Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Polyhexamethylene biguanide or Poly(hexamethylene) biguanide hydrochloride or PHMB

EC number: not allocated (polymer)
CAS number: 27083-27-8 or 32289-58-0

CLH-O-0000003799-56-03/F

Adopted

14 March 2014

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON POLYHEXAMETHYLENE BIGUANIDE HYDROCHLORIDE (PHMB)

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: Polyhexamethylene biguanide hydrochloride (PHMB)
EC number: not allocated (polymer)
CAS number: 27083-27-8 or 32289-58-0
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2013	Belgium		MemberState	1
Comment received				
We thank France for the CLH proposal. We agree with the new classification Acute Tox.2 H 330 based on the LC50 within the range of Acute inhalation toxicity category 2 according to CLP criteria. Clinical signs (moderately/severely laboured respiration with gasping and ronchus, sneezing,…) observed both in males and females as well as body weight loss clearly indicate acute toxicity after 4-hour exposure by inhalation. Besides, as stated in CLP criteria, the particles with MMDA ranging of 1.49-2.20 µm can reach all regions of the respiratory tract and avoid partial overloading of extra-thoracic airways in species like rat. The effects observed are clearly caused by the toxicity of inhaled PHMB. Editorial comment: P18: 5 males are mentioned in the table while 4 are mentioned in the text below.				
Dossier Submitter's Response				
Thank you for your support. On the editorial comment, the information given in the table refer to the overall mortality (3/5 males exposed to 0.3 mg/L) while clinical observations described in the text relates to to clinical observations performed on animals after the exposure period. One male exposed to 0.3 mg/L died at the end of the exposure period so that clinical observations are reported for the 4 surviving males.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2013	Germany		MemberState	2
Comment received				
In the CLH report on PHMB (05/2013) crucial details such as information on dilution of PHMB are missing in the description of the confidential study (2012) proposed as the new key study for acute toxicity - inhalation. For this reason, the German CA can neither evaluate the new study nor support the new classification and labelling proposed by FR, acute tox. 2 for the hazard class acute toxicity – inhalation (CLP) and T; R23 (DSD).				
Dossier Submitter's Response				
See response to the detailed comment of Germany below.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
19.06.2013	Finland		MemberState	3
Comment received				
We support the proposed classification as Acute Tox 2; H330 for PHMB. We agree that the new study available is of good quality and results from the study should be used as a basis for classification and labelling of PHMB for acute inhalation toxicity.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2013	Germany		MemberState	4
Comment received				
RAC concluded in its opinion of 2011 on PHMB that the 28d inhalation study by Carney (1976), assuming a LC50<0.03 mg/l, should be considered for classification for acute toxicity (acute tox. 1). However, a study by Kilgour (1999) estimated a LC50> 0.36 mg/l. RAC discussed possible reasons for the difference in estimated LC50 (by approximately factor 10) between the two studies such as different strains, vehicles and low number of animals used in both studies. Data from a new study (confidential reference 2012) has provided evidence for a LC50< 0.29 mg/l and seems to be in line with indications delivered by the Kilgour study. In contrast to Carney, the new study is reported to have been performed according to TG403. However, several important details are missing, and these are mandatory for interpretation of the results. As a major point, the specifications (dilution) of the solution used to prepare the aerosol of PHMB are missing. Was PHMB applied as a 20% aqueous solution as in the majority of studies on different endpoints? Without this information, a direct comparison with the				

studies by Carney and by Kilgour is not possible.
A further point is that the CLH report does not provide the RAC with a standalone document, including all important data from the original studies. Further, no explanations were given for the existence of a factor of ten between LC50 in the studies of Carney and the new study (confidential reference 2012).

Collectively, we cannot evaluate the new study (confidential reference 2012) based on the present report. Therefore, we do not support the new classification and labelling proposed by FR, acute tox. 2 for the hazard class acute toxicity – inhalation (CLP) and T; R23 (DSD).

Dossier Submitter's Response

Details on the exposure conditions to PHMB are given below:

The test substance was defined as PHMB with purity 99.6%. To generate the test atmosphere different dilutions of PHMB in aqueous water were tested. The best results in terms of stability of the particle size distribution were achieved a 20% w/w dilution of the test item in distilled water and 20% dilution was used for the study under the denomination test material.

The achieved test concentration was calculated from regular samples of the exposure atmosphere. After sampling filters were dried, the difference between the pre and post sampling weights, corrected by a dilution factor (1 in this case –personnal communication from the study author), divided by the volume of atmosphere sampled, was equal to the actual achieved test atmosphere concentration. Nominal concentration therefore relates to concentrations of "pure" PHMB.

The nominal concentration was calculated by dividing the mass of test material (20% dilution) disseminated into the chamber by the total volume of air that flow through the chamber during the same period. Nominal concentration therefore relates to concentrations of the 20% dilution.

Achieved test concentrations and nominal concentrations are reported in the table below.

Part of Study	Mean Achieved Concentration (mg/L)	Standard Deviation of Achieved Concentration (mg/L)	Nominal Concentration (mg/L)
Sighting exposure : Group 0.1	1.01	0.31	3.71
Group 0.2	0.102	0.01	0.38
Main study: Group 1	0.100	0.01	0.42
Group 2	0.497	0.02	2.13
Group 3	0.303	0.01	1.34

LC_{50} calculations were performed based on "pure" PHMB concentrations (0.37 mg/L for males and females combined) and a corresponding LC_{50} value of 1.85 mg/L was calculated for a 20%-PHMB solution.

It is not clearly understood why a factor of ten is observed between the study of Carney and

the new study. Altogether, the table below summarises the various studies available by inhalation and their main characteristics.

LC_{50} ("pure" PHMB)	**Study**	**Rat strain**	**Number of rats/dose**	**Adminis-tration**	**Vehicle**
LC_{50} < 0.030 mg/l	Carney 1976 (28d)	Alderley Park SPF albino	n=4 /sex	Snout-only	Water
LC_{50} > 0.00247 mg/l	Noakes 2003 (28d)	Alpk:APfSD (Wistar-derived)	n=5 /sex	Nose-only	Water
LC_{50} > 0.36 mg/l	Kilgour 1999	Alpk:APfSC (Wistar-derived)	n=5 /sex	Nose-only	?
LC_{50} = 0.29 mg/l	New study	Wistar CRL:(WI)	n=5 /sex	Nose-only	Water

Unlike Kilgour 1999, a clear information is provided in the new study on the vehicle that was used. Water was used in both the Carney study and the new study. The vehicle is therefore not expected to explain the low LC_{50} value reported in Carney 1976. The low number of animals in each study introduce a variability in the statistical estimation of LC_{50} but that is not expected to be of such a magnitude. 95% confidence interval was calculated in the new study for males and females combined and was 0.37 mg/L [0.22-0.51]. Besides, differences in rat strains used in the various studies exist but are unlikely to explain a difference in sensitivity of a factor 10.

The new study is considered reliable and without uncertainties as previously identified in Kilgour 1999 and the results therefore tends to confirm the results of Kilgour 1999 and questions the reliability of Carney 1976.
On the basis of this reliable new study, a classification Acute 2 – H330 is warranted.

RAC's response

Noted.