Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

perestane

ECHA/RAC/CLH-O-0000001562-79-03/A2

Adopted

14 September 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: perestane
CAS number: 847871-03-8
EC number: 432-790-1

General comments

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
01/04/2011	Belgium / Marie-Noëlle Blaude / Individual	The proposal of UK was the removal of the Muta 2 classification and not the removal of the Reprotox classification as reported on the ECHA website.	We can confirm that the proposal is to remove the Muta. 2 H341 classification and to include STOT-SE 2 H371 instead.	Noted.
02/05/2011	Germany / Matthias Plog / Member State	General Comments: Germany supports the change of classification from Muta.2 H341 to STOT-SE 2 H371. In the IUCLID-file the InChI code for the reference substances is missing. 1.2 In contrast to the text of the heading there are no labelling proposals. 1.3 Concerning the labelling proposal (CLP) the corresponding pictograms are missing. Concerning the labelling proposal (DSD) the indication of danger should be "C" only following the rules of precedence. 2.3 In contrast to the text of the heading there are no labelling proposals.	Thank you for your comments. The appropriate changes have been made to the report.	Noted.
05/05/2011	France / Member State	Why the CAS number (847871-03-8) is not specified in the general entry and in the dossier?	Thank you for your comments. It was suggested during the accordance check that the CAS number should be removed as it does not include one of the constituents of the multi-component substance. The current Annex VI entry does not refer to a CAS number.	Noted.
06/05/2011	Ireland / Health and Safety	The Irish CA is in agreement with the proposed changes to the classification of the substance (reaction mass).	Thank you for your comments.	Noted.

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
	Authority			

Carcinogenicity

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

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comments
02/05/2011	Germany / Matthias Plog / Member State	In our opinion the available data on Perestane, as presented in this report and technical dossier, do not support classification with Muta 2 H341 (Muta. Cat. 3; R68). Therefore, we support the proposal of this dossier to amend the classification of this substance to reflect the original UK proposal of STOT-SE 2; H371 (R68/20/21/22).	Thank you for your comments.	Noted.
05/05/2011	France / Member State	4.9 Germ cell mutagenicity (Mutagenicity) p.22 – 23 We would like to know on the basis of which tests the perestane was classified in the category 2 of the mutagenicity aiming at better understand the context of this new proposition.	The available data do not support classification for mutagenicity. The UK originally proposed to classify this substance with C; R34; R20/21/22-40/20/21/22, with the R20/21/22-40/20/21/22 coming from the presence of methanol in the substance at levels ≥ 3% and < 10%. When the wording of the R40 phrase was changed from "possible evidence of irreversible effects" to 'limited evidence of a carcinogenic effect' at the 28th ATP, the proposed classification of Perestane should have been amended to C;R34 R20/21/22-68/20/21/22. However, the R40 classification was mistakenly translated to include Muta. Cat. 3; R68, Xn; R20/21/22 instead. This was done in error and included on the harmonised list. The only way to amend this error, has been through a new CLH proposal.	Noted.

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		Besides, it would be useful to develop more the method of the mutagenic tests in order to facilitate understanding and make easier the decision making. 4.9.1.1 In vitro data p.22 Concerning the mammalian cell gene mutation test, important information is mentioned in the biocidal dossier: Could you please add « In the presence of metabolic activation the response was only observed at the highest test concentration where a cytotoxic response was also observed". Moreover, there is a discrepancy between CLP report and biocidal dossier, cytotoxicity is observed at > 2500µg/ml and at 2500µg/ml, respectively, could you please clarify this point? Finally, to support the fact that positive results can be put into perspective, could you please complete by the following words in bold: "The increase in mutant frequency was predominantly due to small colony formation, suggesting clastogenic activity resulting in structural chromosome damage which is not confirmed in the in vitro chromosome aberration test and in the in vivo micronucleus test.". Overall, on the basis of the supplied tests, we support the UK proposal but, before concluding, it should be know why perestane was first classified in category 2 of mutagenicity.	We urge the RAC rapporteur to acknowledge the additional comments submitted by France regarding section 4.9.1.1 Furthermore we can clarify that, in the MCGMT, cytoxicity was observed at 2560 □g/ml in the main study (cytotoxicity was observed at 2500 □g/ml in the preliminary study).	Thanks for clarification.
06/05/2011	Ireland / Health and Safety Authority	The Irish CA agrees that the substance (reaction mass) does not meet the criteria for classification as a Germ Cell Mutagen, and as such the classification Muta 2 H341 should be removed from Annex VI.	Thank you for your comments.	Noted.
06/05/2011	Sweden / Alicja Andersson / Member state	KemI agrees with the submitting MS that the data available are not sufficient for classification of Perestane in Muta Cat3. There are positive results measured in one in vitro test for gene mutation in mammalian cells (Durward, 2001). This test does also imply induction of chromosome aberrations due to formation of small colony. Since no raw data are presented in the dossier it is difficult to assess the extend of the effect observed. Negative results for Perestane in vitro were obtained in the Ames test and Mammalian chromosome aberration test. It is not possible to make any judgement of the quality of the studies from the data shown in the report. In vivo a micronucleus test in mouse (Durward&Nolan, 2002) gave negative results.	Thank you for your comments. All of the reported studies were conducted in accordance with appropriate OECD guidelines and GLP. As a consequence there is no cause to doubt the quality of these studies. The test material induced a statistically significant and dose-related increase in the mutant frequency both with and without metabolic activation. In the presence of	Noted.

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comments
		Clinical signs were observed at the top dose, which implies that the substance was systematically available although no data on plasma concentration are presented in the dossier. In addition, the lack of cytotoxicity makes an assessment of the extent to which bone marrow was exposed during the test uncertain. Negative results were obtained in vivo in an UDS test (Durward, 2002).	metabolic activation the response was only observed at the highest test concentration (2560 µg/ml) where a cytotoxic response was also observed. In the in vivo bone marrow micronucleus study, clinical signs (hunched posture, lethargy and decreased respiratory rate) were observed in animals dosed with the test material at 2000 mg/kg in both the 24 and 48-hour groups, indicating that systemic exposure occurred. However we acknowledge that there was no effect on the PCE/NCE ratio. Whilst this may suggest that the bone marrow was not adequately exposed it could also mean that the substance was not toxic to the bone marrow at the dose used. No additional data are available. However, even taking this into consideration, the available data do no support classification with Muta 2 H341.	

Toxicity to reproduction

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

Respiratory sensitisation

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

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
27/04/2011	Netherlands / Bureau REACH RIVM / National Authority	Any other hazard classes or endpoints It is noted that the classification of perestane in Annex VI dossier is based on the classification of methanol and not on the tests of perestane. This conclusion is in line with the NL NONS evaluation. In 2002, the NL evaluated perestane as NONS (02-03-0531) and confirmed the classification with Xn;R68/20/21/22. The classification with Xn;R68/20/21/22 was derived using the classification criteria from the preparations directive, and the classification of methanol (including the specific concentration limits). This classification of perestane is included in Table 3.2 of Annex VI. Methanol (603-001-00-X) has been classified with STOT SE1, H370, with specific concentration limits, but not with Muta2 H341 in Table 3.1 of Annex VI of CLP. Based on the methanol content of perestane, using the harmonised classification of methanol we agree with the UK proposal to remove Muta 2 H341 and add STOT SE2, H371.	Thank you for your comments.	Noted.
02/05/2011	Germany / Matthias Plog / Member State	Perestane contains peroxy and nonperoxy carboxylic acid derivates, and has a very low pH (2.44 at 25°C for a 1% solution, which would equate to 2 pH units lower for the pure solution i.e. pH < 1). For this reason Perestane is considered to be corrosive and labelled Skin Corr. 1B; H314 (C; R34). The acute dermal toxicity study (Sanders 2000) of this dossier showed for a concentration of 500 mg/ml (dose level of 2000 mg/kg bw) signs of skin irritation like: erythema, crust formation, small superficial scattered scabs and haemorrhage of the dermal capillaries, at the treatment sites. However, five to seven days after dosing the skin appeared normal. Classification of a substance as being corrosive implies that damage of the skin is not reversible, therefore the finding of reversibility of the skin damage by Sanders (2000) poses questions on the current classification. More data would be helpful to clarify this disagreement.	We do not propose to address the current classification for skin corrosion in this proposal. We note the comments, but the current classification is based on the low pH of the substance and further testing was not conducted on animal welfare grounds.	Noted.
06/05/2011	Ireland / Health and Safety Authority	STOT-SE The Irish CA agrees that the substance should be classified STOT-SE 2 H371, based upon the methanol content of the substance (reaction mass).	Thank you for your comment.	Noted.
06/05/2011	Sweden / Alicja	Specific target organ toxicity – single exposure	Thank you for your comment.	Noted.

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Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
	Andersson / Member state	KemI agrees with the submitting MS that Perestane meets the criteria for classification as STOT SE 2 H371 due its content of methanol at concentrations of ≥3% but < 10%.		