Committee for Risk Assessment

RAC

Annex 1

Background document

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

perestane

ECHA/RAC/CLH-O-0000001562-79-03/A1

EC number: 432-790-1
CAS number: 847871-03-8

Adopted

14 September 2011

CONTENTS

Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Perestane*** Reaction mass of: succinic acid, monopersuccinic acid, dipersuccinic acid, monomethyl ester of succinic acid, monomethyl ester of persuccinic acid, dimethyl succinate glutaric acid, monoperglutaric acid, diperglutaric acid, monomethyl ester of glutaric acid, monomethyl ester of perglutaric acid, dimethyl glutarate adipic acid, monoperadipic acid, diperadipic acid monomethyl ester of adipic acid, monomethyl ester of peradipic acid, dimethyl adipate, hydrogen peroxide, methanol and water
EC number:	***432-790-1***
CAS number:	***N/A***
Annex VI Index number:	***607-613-00-8***
Degree of purity:	***95.6-99%***
Impurities:	***None reported***

1.2 Harmonised classification and labelling proposal

Classification and labelling proposed by RAC

Table 2. Classification and labeling 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)		
	Perestane	**432-790-1**	**847871-03-8**	**Skin Corr. 1B** **Acute Tox. 4*** **Acute Tox. 4*** **Acute Tox. 4*** **STOT SE 2 (eye)**	**H314** **H332** **H312** **H302** **H371**	**GHS05** **GHS07** **GHS08** **Dgr**	**H314** **H332** **H312** **H302** **H371**	-	-	-

Table 3. 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
	Perestane	**432-790-1**	**847871-03-8**	**C; R34** **Xn; R20/21/22** **Xn; R68/20/21/22**	**C** **R: 20/21/22-68/20/21/22** **S: 1/2-26-28-36/37/39-45**	-	-

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Perestane was notified under the Notification of New Substance (NONS) Regulations in the UK in 2000 (Notification number 00-06-1353). 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 agreed at the 13th Working Group on the classification and labelling of new notified substances in May 2003 and was included in the 1st ATP to CLP.

2.2 Short summary of the scientific justification for the CLH proposal

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) and therefore this proposal seeks to amend the classification of this substance to reflect the original UK proposal of STOT-SE 2 H371 (R68/20/21/22).

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Muta. 2 H341
Skin Corr. 1B H314
Acute Tox. 4 * H332
Acute Tox. 4 * H312
Acute Tox. 4 * H302

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Muta. Cat. 3; R68 - C; R34 - Xn; R20/21/22

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Not currently classified in accordance with CLP. From the 1st December 2010 the Annex VI classification will apply:

Muta. 2 H341
Skin Corr. 1B H314
Acute Tox. 4 H332
Acute Tox. 4 H312
Acute Tox. 4 H302

2.4.2 Current self-classification and labelling based on DSD criteria

The current self classification is C ; R34 R20-68/20/21/22. From the 1st December 2010 the Annex VI classification will apply: Muta. Cat. 3; R68 - C; R34 - Xn; R20/21/22

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

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) and therefore this proposal seeks to amend the classification of this substance to reflect the original UK proposal of STOT-SE 2 H371 (R68/20/21/22).

Part B.

SCIENTIFIC EVALUATION OF THE DATA

*Please note that this Background Document supporting the RAC opinion has been prepared on the basis of the submitted CLH report. According to the "**RAC Working Procedure on Processing of Dossiers for Harmonised Classification and Labelling (May, 2010**)" the dossier submitter has integrated the comments received during the public consultation where relevant. For transparency, the information provided by the dossier submitter in the revised CLH report has not been modified. The RAC assessment of the relevant information has been included in separated sections through the document.*

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	432-790-1
EC name:	Perestane Reaction mass of: succinic acid, monopersuccinic acid, dipersuccinic acid, monomethyl ester of succinic acid, monomethyl ester of persuccinic acid, dimethyl succinate glutaric acid, monoperglutaric acid, diperglutaric acid, monomethyl ester of glutaric acid, monomethyl ester of perglutaric acid, dimethyl glutarate, adipic acid, monoperadipic acid, diperadipic acid monomethyl ester of adipic acid, monomethyl ester of peradipic acid, dimethyl adipate, hydrogen peroxide, methanol and water
CAS number (EC inventory):	N/A
CAS number:	N/A
CAS name:	N/A
IUPAC name:	Reaction mass of: succinic acid, monopersuccinic acid, dipersuccinic acid, monomethyl ester of succinic acid, monomethyl ester of persuccinic acid, dimethyl succinate glutaric acid, monoperglutaric acid, diperglutaric acid, monomethyl ester of glutaric acid, monomethyl ester of perglutaric acid, dimethyl glutarate, adipic acid, monoperadipic acid, diperadipic acid monomethyl ester of adipic acid, monomethyl ester of peradipic acid, dimethyl adipate, hydrogen peroxide, methanol and water
CLP Annex VI Index number:	607-613-00-8
Molecular formula:	Not applicable
Molecular weight range:	Not applicable

Structural formula: Not applicable.

1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Succinic acid	Confidential	Confidential	Confidential
Monopersuccinic acid	Confidential	Confidential	Confidential
Dipersuccinic acid	Confidential	Confidential	Confidential
Monomethyl ester of succinic acid	Confidential	Confidential	Confidential
Monomethyl ester of persuccinic acid	Confidential	Confidential	Confidential
Dimethyl succinate	Confidential	Confidential	Confidential
Glutaric acid	Confidential	Confidential	Confidential
Monoperglutaric acid	Confidential	Confidential	Confidential
Diperglutaric acid	Confidential	Confidential	Confidential
Monomethyl ester of glutaric acid	Confidential	Confidential	Confidential
Monomethyl ester of perglutaric acid	Confidential	Confidential	Confidential
Dimethyl glutarate	Confidential	Confidential	Confidential
Adipic acid	Confidential	Confidential	Confidential
Monoperadipic acid	Confidential	Confidential	Confidential
Diperadipic acid	Confidential	Confidential	Confidential
Monomethyl ester of adipic acid	Confidential	Confidential	Confidential
Monomethyl ester of peradipic acid	Confidential	Confidential	Confidential
Dimethyl adipate	Confidential	Confidential	Confidential
Hydrogen Peroxide	Confidential	Confidential	Confidential
Methanol	Confidential	Confidential	Confidential
Water	Confidential	Confidential	Confidential

Perestane is a reaction mass containing the substances listed above. The details of the exact composition of perestane are confidential and are provided in the IUCLID dossier. The classification of the individual substituents has been taken into consideration in the classification and labelling proposed for perestane. Note that water is a constituent of the substance and can not be removed without affecting the composition of the other components which contribute to the overall desired effect of the substance.

Current Annex VI entry: As above.

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks

No impurities are reported.

Current Annex VI entry: As above.

Table 8: Additives (non-confidential information)

A number of additives are included in perestane. This information is confidential and is included in the IUCLID. The classification of the individual additives has been taken into consideration in the classification and labelling proposed for perestane.

Current Annex VI entry: As above.

1.2.1 Composition of test material

As above

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Colourless liquid	IUCLID	Observation
Melting/freezing point	< -22 °C	IUCLID	92/69/EEC A1 (Pour point)
Boiling point	≤ 103 °C at 101.3kPa	IUCLID	92/69/EEC A2 (DSC) Value is thought to be due to the presence of water.
Relative density	1.09 at 20 °C	IUCLID	92/69/EEC A3 (pycnometer)
Vapour pressure	5600 Pa at 25 °C	IUCLID	92/69/EEC A4 (isoteniscope)
Surface tension	71.7 mN/m at 20 °C	IUCLID	92/69/EEC A5 (ring method)
Water solubility	Miscible in all proportions	IUCLID	Not measured
Partition coefficient n-octanol/water	Log Pow: ≤ 1.45 at 25 °C	IUCLID	92/69/EEC A8 (HPLC)
Flash point	> 102 °C	IUCLID	92/69/EEC A9
Flammability	The substance is not flammable. The substance is not pyrophoric and will not spontaneously ignite on contact with water.	IUCLID	Experience in handling and use
Explosive properties	Not explosive	IUCLID	92/69/EEC A14
Self-ignition temperature	Autoflammability: 268 oC	IUCLID	92/69/EEC A15
Oxidising properties	Not oxidising	IUCLID	Substance contains < 0.5% available oxygen from organic peroxide

2 MANUFACTURE AND USES

2.1 Manufacture

The substance is manufactured in the EU.

2.2 Identified uses

The substance is a general purpose disinfectant that is used in hard surface cleaners.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

3.1.1 Summary and discussion of

3.1.2 Comparison with criteria

3.1.3 Conclusions on classification and labelling

The classification for physico-chemical properties is not considered in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

4.1.2 Human information

4.1.3 Summary and discussion on Toxicokinetics

Not relevant for this dossier.

4.2 Acute toxicity

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Species	LD50	Observations and remarks
Rat 3/sex/group 200 and 2000 mg/kg OECD 473 IUCLID 7.2.1	> 2000 mg/kg	No adverse effects or signs of toxicity.

4.2.1.2 Acute toxicity: inhalation

No data are available.

4.2.1.3 Acute toxicity: dermal

Species	LD50	Observations and remarks
Rat 5/sex/group 2000 mg/kg OECD 402 IUCLID 7.2.3	> 2000 mg/kg	Signs of skin irritation included very slight erythema, light brown discoloration of the epidermis, desquamation, crust formation, small superficial scattered scabs and haemorrhage of the dermal capillaries. Treatment sites appeared normal five to seven days after dosing.

4.2.1.4 Acute toxicity: other routes

No data are available.

4.2.2 Human information

No human data are available on perestane itself. However, methanol is a known constituent in the substance and can be present at a concentration of between ≥ 3% and < 10%. Methanol is listed in Annex VI of CLP and is classified with T; R23/24/25-39/23/24/25. The acute toxicity of methanol in humans and primates is clearly different to that in non-primates. Humans are more susceptible due to differences in metabolism, in particular the production of formic acid and the consequent metabolic acidosis. The classification for potential irreversible effects following a single exposure (R39/23/24/25) is also justified due to evidence of permanent visual loss in humans. Since the classification for the acute toxicity of methanol is based on adequate, reliable and representative human data, a substance or preparation containing methanol as a component, impurity or additive should be classified accordingly even though animal data (non-primate) on that substance or preparation are available.

4.2.3 Summary and discussion of acute toxicity

This proposal does not address the acute toxicity classification. However, please note that methanol is currently listed on Annex VI of CLP and is classified with T; R23/24/25. However it has a specific concentration limit such that at concentrations of ≥ 3% and < 10% this changes to Xn; R20/21/22

4.2.4 Comparison with criteria

4.2.5 Conclusions on classification and labelling

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

The available animal data on perestane do not indicate that classification for STOT-SE is applicable. However, perestane contains methanol at concentrations of ≥ 3% and < 10%. Methanol

is listed on Annex VI of CLP with a specific concentration limit such that when present at concentrations of ≥ 3% but < 10% it should be classified with STOT-SE 2 H371 under CLP (or R68/20/21/22 under DSD) due to evidence of permanent visual loss in humans.

4.3.2 Comparison with criteria

Methanol is listed in Annex VI of CLP and at concentrations of ≥ 3% but < 10% it should be classified with STOT-SE 2 H371 under CLP or R68/20/21/22 under DSD due to evidence of permanent visual loss in humans. Therefore perestane, which contains methanol at such a concentration, should be classified accordingly.

4.3.3 Conclusions on classification and labelling

CLP: STOT-SE 2 H371 – May cause damage to organs
DSD: Xn R68/R20/21/22

RAC assessment

RAC checked and discussed the proposed classification for specific target organ toxicity (single exposure). There was no comment neither in RAC nor by concerned parties questioning the proposed classification. For corresponding details of the classification proposal please refer to the background document.

Overall, RAC concluded to propose to classify perestane for specific target organ toxicity (CLP: STOT SE 2; H371 and DSD: Xn; R68/20/21/22).

4.4 Irritation

4.4.1 Skin irritation

4.4.1.1 Non-human information

4.4.1.2 Human information

4.4.1.3 Summary and discussion of skin irritation

4.4.1.4 Comparison with criteria

4.4.1.5 Conclusions on classification and labelling

This proposal does not address the classification for skin irritation.

4.4.2 Eye irritation

4.4.2.1 Non-human information

4.4.2.2 Human information

4.4.2.3 Summary and discussion of eye irritation

4.4.2.4 Comparison with criteria

4.4.2.5 Conclusions on classification and labelling

This proposal does not address the classification for eye irritation.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

4.4.3.2 Human information

4.4.3.3 Summary and discussion of respiratory tract irritation

4.4.3.4 Comparison with criteria

4.4.3.5 Conclusions on classification and labelling

This proposal does not address the classification for respiratory tract irritation.

4.5 Corrosivity

4.5.1 Non-human information

4.5.2 Human information

4.5.3 Summary and discussion of corrosivity

4.5.4 Comparison with criteria

4.5.5 Conclusions on classification and labelling

This proposal does not address the classification for corrosivity.

4.6 Sensitisation

4.6.1 Skin sensitisation

4.6.1.1 Non-human information

4.6.1.2 Human information

4.6.1.3 Summary and discussion of skin sensitisation

4.6.1.4 Comparison with criteria

4.6.1.5 Conclusions on classification and labelling

This proposal does not address the classification for skin sensitisation.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

4.6.2.2 Human information

4.6.2.3 Summary and discussion of respiratory sensitisation

4.6.2.4 Comparison with criteria

4.6.2.5 Conclusions on classification and labelling

This proposal does not address the classification for respiratory tract irritation.

4.7 Repeated dose toxicity

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

4.7.1.2 Repeated dose toxicity: inhalation

4.7.1.3 Repeated dose toxicity: dermal

4.7.1.4 Repeated dose toxicity: other routes

4.7.1.5 Human information

4.7.1.6 Other relevant information

4.7.1.7 Summary and discussion of repeated dose toxicity

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

This proposal does not address the classification repeat dose toxicity.

4.9 Germ cell mutagenicity (Mutagenicity)

Table 18: Summary table of relevant in vitro and in vivo mutagenicity studies

4.9.1 Non-human information

4.9.1.1 In vitro data

Method	Organism/Strain	Concentration	Result
Bacterial Mutation Assay (Ames) OECD 471 IUCLID 7.6.1 (1) (Thompson and Bowles 1999)	S. typhimurium (TA1535, TA1537, TA98 and TA100) and E.coli WP2 uvrA	5-5000 µg/plate Cytotoxicity at 5000 µg/plate + S9 and at 500 µg/plate – S9	**Negative** ± S9 metabolic activation
Mammalian chromosome aberration test OECD 473 IUCLID 7.6.1 (2) (Durward and Jenkinson 2001)	Human lymphocytes	625-2500 µg/ml Cytotoxicity at >2500 µg/ml + S9 and 1875 µg/ml – S9	**Negative** ± metabolic activation
Mammalian cell gene mutation test OECD 476 IUCLID 7.6.1 (3) (Durward 2001)	L5178Y TK +/- mouse lymphoma cells	160-2560 µg/ml + Metabolic activation. Cytotoxicity at >2500 µg/ml 5- 160 µg/ml - Metabolic activation. Cytotoxicity at 160 µg/ml	**Positive** ± metabolic activation The response was more pronounced in the absence of metabolic activation. The increase in mutant frequency was primarily due to small colony formation.

4.9.1.2 In vivo data

Method	Organism/Strain	Concentration	Result
Mouse Micronucleus Test OECD 474 IUCLID 7.6.2 (1) (Durward and Nolan 2002)	Mouse CD-1 (7 males/group)	0,500, 1000 and 2000 mg/kg Oral in water Sacrifice times 24 hours for all doses and 48 hours for (0 and 2000 mg/kg).	**Negative** Clinical signs observed at the top dose included hunched posture, lethargy and decreased respiratory rate. However there was no effect on the PCE/NCE ratio.
Liver Unscheduled DNA Synthesis OECD 486 IUCLID 7.6.2(2) (Durward 2002)	Rat 4 males/group (6 in negative controls)	0, 666.7 and 2000 mg/kg	**Negative**

Positive and negative controls produced the expected results.

4.9.2 Human information

None.

4.9.3 Other relevant information

None.

4.9.4 Summary and discussion of mutagenicity

Three standard *in vitro* studies have been performed on perestane. There was no evidence of genotoxicity in the Ames test or in the mammalian cell chromosome aberration test. However, a positive result was observed in a mammalian cell gene mutation test both with and without metabolic activation.

An *in vivo* liver UDS assay and a mouse micronucleus study were also conducted on perestane. A negative result was obtained in both studies.

4.9.5 Comparison with criteria

Substances are classified in Category 2 for germ cell mutagenicity when they cause concern owing to the possibility that they may induce heritable mutations in the germ cells of humans, but insufficient evidence is available to place them in Category 1A or 1B. Classification in Category 2 is based on positive evidence obtained from experiments in mammals and/or, in some cases, from *in vitro* experiments. Such evidence is obtained from somatic cell mutagenicity tests *in vivo* in mammals or other in vivo somatic cell genotoxicity tests which are supported by positive results in *in vitro* mutagenicity assays.

An *in vivo* mouse micronucleus assay conducted on perestane at concentrations up to 2000mg/kg was negative. In addition, an *in vivo* rat liver UDS assay also gave a negative response. Therefore, based on these results, there is no positive evidence from *in vivo* somatic cell mutagenicity or genotoxicity tests. A positive result was only obtained in an *in vitro* mammalian cell gene mutation test, both with and without metabolic activation. However, in the presence of metabolic activation, the response was only observed at the highest test concentration where a cytotoxic response was also observed. In addition, 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

4.9.6 Conclusions on classification and labelling

In conclusion, as a positive result was only obtained in one *in vitro* study and a negative result was obtained in two other *in vitro* studies and in two *in vivo* studies, the available data on perestane do not meet the criteria for classification with Muta 2 H341 under CLP or with Muta Cat 3 R68 under DSD.

Classification under CLP: No classification based on available data
Classification under DSD: No classification based on available data

RAC assessment

RAC recognises that perestane was mistakenly classified as a mutagen; this misclassification was related to a change in the definition of the risk phrase 40 with the 28th ATP. RAC appreciates that the dossier submitter nevertheless summarised and discussed the available mutagenicity data. This background summary above contains a valid summary, discussion and evaluation of the mutagenicity data.

Finally, RAC agrees to the conclusion of the dossier submitter that the available *in vitro* and *in vivo* mutagenicity data for perestane do not give evidence for *in vivo* soma cell mutagenicity and do not meet the criteria for a mutagenicity classification. Thus RAC concluded to propose to remove the current classification for mutagenicity.

4.10 Carcinogenicity

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

4.10.1.2 Carcinogenicity: inhalation

4.10.1.3 Carcinogenicity: dermal

4.10.2 Human information

4.10.3 Other relevant information

4.10.4 Summary and discussion of carcinogenicity

4.10.5 Comparison with criteria

4.10.6 Conclusions on classification and labelling

This proposal does not address the classification for carcinogenicity.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

4.11.1.1 Non-human information

4.11.1.2 Human information

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

4.11.2.2 Human information

4.11.3 Other relevant information

4.11.4 Summary and discussion of reproductive toxicity

4.11.5 Comparison with criteria

4.11.6 Conclusions on classification and labelling

This proposal does not address the classification for reproductive toxicity.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

4.12.1.2 Immunotoxicity

4.12.1.3 Specific investigations: other studies

4.12.1.4 Human information

4.12.2 Summary and discussion

4.12.3 Comparison with criteria

4.12.4 Conclusions on classification and labelling

This is not considered in this proposal.

5 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental classification is not considered in this proposal.

6 OTHER INFORMATION

No other information is available to support this proposal.

7 REFERENCES

Reference should be made the dataset presented in the IUCLID.

8 ANNEXES

Not applicable.