lactation period in rats, BASF AG, Department of Toxicology, 1999). For the same developmental effects from the three key studies the $ED_{10}$ values calculated by linear interpolation were 511 mg/kg bw/day (post-implantation loss, LOAEL 500 mg/kg bw/day), 301 mg/kg bw/day (post-implantation loss, LOAEL 540 mg/kg bw/day) and 205 mg/kg bw/day (complete litters lost at the end of the lactation period, LOAEL 500 mg/kg bw/day), which showed that the $ED_{10}$ values were in the same range for both methods used. According to the CLP Guidance, the lowest $ED_{10}$ value of all the key studies for effects warranting classification determines the overall $ED_{10}$ of the substance. RAC agreed that for NMP this was the $ED_{10}$ values of 225 mg/kg bw/day derived by PROAST for post-implantation loss in the developmental toxicity study in rabbits (IRDC, 1991), and 205 mg/kg bw/day derived by linear interpolation for complete litters lost at the end of the lactation period in rats (BASF AG, Department of Toxicology, 1999).

The $ED_{10}$ values from the Sitarek et al. (2012) study submitted during Public Consultation were calculated by the DS by linear intrapolation based on pup mortality. The calculated $ED_{10}$ values were 199 and 84 mg/kg bw/day for indices of pup viability on pnd 4 and on pnd 21, respectively. The $ED_{10}$ values from the Sitarek et al. (2012) study were shown to be lower than the $ED_{10}$ values included in the CLH report. However, there were some uncertainties concerning whether the effect on pup mortality was a true developmental effect since it could also be related to an effect of NMP during lactation.

The $ED_{10}$ values included by the DS and in Sitarek et al. (2012) corresponded to the medium potency group (i.e. within the range: 4 mg/kg bw/day < $ED_{10}$ value < 400 mg/kg bw/day) for NMP. Furthermore, the oral rabbit study and the rat 2-generation study included additional $ED_{10}$ values corresponding to the medium potency group (i.e. 337 mg/kg bw/day for an interventricular septal defect, 379 mg/kg bw/day for a bulbous aortic arch, 263 mg/kg bw/day for complete litters lost at the end of the lactation period and 360 mg/kg bw/day for pup mortality).

According to the CLP Guidance (section 3.7.2.5.5) for setting SCL, 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 situations where the data indicate that the potency group for a substance as obtained by the preliminary assessment should be changed. The modifying factors were assessed for NMP as follows:

Type and severity of the effect:

The type of effects observed in reproductive toxicity studies following exposure to NMP included post-implantation loss, malformation and foetal mortality and were considered to be severe. However, the $ED_{10}$ was not close to the boundary of a higher potency group (ie not close to 4 mg/kg bw/day). Therefore, this did not change the potency group.

Data availability:

The data available for NMP were considered more than adequate considering the REACH requirements and did not justify adaptation of the potency group.

Dose-response relationship:

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

Mode or mechanism of action:

No information was available on the mode or mechanism of action of NMP for the induction of developmental effects. Therefore adaptation of the potency group was not necessary.

Toxicokinetics:

The lowest $ED_{10}$ derived by the most precise method (PROAST) was from the rabbit oral developmental toxicity study (225 mg/kg bw/day) and a comparison of the kinetics of NMP after oral exposure in rabbit and human (if known) should be taken into account for the determination of the potency group for NMP. For humans, some information was available on the kinetics of NMP after oral exposure. However, this was limited to a study assessing the metabolic pathway of NMP. For rabbits, information on the kinetic profile of NMP after oral exposure was not found. A comparison between kinetics in humans and rabbits after oral exposure to NMP is therefore not considered possible. Therefore, no adaptation is needed.

Bio-accumulation of substance:

NMP 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 necessary which could affect the assessment of the potency of NMP. Therefore, NMP was considered a medium potency reproductive toxicant.

## *Conclusion*

RAC agrees that the data for setting SCLs for developmental toxicity for NMP clearly shows that NMP corresponds to the medium potency group (i.e. boundaries: 4 mg/kg bw/day < $ED_{10}$ value < 400 mg/kg bw/day, CLP Guidance table 3.7.2-d). According to CLP Guidance table 3.7.2-e, an SCL of 0.3% should be applied for NMP. However, since NMP is classified according to CLP as Repr. 1B, the SCL of 0.3% is the same as the GCL for Repr. 1B substances. RAC therefore considers that the current SCL of 5% should be removed and the GCL should be applied for NMP.

## References

Sitarek K., Stetkiewicz J., Wasowicz W., 2012. Evaluation of Reproductive Disorders in Female Rats Exposed to N-Methyl-2-Pyrrolidone. Birth Defects Res (Part B) 95:195-201, 2012.

## 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).