Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

N-ethyl-2-pyrrolidone (NEP)

ECHA/RAC/CLH-O-0000002192-83-01/F

Adopted

29 November 2011

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

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

Substance Name: ***N-ethyl-2-pyrrolidone (NEP)***

EC Number: ***220-250-6***

CAS Number: ***2687-91-4***

The proposal was submitted by ***France***
and received by RAC on ***25 March 2011***.

Harmonised classification proposed by the dossier submitter

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI CLP Regulation	-	-
Current proposal for consideration by RAC	Repr. 1B – H 360D	Repr. Cat. 2; R61
Resulting harmonised classification (future entry in Annex VI of CLP Regulation)	Repr. 1B – H 360D	Repr. Cat. 2; R61

PROCESS FOR ADOPTION OF THE OPINION

France 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on ***25 March 2011***. Parties concerned and MSCAs were invited to submit comments and contributions by ***9 May 2011***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Thomasina Barron***

Co-rapporteur, appointed by RAC: ***Teresa Borges***

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

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***29 November 2011*** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment.

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

OPINION OF RAC

The RAC adopted the opinion that ***N-ethyl-2-pyrrolidone (NEP)*** should be classified and labelled as follows:

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 state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state ment Code(s)	Suppl. Hazard statement Code(s)		
-	N-ethyl-2-pyrrolidone (NEP)	220-250-6	2687-91-4	Repr. IB	H360D	GHS08	H360D	-	NA	

Classification and labelling in accordance with the criteria of Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
-	N-ethyl-2-pyrrolidone (NEP)	220-250-6	2687-91-4	Repr. Cat. 2; R61	TR: 61S: 45-53	NA	

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by *France*.

Background

N-ethyl-2-pyrrolidone is an industrial solvent, catalyst and surfactant. A classification proposal relating to the reproductive toxicity has been submitted by France as follows. No other endpoint will be addressed.

Proposal of the dossier submitter

Reproductive Toxicity

A significant data base of experimental animal studies were submitted by the notifier and evaluated by the dossier submitter (DS). These include both dermal (BASF 2010) and oral gavage (BASF 2007a/BASF 2007b) studies in the rabbit and oral gavage (Saillenfait 2007) and dermal (BASF 2005) studies carried out in the rat. All data were either compliant or consistent with current OECD guidelines. In addition, the developmental profile of a closely related substance N-methyl-2-pyrrolidone (NMP) currently classified as Cat 1B H360 (1st ATP CLP) and Repr. Cat.2; R61 (31st ATP Directive 67/548/EEC and) was included for comparative purposes. Based on the animal studies carried out, it was clearly demonstrated that NEP induces:

- adverse effects on foetal body weights in rabbits by oral route, in rats by dermal route and in rats by oral route

- effects on post-implantation loss and in particular late resorptions in rats by oral route.

- malformations in rabbits by dermal and oral route and in rats by oral route.

There was a significant increase in skeletal malformations by oral route in both rats and rabbits. Besides, rare cardiovascular malformations were observed above historical controls in rabbit by dermal and oral routes and in rats by oral route. On this basis, it is concluded that there is clear evidence of teratogenic and foeto-toxic effects of NEP.

Developmental effects of NEP and in particular the profile of malformations observed in the rat by oral route, are similar to the developmental effects observed with NMP, which strengthen the weight of evidence that the effects observed in the NEP studies are related to administration of the test substance.

It is noted that the decrease in foetal weight in the rat and in the rabbit by oral route, the induction of late resorptions in the rat by oral route and of malformations in rabbit by dermal and oral route and in rat by oral route cannot be correlated to a limited maternal toxicity. While maternal toxicity was clearly demonstrated, the possibility that the serious specific malformations and developmental toxicity may be treatment-related cannot the discounted. Such an effect must be critically assessed irrespective of maternal toxicity. Such malformations and other adverse developmental effects observed cannot be considered as consequential on maternal toxicity. The similarity of effects between NEP and NMP also support that these effects are an intrinsic property of these compounds.

A classification Repr. 1B –H360D is warranted (Repr. Cat. 2; R61 according to Directive 67/548/EEC). As no developmental study is available by inhalation, it is proposed not to specify route of exposure in the hazard statement.

Guidelines to set specific concentration limits (SCL) for reproductive toxicity are currently under discussion. In absence of adopted guidelines at this point in time, no SCL are proposed.

Comments submitted during the public consultation

The comments received from a number of Member States were in support of the dossier submitter's classification proposal. A number of Member State Competent Authorities (MSCAs) pointed out that the designation of H360D instead of the general statement H360 was incorrect. According to the CLP Guidance Document (Section 3.7.4.1) only the general statement can be applied in the absence of specific reliable and adequate data on fertility which excludes this effect. This point was agreed by the DS and the draft of CLH report was amended accordingly.

The industry comment was in general support of the classification proposal. A reference was made by the industry federation CEFIC to new data (28 day inhalation study OECD 412) which they considered relevant to fertility (CEFIC 6/5/2011 Annex 2 Draft RCOM). Reference was also made to a 2 generation study protocol. Industry suggested that the current consultation should await the results of these studies when completed. In addition, it was proposed that due to similarity (structural and toxicity profile) to NMP which is classified as GHS Repro. Cat 1B H360D with a specific concentration limit of >5%, the same concentration limit should be applied to NEP.

Outcome of RAC consultation

RAC supports the classification proposal of the dossier submitter.

The original labelling proposal of the dossier submitter was allocation of H360D, which was amended to H360 in the revised CLH Report following comments made during the public consultation. There were different opinions on this issue raised at RAC 17 and during the written follow up (ORCOM). RAC agreed upon the allocation of 'D' to specify the development endpoint, i.e., H360D. This is in line with a number of previous RAC recommendations where only one of the two reproductive endpoints has been addressed. The rationale is that the relevant positive adverse effect should be identified in the labelling phrase to offer greater protection to the user, even though it is acknowledged that this procedure is not strictly in line with the guidelines.

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)[1]
Annex 2	Comments received on the CLH report, response to comments provided by the dossier submitter and RAC comments (excl. confidential information)

[1] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.