Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at Community level of

N-ethyl-2-pyrrolidone (NEP)

ECHA/RAC/CLH-O-0000002192-83-01/A2

Adopted

29 November 2011

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: N-ethyl-2-pyrrolidone (NEP)
CAS number: 2687-91-4
EC number: 220-250-6

General comments

Date	Country / Person / Organisation / MSCA	Comment	Response of the dossier submitter	RAC comments
29/04/2011	Denmark / Trine Thorup Andersen / Member State	p. 4: Proposal for harmonised classification and labelling: Denmark agrees with the proposed classification for N-ethyl-2-pyrrolidone (NEP), CAS No. 2687-91-4	Your support is noted.	
06/05/2011	Germany / Matthias Plog / Member State	The German CA supports the proposed classification. The report focuses exclusively on developmental toxicity. We agree to the proposed classification Repr. 1B - H 360D according to Regulation (EC) 1272/2008 (CLP) and Repr. Cat. 2; R61 according to directive 67/548/EEC, respectively. There is clear evidence in two species for developmental toxicity. In Rabbits NEP has adverse effects on foetal body weights after oral (220 mg NEP/kg/d) application. Furthermore, malformations have been caused by NEP after oral (200 mg NEP/kg/d) and dermal (1000 mg NEP/kg/d) application in rabbits. In Rats NEP has adverse effects on foetal body weight after dermal (800 mg NEP/kg/d) and oral (250 mg NEP/kg/d) application. NEP increases post-implantion loss and late resorptions. Finally, NEP causes malformations in rats after oral (500 mg NEP/kg/d) treatment. NEP caused rare cardiovascular malformations in rats and rabbits, the incidence was higher compared to the historical controls. Maternal toxicity appeared as mild to transient deficiencies in body weight gain. In the discussion it becomes evident that the above mentioned effects on development can not be considered secondary to maternal toxic	Your support is noted.	

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		effects. In the IUCLID file some data are missing and should be added for consistency: - Chapter 1.2: The identity is not stated in detail. The concentrations of the Impurities are not known. - Chapter 4: The physico-chemical properties are only stated in the report. They should also be included in the IUCLID file.	Information in the CLH dossier is based on literature and MSDS. Data from the registration dossiers have been included in a confidential Annex to the CLH report. The inclusion of physical-chemical properties into is not a requirement for a CLH dossier and information is available in the CLH report.	All physico-chemistry data should be included in the IUCLID file Sufficient information is included in the CLH report for the purpose of classification discussions.
06/05/2011	Belgium / Walter Cremers / CEFIC / Industry or Trade Association	Dear Sir or Madam: On behalf of the Cefic BDO and Derivatives Sector group we submit the following comments on the Annex VI report, the Proposal For Harmonized Classification And Labeling of N-Ethylpyrrolidone (CAS Number: 2687-91-4; EC Number: 220-250-6). Basically we agree that "NEP induces adverse effects in rabbits and rats by oral route." Due to the available studies for NEP we agree with GHS Repro. Cat1B H360D via the oral route. Due to the similarity with NMP, CAS 872-50-4 we propose a concentration limit for Repro. Cat 1B of $\geq$ 5%.	Your support regarding classification is noted. Guidelines to set specific concentration limits (SCL) for reproductive toxicity are currently under discussion. In absence of adopted	Support noted.

Date	Country / Person / Organisation / MSCA	Comment	Response of the dossier submitter	RAC comments
			guidelines at this point in time, no SCL are proposed.	The RAC agrees with the DS
		NMP and NEP are similar compounds but also have distinct differences. Due to the differences in study design over time, particularly with respect to the data available and relevant to the assessment of maternal toxicity, the application of NMP data to the assessment of the developmental toxicity classification of NEP is inappropriate. NEP is not a developmental toxicant via the dermal route of exposure. Any developmental effect described in the dermal developmental toxicity studies is clearly linked to overt maternal toxicity or falls within the range of historical control data.(Details see specific comments below).	See response to specific comments below.	
		Fertility effects are not covered in the CLH dossier yet. There are new data for exposure via the inhalation route relevant for fertility (28d study according to OECD412, experimental phase completed 21.03.2011 – final study report expected mid of 2011). This has already been notified to France (Philippe Juvin and Elodie Pasquier (ANSES) 08.02.2011 16:49) and ECHA (Comment to ECHA on NEP 2 generation study testing proposal 11.03.2011). Consequently we suggest awaiting the final result before concluding any harmonized classification and labeling for the reprotoxicity of NEP.	The CLH dossier focus on developmental toxicity of NEP and these data are not expected to impact assessment of developmental toxicity of NEP.	RAC considers that the new data referred to by the notifier with regard to fertility should be used to expand the current discussion to include fertility.
		If there are still open questions on Cefic BDO group comments please do not hesitate to contact us. We will make the study director available for Echa or French CA to discuss all BASF studies e.g. historical controls, raw data etc. Sincerely, Walter Cremers Secretary General BDO and Derivatives Sector Group. wcr@cefic.be Specific comments on the C&L Dossier:		
		1. Specific comments on the conclusions for the dermal and oral studies in rabbit and rat: a.) Rabbit dermal application (study report 44R0033/04110; NEP, rb, dermal, BASF 2010) Generally various external and skeletal malformations occurred throughout all test groups including the control in	We agree with this analysis for external and skeletal malformations.	RAC agrees with DS

Date	Country / Person / Organisation / MSCA	Comment	Response of the dossier submitter	RAC comments
		the dermal developmental study (study report 44R0033/04110; NEP, rb, dermal). Malformations showed neither a consistent pattern since a number of morphological structures of different ontogenic origin were affected nor a clear dose-response relationship. Furthermore, the overall incidences were comparable to the historical control data. Thus, none of the observed malformations can be considered to be related to the treatment but have to be taken as a spontaneous naturally occurring background rate. Clinically, the food consumption at the 1000 mg/kg does was statistically significantly reduced (up to 42% below the corresponding control on GD 6-17, 17% if calculated for the entire treatment phase). The high dose rabbits showed a distinct weight loss at initiation of treatment (-15 grams on GD 6–9) and impaired weight gain thereafter (61% below control for GD 9–11), and recovered afterwards. In conclusion there was clear general maternal toxicity at 1000 mg/kg in the sensitive phase of organogenesis. p. 13 French C&L dossier, dermal rabbit study (BASF 2010), cardiovascular malformations: In the high dose group (1000 mg/kg bw/d) a ventricular septum defect was found in 2 fetuses; one also with absent subclavian. Both malformations (each n = 1) are described also in the historical controls: „membraneous ventricular septum defect“ in the study report 44R0033/04110 (NEP, rb, dermal) and „absent subclavian“ in 40R0033/04058 or 40R/033/04075 (NEP, rb, oral). Furthermore, the three fetuses, which showed dextrocardia, were of one litter. This defect was also found in the control group of the oral study (40R/033/04075) demonstrating the spontaneous nature of this finding. Considering the transient but relevant maternal toxicity at 1000 mg/kg bw/d , as well as historical control data (described above) an association of the cardiovascular malformations to NEP as is assumed in the French CLH dossier can not be concluded. □ NOAEL (dermal, rb, mat.tox.) = 300 mg/kg bw/d NOAEL (dermal, rb, dev.tox.) = 1000 mg/kg bw/d	We agree that transient maternal toxicity is observed at initiation of treatment. See below the table for further details on the analysis of cardiovascular malformations in the rabbit. The cardiovascular malformations observed at high dose in the rabbit dermal study (BASF 2010) and at 220 mg/kg in the second rabbit oral study (BASF 2007b) are considered to be related to treatment. Besides, it is not considered that transient general toxicity can be linked to specific malformations such as cardiovascular	RAC agrees with DS RAC agrees with DS

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			malformations.	
		b.) Rabbit oral application (study report 40R0033/04058 + 40R0033/04075; NEP, rb, oral, BASF 2007 a+b) p. 16 and 19/20: oral rabbit studies (BASF 2007 a+b) In the CLH report, the maternal toxicity is described as „a slight maternal toxicity with transient significant effects on food consumption and bw gain". But there was also a substance-induced liver weight increase in the high dose groups (200 or 220 mg/kg bw/d, respectively). Furthermore, the clinical chemistry showed increased alanin aminotransferase (ALT) and gamma-glutamyltransferase (GGT) activities in the high dose groups and high ALT activities also at 60 mg/kg bw/d, indicating mild liver damage.	The effects on liver weight and hepatic enzyme activity are indicative of adaptative metabolism and of mild liver damage. They are not considered as a toxic effect in the meaning of the CLP that could secondarily induce developmental effect and could prevent consideration of the developmental effects for classification.	RAC agrees with DS
		This is a hint that oral exposure leads to toxicological effects at lower applied doses than dermal exposure. Considering the similarity to NMP, CAS 780-50-4, with a dermal absorption of 67.9% the estimated effective dermal NEP uptake is 700 mg/kg bw/d in the dermal rabbit study.	Comparing the maternal toxicity of the oral and dermal teratogenicity studies in rat and rabbit it can be concluded that absorption via skin is less than via the oral route for NEP. Besides, available data from the registration dossiers of NMP	RAC agrees with DS

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			show that the dermal absorption in rats of NMP in aqueous solutions vary from 15% to 77% depending on the study and NMP concentration tested.	
		In the French CLH dossier it is concluded that cardiovascular malformations, described at 1000 mg/kg bw/d in the dermal rabbit study, were found at the highest oral dose (220 mg/kg bw/d) as well. We disagree with this conclusion and find that the cardiovascular malformations described in the study report were of spontaneous nature for the reasons previously stated above, specifically that cardiovascular malformations occurred in the control as well and showed neither a consistent pattern nor a clear dose-response relationship up to 200 mg/kg. At 220 mg/kg visceral malformations were rather unspecific and effecting multiple organs. Skeletal malformations can be considered the characteristic malformation type observed in studies of NEP in rabbit and rat. However the skeletal malformations and variations as described in the study reports at 200 and 220 mg/kg bw/d are not mentioned in the summary and discussion part of the CLH report (p.36/37). Since no increases in skeletal malformations above background occurred after dermal application, the data support the conclusion that dermal exposure to NEP does not lead to any developmental toxicity. □ NOAEL (oral, rb, mat.tox.) = 60 mg/kg bw/d NOAEL (oral, rb, dev.tox.) = 60 mg/kg bw/d	See detailed comments below the table. Induction of skeletal malformations in rabbit by oral route is considered in the discussion (see first line of the second paragraph in page 39 of the revised CLH) and in the weight of evidence for classification in Repr 1B.	Agreed RAC agrees with DS .
		c.) Rat dermal application (study report 34R0033/040; NEP, rt, dermal, BASF 2005) p. 22 French CLH dossier, dermal, rat study (BASF 2005): Significant maternal toxicity was found in the high dose group (800 mg/kg bw/d). Food consumption of the 800 mg/kg does was statistically significantly reduced (10% below the corresponding control on GD 6-10). The high dose rabbits showed a distinct weight loss at initiation of treatment (5 % on GD 6–9) and impaired weight gain thereafter (corrected body weight gain 43% below control). In conclusion there was a clear general maternal toxicity at 800 mg/kg.	This analysis is consistent with our analysis stating that "In rats by dermal route (**BASF 2005**), NEP induced growth retardation as evidenced by a	RAC agrees with DS.

Date	Country / Person / Organisation / MSCA	Comment	Response of the dossier submitter	RAC comments
		These effects were - although less pronounced – were still observed at 400 mg/kg bw/d: reduced food consumption (13% below the corresponding control on GD 6-8), body weight loss, 10% reduction in body weight gain on GD 6–9, decreased corrected body weight gains (21 % below control). Signs of substance-induced prenatal developmental toxicity occurred exclusively at the high dose level, but no indications for any selective teratogenicity were observed up to and including 800 mg/kg body weight/day. The only effects observed were reduced mean placental and mean fetal body weights (17% by placental weights or 11 % by fetal weights) and statistically significantly increased rates of fetuses/litters with skeletal variations (delays/minor disturbances in ossification, predominantly of skull and sternebrae ; supernumerary 14th ribs). Delayed ossification and reduced fetal body weight are transient effects on the offspring. The observed nonspecific increases of skelletal variations can be regarded as a consequence of NEP induced maternal toxicity, including incidence rates of some skeletal variations that were above the historical controls. □ NOAEL (dermal, rat, mat.tox.) = 200 mg/kg bw/d NOAEL (dermal, rat, dev.tox.) = 400 mg/kg bw/d	decrease in foetal body weight. The observation of skeletal variations such as delayed ossification can also reflect a retarded development. These effects were reported only at the highest dose of 800 mg/kg/d in presence of significant maternal toxicity. Maternal corrected body weight gain was reduced by 21% of controls and maternal corrected weight by 5% whereas foetal body weight was reduced by 11%. and it is possible neither to exclude nor to clearly establish a link between maternal toxicity and foetal growth retardation." In rat by oral route, from 250 mg/kg maternal body weight change was	RAC agrees
		c.) Rat oral application (Saillenfait et al. (2007) J Appl Toxicol 27(5); 491-7) p.25 French C&L dossier, oral, rat study (Saillenfait, 2007)		

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		Remark: As the original study report is not available to Cefic BDO the comment can not go to deep into the details. Comparable to the rabbit studies, toxicity in rats was detected earlier after oral than dermal exposure: Maternal toxicity, as evidenced by pronounced decreases in body weight gain and food consumption, was observed at all doses at the beginning of treatment. Reduction of food consumption persisted in the highest dose group. The overall corrected pregnancy weight gain was slightly reduced in NEP treated rats, but was not statistically significant and without a no dose-related relationship was observed. Statistically significant malformations and variations in the fetuses were found at doses ≥ 250 mg/kg bw/d. The author concluded in the publication: "In conclusion, our results indicate that NEP is embryolethal and teratogenic in rats at high doses, which also induced maternal toxicity." □ LOAEL (oral, rat, mat.tox.) = 50 mg/kg bw/d NOAEL (oral, rat, dev.tox.) = 50 mg/kg bw/d 2. Specific comments on the overall conclusion (CLH report p. 38): • We agree "NEP induces adverse effects on foetal body weights in rabbits and rats by the oral route." After	significantly altered but it can be largely explained by induction of post-implantation loss from 500 mg/kg and reduction of foetal weight from 250 mg/kg as corrected maternal body weight gain was not significantly affected at any dose. Maternal toxicity was therefore present but restricted to a transient decrease of food consumption and body weight change at initiation of treatment. We therefore conclude that the following effects cannot be secondary to maternal toxicity: decrease of fetal weight, late resorptions and malformations. We acknowledge your agreement on these points.	

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		dermal application the effects on foetal body weights are related to the maternal toxicity. • We agree with the effects on post-implantation loss and in particular late resorptions in rats by oral route in doses causing maternal toxicity. • We agree with the significant increase of skeletal malformations in rabbits and rats by oral route. However, there is no evidence of a causal association between cardiovascular malformations and NEP exposure by either oral or dermal application. On this basis it is concluded, that there is evidence of teratogenic and foeto-toxic effects by NEP after high oral exposure in the presence of maternal toxicity. 3. Specific comments on the proposed harmonized classification and labeling (CLH report p. 4 and 39): • Due to the available studies for NEP we propose GHS Repro. Cat 1B– H360D via the oral route due to the induction of skeletal malformations. • Due to the similarity with NMP, CAS 872-50-4 we propose a concentration limit for Repro. Cat 1B of ≥ 5%. • So far, fertility effects are not covered in the CLH dossier. As there are new data for exposure via the inhalation route (28d study according to OECD412), we suggest awaiting the final result before concluding a harmonized classification and labeling for the reprotoxicity of NEP.	As discussed above we conclude that the following effects cannot be secondary to maternal toxicity: decrease of fetal weight, late resorptions and malformations. See response to previous comments.	Noted RAC agrees With regard to fertility, it may be prudent to await the presentation of the new data and conclude on this related endpoint at the same time.

Additional response from FR

Analysis of cardiovascular malformations in the rabbit studies

In rabbit, historical control data report no **absent subclavian** out of 1745 fetuses examined from 24 studies (HC from the dermal study that include orally, inhalatory and non-treated control groups) and absent subclavian in 1 fetus from 1 study (HC from the oral studies) out of 1231 fetuses examined from 9 studies. It is noted that 7 of these 9 studies were also included in the HC database of the subsequent dermal studies whereas the study reporting the single case of absent subclavian was not retained for an unknown reason.

Absent subclavian was also never reported in controls of the studies performed on NEP. The induction of absent subclavian in 1 fetus at mid- and at high-dose in the rabbit dermal study and in 3 fetuses from 3 litters at 220 mg/kg in the second rabbit oral study (BASF 2007b) is not considered incidental. Besides, in the latter study, two additional fetuses (from two litters) with multiple visceral malformations had absent or malpositioned subclavian branch.

For **ventricular septum defect (VSD),** membranous VSD are reported in the dermal rabbit study whereas muscular VSD are reported in both rabbit oral studies and this distinction has been added in the revised CLH report. Muscular VSD are reported in the HC of the oral studies in 8 fetuses out of 1231examined from 8 litters out of 231. Similar incidence is reported in the HC of the dermal study (8 fetuses out of 1745examined from 8 litters out of 265). Spontaneous occurrence may therefore happen as evidenced by the single case of the control groups of both oral studies. The observation of 2 fetuses from 2 litters with muscular VSD in the high dose group (200 mg/kg) of the first oral study (BASF 2007a) may be incidental. However, membranous VSD are reported in the HC of the oral studies in none of 1231fetuses examined and in 1 fetus out of 1745 in the HC database of the dermal study. The observation of two fetuses with this malformation at the high dose in the dermal study is therefore not considered incidental.

Besides, isolated case of rare cardiovascular malformations were reported such as dextrocardia (never reported in HC from the dermal or oral rabbit studies *vs* 3 cases in the dermal high-dose group) and persistent *truncus arteriosus* (never reported in HC from the oral rabbit studies and reported in 1/1745 fetuses in the HC of the dermal study vs 1 case at 220 mg/kg by oral route) were reported.

Cardiovascular malformations are also reported in the rat by oral route and with NMP in the rat and rabbit by oral route (but not by other routes). The cardiovascular malformations observed at high dose in the rabbit dermal study (BASF 2010) and at 220 mg/kg in the second rabbit oral study (BASF 2007b) are considered to be related to treatment.

Carcinogenicity

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteurs' comments
		No comments received.		

Mutagenicity

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteurs' comments
		No comments received.		

Toxic to Reproduction

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteurs' comments
22/04/2011	Netherlands / Bureau REACH RIVM / National Authority	Page 11 and 13, conclusion: A dermal developmental study is described. However, effects on food intake and body weight are observed during the gavage period. It is not clear what is meant by the gavage period, or if the described results belong to a gavage study instead of the dermal study.	The information has been checked and modified: gavage has been wrongly used instead of treatment.	Noted

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON N-ETHYL-2-PYRROLIDONE (NEP)

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteurs' comments
		Page 13, table 4: It is indicated that the percentage litters with any malformations is significantly increased in the high dose group, but not in the low- and mid dose group (where the percentage is higher. This seems not correct.	It has been corrected.	Noted
		Page 35, table 20: In the oral rabbit studies, blood parameters and organ weights are analysed and several effects were observed (among others increased relative liver weight, ALAT and GGT were observed in both studies). These effects should be included in the summarizing table and it should be discussed whether these effects are considered adverse or not.	The effects have been added in the table. They are indicative of adaptative metabolism and mild liver damage but it is not considered as a toxic effect in the meaning of the CLP and discussion of its relationship with developmental effects is therefore not relevant.	Noted. RAC agrees with the DS
		The gestational parameters and malformations are given in percentages. In general, it would be more informative to know in how many litters or fetuses (absolute numbers) the effects are observed. It is therefore suggested to include the number of evaluated animals at the top of the tables.	The information has been added in the table reporting malformations and variations.	Agree that this additional information is necessary and has been added.
		In IUCLID, a repeated dose toxicity study is included. We suggest to also include this study in the CLH report, to increase the information on maternal toxicity at similar dosages.	Information has been added based on the information given in the registration dossiers.	Agree that this additional information is necessary and has been added.
		In several of the summarized studies a decrease in body weight gain of the dams is observed. We agree that, in the cases where the corrected body weight gain is not significantly altered, this should not be considered an adverse effect. Therefore, the observed effects on fetal body weight (rats and rabbit), post implantation loss (rat),	Your support is noted. In agreement with section 3.7.4.1 of	Agreed by RAC

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteurs' comments
		rare cardiovascular malformations above historical control values (rat and rabbit) and skeletal malformations/variations (rat and rabbit) are considered direct adverse effects of NEP on the reproduction. We therefore agree with the proposed classification according to Regulation1272/2008: Repr. Cat. 1B; H360. However, we do not agree with the assignment of the letter 'D' to the hazard statement, since this is only acceptable when effects on fertility can be excluded according to reliable and adequate data. Since there are no data on fertility, assignment of H360D is not correct. We do agree with classification as Repr Cat 2; R61, according to Directive 67/548/EEC	the guidance on CLP criteria and in absence of evaluation of fertility, we agree that the general hazard statement applies.	
29/04/2011	Denmark / Trine Thorup Andersen / Member State	***ECHA's comment: The attachment "Danish Comments to N-ethyl-2-pyrrolidone classification for reprotox Cat 1B.doc" is copied below:*** **Regarding the proposed classification of N-ethyl-2-pyrrolidone (NEP) for reproductive toxicity (Repr. Cat. 1B; H360D)** Denmark agrees with the proposed classification for reproductive toxicity in category 1B with H360D. We find that the animal studies presented provide convincing evidence for developmental toxicity of NEP. The available data include studies with both rats and rabbits and indicate that NEP induces adverse teratogenic and foeto-toxic effects in both species, both via dermal and oral exposure. The limited maternal toxicity observed was not correlated to the effects on foetal development. Furthermore, NEP is structurally close related to the substance NMP (N-methyl-2-pyrrolidone), which already holds a harmonised classification as Repr. Cat. 1B; H360D. The data presented for NMP further supports the proposed harmonised classification of NEP. Kind regards Trine Thorup Andersen Danish Environmental Protection Agency Chemicals	Your support is noted.	Noted
06/05/2011	Germany / Matthias Plog / Member State	Minor points to be considered: Page 10, 5.1: It would be helpful if toxicokinetic data would be presented. The lack of toxicokinetic data seems to be unlikely. Page 11, 5.9.2.1, third and fourth paragraph: Since this section describes the effects after dermal application the use of "gavage" doesn't make sense. Page 12, 5.9.2.1, third paragraph: please add the number of membraneous ventricular septum defects in the high and the low dose.	No toxicokinetic studies has been located either in the literature or in the registration dossiers. This mistake has been corrected. All incidences are given in table 4.	Noted

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteurs' comments
		Page 13, 5.9.2.1, first paragraph: Replace "gavage" by "treatment".	Done.	Noted
		Page 15/16, 5.9.2.1, Comparing the historical control data from table 7 with those from table 10 (page 18/19) differences can be observed in thirteen cases though the species and the defining footnotes are identical. Please adjust or explain the differences.	Each set of historical data is based on 9 studies. Eight of them are similar but the nineth study differs in the two data sets. The reason for this discrepancy is not known as both study reports were completed at the same date. However, the slight differences (mainly on mean value) between the two historical control data sets have no impact on the evaluation.	Noted
		Page 16, 5.9.2.1, third paragraph: It should be explained why this supplementary study has been performed. The dose is only 10% higher compared to the highest dose in the initial study.	The second supplementary study was performed to allow a sound assessment of the results from the previous study, which was considered to show some borderline effects. This information has been added in the	Noted

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteurs' comments
			revised CLH report.	
		Page 19, 5.9.2.1, table 10: The historical control of small spleen is described to be 0.8% (0-0.8%). An average of 0.8% based on data ranging from 0-0.8% is not plausible.	The average is 0.08% instead of 0.8%. it has been corrected in the revised CLH report.	Noted
		Page 20, 5.9.2.2, first paragraph: Did the experiment really contain an artificial insemination of the female rats? It is quite unusual for studies in rats.	It has been corrected.	
		Page 21, 5.9.2.2, table 11: The term "corrected weight gain GD29" should be changed, because the study was terminated on day 20. Accordingly footnote a and b should both be corrected.	It has been corrected.	
		Page 21, 5.9.2.2, table 12: The fetal body weight is quite low with 3.1 to 3.5 g/fetus, even for a Wistar rat. Would it be possible to present historical data for the control animals?	The information has been added.	
		Page 23, 5.9.2.2, table 14: footnote b: The text could be simplified by exchanging "body weight at GD0 plus gain during GD0-21" by "body weight at GD21"	Done.	
		Page 24, 5.9.2.2, first paragraph: The reference to table 4 is wrong. It could be table 15 or 16 and should be changed.	Done.	
		Page 34, 5.9.5, Table 20, first row: Here GD 6 to 28 are mentioned, in Table 2 it was GD 6 to 29.	The information in table 20 is correct. NEP was administered from GD 6 to 28 and dams were sacrificed on GD 29.	
		Page 36, 5.9.5, fourth paragraph, rephrase first sentence as follows: "In orally treated rats (Saillenfait, 2007) foetal body weights were already significantly reduced at the dose of 250 mg/kg/d."	Not relevant.	
		Page 37, 5.9.5, first paragraph, rephrase first sentence as follows: "The dose-related increase in post-implantation losses reached the level of significance at a dose of 500 mg/kg/d."	Done.	
06/05/2011	Sweden / Member State	We agree with the proposed classification (Repr. 1B, H360D (CLP) / Rep Cat 2, R61 (DSD)) based on; • Statistically significant malformations (skeletal, cardiovascular, and cleft palate) as well as other feto-toxic	Your support is noted.	Noted

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteurs' comments
		effects in the absence of maternal toxicity • most effects were observed in 2 species after both oral and dermal exposure • most effects clearly exceeded the historical control incidences • the causality being supported by similar developmental effects caused by the analogue N-methyl-2-pyrolidone.		
06/05/2011	Ireland / Health and Safety Authority	The Irish CA is in agreement with the proposal to classify N-ethyl-2-pyrrolidone as Repr. 1B H360D (Repr. Cat 2; R61).	Your support is noted.	Noted
09/05/2011	United Kingdom / Andrea Caitens / Member State	We agree that NEP meets the classification criteria for Category 2 under DSD and Repr, 1B under CLP. However, in accordance with Annex I and Section 1.2.3 of Annex VI of CLP, as an effect on fertility has not been excluded (i.e. no information provided in the dossier), we do not consider it appropriate to specify that the classification is for development only and would prefer the more general hazard statement be used.	Your support is noted. In agreement with section 3.7.4.1 of the guidance on CLP criteria and in absence of evaluation of fertility, we agree that the general hazard statement applies.	RAC agrees

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteurs' comments
		No comments received.		

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteurs' comments

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON N-ETHYL-2-PYRROLIDONE (NEP)

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteurs' comments
06/05/2011	Germany / Matthias Plog / Member State	Page 7, Table 1 Summary of physico-chemical properties: Although the physico-chemical properties are not relevant for the classification and labelling we recommend the use of "data waiver" because of the plausibility of the CLH dossier. A justification for non-submission of data should be provided for – 7.10 Flammability (EC method A.10 Flammability (Solids), A.12 Flammability (Contact with water), A.13 Pyrophoric properties of solids and liquids) – 7.11. Explosive properties (EC method A.14 Explosive Properties) – 7.12. Self-ignition temperature (EC method A.16 Relative Self-ignition temperature for solids) – 7.13. Oxidising properties (EC method A.21 Oxidizing Properties (Liquids)) For the Flash point (VII, 7.9) and the Auto-ignition temperature (Liquids and Gases), the method should be indicated. The statement under VII, 7.11 "Vapors can form explosive mixtures with air" should be stated under VII, 7.10 with indication of the explosion range / explosion limits.	Hazard related to physico-chemical properties are not evaluated in this dossier and these data are given only for information to understand the profile of the substance. The information was found in the literature and details on the methods are not available. However, it has no impact on evaluation of reproductive toxicity of NEP.	RAC agrees

ATTACHMENTS RECEIVED:

– MSCA Denmark: Danish Comments to N-ethyl-2-pyrrolidone classification for reprotox Cat 1B.doc

Response from FR: Danish comment have been included in the table: see above for response to comment.