# Committee for Risk Assessment
# RAC

Annex 2

## Response to comments document (RCOM)

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

**Polyhexamethylene biguanide or Poly(hexamethylene) biguanide hydrochloride or**
**PHMB**

**ECHA/RAC/CLH-O-0000001973-68-01/A2**

**Polyhexamethylene biguanide or Poly(hexamethylene) biguanide hydrochloride or**
**PHMB**
**EC Number: not allocated (polymer)**
**CAS Number: 27083-27-8 or 32289-58-0**

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**Adopted**
**9 September 2011**

## ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPSAL ON PHMB

**COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION**

***[For this substance, ECHA has entered the comments under the headings as provided by their authors given the number and the complexity of the received comments.]***

**Substance name: PHMB (poly(iminoimidocarbonyl)iminohexamethylene hydrochloride)**
**CAS number: 27083-27-8 or 32289-58-0**

**General comments**

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| 06/05/2010 | Germany / Jan Averbeck / Member State | The German CA supports to harmonize the classification & labelling for Polyhexamethylene biguanide (PHMB). | Your support is noted. | Noted |
| 07/05/2010 | France / Christophe Morice / Lannion-Tregor Agglomeration / Regional or local authority | Notre équipement aquatique utilise le PHMB pour la désinfection des eaux de baignade depuis mars 2008. | Noted | Noted |
| 07/05/2010 | France / Picot Alexandre / Individual | I have a life guard in the aquatic center of cote saint-andre in the Isere in France who use PHMB since November 2007.<br>Since : no wart, no fungus etc... | Noted. However, efficacy is not relevant for the purpose of classification. | No additional comment |
| 07/05/2010 | France / Gerald Rioual / Communauté de communes de Kaysersberg / Regional or local authority | Utilisation depuis plus de 2 ans pour la piscine de Kaysersberg car seul alternative provisoirement possbile au traitement au chlore qui lui est très corrosif, très agressif et pour lequel on ne se pose pas de question (provoque asthme, problème chloramine etc...).<br>Le PHMB procure de façon évidente et immédiate un confort respiratoire manifeste par rapport au traitement de l'eau d'une piscine avec du chlore. | Noted. PHMB is however used at very low concentration (application dose of 10 ppm recommended by manufacturer) in pools and absence of discomfort in this context does not preclude existence of toxic properties relevant for classification. | No additional comment |
| 10/05/2010 | France / Xavier Debrenne / Individual | avec 2 ans d'expérience au PHMB sur la piscine publique de Fondbonnière à l'Isle d'Abeau nous sommes aujourd'hui totalement satisfait de la formule PHMB | Noted. PHMB is however used at very low | No additional comment |

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| | | + UV. notre appartenance au protocole national engagé depuis 2008 en ce qui nous concerne conforte notre opinion en matière de traitement alternatif au chlore et permet à l'ensemble de la clientèle de comparer et apprécier cette nouvelle forme de traitement plus douce au contact de la peau et inodore dans l'ensemble du hall bassin. | concentration (application dose of 10 ppm recommended by manufacturer) in pools and absence of discomfort in this context does not preclude existence of toxic properties relevant for classification. | |
| 10/05/2010 | France / Daniel Cros / Laboratoire PAREVA / Company-Manufacturer | Our comments are dealing with :<br>- the "Very toxic" and "Toxic" classification of PHMB, based on inhalation studies<br>- the Carcinogenic Category 3 classification.<br><br>In both cases, the proposed new classification (labelling) of PHMB are premature, and not correctly motivated.<br><br>=> Premature because there was no urgency to establish a new harmonised classification proposal, due to any new event or any new study of concern regarding this product, which is still in the review program under Directive 98/8/EC(BPD).<br><br>=> Not correctly motivated because in the Inhalation toxicity study, there is a confusion between the observed effects due to the physico-chemical properties of PHMB and what has been assessed as being its systemic toxicity (which was NOT systemic toxicity).<br><br>For the prematurely proposals for harmonised classification & Labelling, please, see our attached file " 2010 05 06 - 2 - Legal arguments to EChA web-site - EN.pdf " (ZIP file).<br><br>For the confusion in inhalation toxicity study, please, see our attached file " 2010 05 06 - 1 - Scient Devel against T+ Classif (inhal) -en.pdf " (ZIP file). | Harmonisation of the classification of substances under Directive 98/8/EC is required by article 36(2) of CLP.<br><br>Responses to position papers on both legal and scientific arguments are included in the attached document: AdditionalRCOM_FR.docx | Deaths with ante-mortem signs of severe irritation and dyspnoea are not covered by the endpoint of transient, fully reversible respiratory tract irritation (as defined for STOT SE Cat 3). |
| 10/05/2010 | France / Daniel Cros / | | | No additional |

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| | Laboratoire PAREVA / Company-Manufacturer | *[ECHA: This part of the comments by France / Daniel Cros / Laboratoire PAREVA / Company-Manufacturer is copied from the attachment 2010 05 06 - 2 - Legal arguments to EChA web-site -EN.pdf]*<br><br>**<u>Inhalation Toxicity</u>**<br>Re: Polyhexamethylene biguanide or Poly(hexamethylene) biguanide hydrochloride (PHMB)<br><br>Submission of Laboratoire Pareva ("Pareva"), recording the proposal for harmonised classification of the biocidal active substance PHMB. We understand that the proposal has been submitted by France under Article 37(1) of Regulation 1272/2008 and that it was subsequently published on the web-site of the European Chemicals Agency ("ECHA"). The classification proposal is for Xn; R22 / T+; R26 / Xi; R41 / Xi ; R43 / T; R48/23 / Carc. Cat. 3, and R40 / N, R50/53.<br><br><u>Pareva respectfully, but urgently, requests that Echa suspends the consideration of this classification proposal.</u><br><br>The grounds for requesting suspension are that the proposal (i) is premature and not<br>motivated; (ii) is scientifically flawed and based on misinterpretation of applicable<br>guidance, and (iii) disrespects a series of procedural rights and expectations of Pareva.<br><br>**(1) The Proposal is Premature and not Motivated**<br><br>(a) The Biocidal Products Directive 98/8/EC ("the BPD")<br><br>PHMB is a biocide active substance which has been notified by two companies, Pareva and Arch Chemicals, under the BPD and its implementing Regulations, in particular Regulation (EC) 1451/2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC ("the Second Review Regulation"). PHMB was<br>notified in the following uses or product types ("PTs"): 1 (human hygiene | On the first point, it should be noted that the dossiers submitted on PHMB under BPD by the company Arch were accepted as complete on February and April 2008. These dossiers contain sufficient | comment |

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| | | biocidal<br>products), 2 (private area and public health area disinfectants and other biocidal products), 3 (veterinary biocidal products), 4 (food and feed area disinfectants), 5 (drinking water disinfectants) and 6 (in-can preservatives).<br><br>France is the Rapporteur Member State ("RMS") designated to carry out the review of PHMB and to produce a Competent Authority Report ("CAR") in accordance with Article 14(1) of Regulation 1451/2007. The current status of that review is that France is yet to produce its CAR. Indeed, in application of Articles 13(4) and 14(2) of the Second<br>Review Regulation, France has granted Arch Chemicals and Pareva additional time to complete and update their dossier. Both companies have set up a consortium agreement to jointly prepare and submit some of the supplementary studies requested.<br>In this respect, Article 13(4) provides that "[i]f the [RMS] considers that it has received sufficient evidence, it shall carry out its evaluation in accordance with Article 14 as if the dossier were complete. Otherwise, the evaluation shall not commence until the missing information is submitted" (underlining added). In the present case, we understand that France will prepare a CAR after the requested supplementary studies will be made available.<br><br>(b) Regulation 1272/2008 ("the CLP")<br><br>In its classification proposal, France states that "PHMB is currently under evaluation by the Rapporteur Member State France in the context of the Biocidal Products Directive (98/8/EC). In accordance with Article 36(2) of the CLP Regulation, PHMB should be considered for harmonized classification and labelling. Therefore, this proposal considers all human health and environmental end points." (page 55)<br>While it is not contested that Article 37(1) of the CLP allows Member States to submit classification proposals, Pareva submits that such proposals must be accurate in terms of contents. At the outset, Article 36(2) CLP states that biocide active substances should "normally" be made subject to a harmonized classification. This is not an absolute legal requirement, but leaves a certain margin of discretion to Member States to decide on whether harmonized classification is needed. | information to justify a classification proposal on PHMB, in particular concerning a classification proposal as carcinogenic of category 2 according to CLP regulation (EC 272/2008). Although additional information are still awaited from applicants at this time, the whole database of available information is considered sufficient to establish a classification proposal.<br><br>As indicated, national authorities have applied their discretion to submit a proposal of harmonised classification for PHMB considering on one hand that harmonization of the market intended by the Biocidal Products Directive 98/8/EC (BPD) implies an harmonization of the classification of active substance at the European level in agreement with article 36(2) of CLP and on the other hand, that data available on PHMB raise sufficient levels of concern to motivate evaluation of PHMB classification, in particular regarding | |

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| | | Paréva stress the fact that the RMS does not base its harmonised classification proposal on urgency, denying from a new study or any new event concerning the product.<br>In the present case, Pareva submits that France misapplied its discretion by proposing a harmonized classification that was not included by any of the notifiers, *i.e.*, Pareva and Arch Chemicals, in their biocide dossiers, while at the same time it expressly stated that its proposal is based on these dossiers. Specifically, the proposed classification by France for respiratory toxicity (T+R2; TR48/23) comes as a complete surprise to both notifiers, as it was not proposed by them in their biocide dossiers and seems to be based on misinterpretation of scientific data and applicable guidelines by the RMS(see below). | carcinogenicity and acute toxicity. A delay in the evaluation of such elements by European authorities is therefore not acceptable.<br><br>Finally, the absence of classification for some properties in the dossiers submitted by the applicants under BPD cannot be a scientific or legal argument against the proposed classification. As Member State Competent Authority (MSCA) and in particular as Rapporteur Member State for the substance under BPD, it is our responsibility to evaluate the data submitted under BPD and all relevant data to our knowledge to establish the classification proposal. It reflects MSCA position and may therefore differ from initial conclusions of the applicants. A public consultation takes place in the process of the harmonization of the classification of substances to allow interested parties to comment. The applicants of PHMB have obviously used this opportunity to present their positions and all their | |

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| | | **(2) The Proposal is Scientifically Flawed and based on Misinterpretation of Guidance**<br><br>The proposed classification for respiratory toxicity effects is based on erroneous interpretations of certain old studies (*e.g*. 1976 Carney inhalation study) from which certain conclusions were drawn which are not scientifically sustainable. Indeed, the observed mortality (in rats) in these studies is caused by physico-chemical properties of PHMB (because it is a cationic substance, surfactant and coating agent), not by the inherent systemic toxicity of the substance. Because of interfererence due to these physico-chemical properties, the toxicity of PHMB through inhalation cannot be determined using the normal test methods. In addition, such inhalation studies should no longer be conducted or repeated because they cause unnecessary suffering on vertebrate animals, which should be avoided, and produce no useful result.<br><br>Pareva also points to the applicable guidance on inhalation toxicity testing, specifically:<br>• "*The Technical Guidance document in support of the Directive 98/8/EC concerning the placing of Biocidal Products on the Market; Guidance on Data Requirements for Active Substances and Biocidal Products (ECB, February 2008)*".<br>• "*OECD Guidance 403 (Adopted on 7 September 2009 - © OECD, 2009); OECD* | comments will be available to the Risk Assessment Committee (RAC) when the RAC will issue its opinion on the harmonized classification of PHMB so that all arguments are considered in their final decision.<br><br>On the second point, the arguments presented are strictly scientific arguments and they are commented below in response to the scientific arguments. | |

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| | | *Guideline for the Testing of Chemicals; Acute Inhalation Toxicity*".<br>• "*Series on Testing and Assessment, Number 39, Guidance Document on Acute Inhalation Toxicity Testing (21.07.2009)*".<br><br>The first guidance supports the argument that inhalation toxicity studies are not appropriate for PHMB because the substance is not volatile, not a powder and is not applied in preparations which are powders or are to be applied in a manner which generates aerosols, particles or droplets in the inhalable size range (similar to corrosive substances, actual inhalation toxicity cannot be determined because of its physicochemical properties). The two other guidance documents also support the argument that acute inhalation testing is not required if the physical form of a test article, as it is marketed or used, precludes any human inhalation exposure. Reference is made to the attached scientific position paper which provides a more detailed explanation.<br><br>**(3) Procedural Rights and Expectations of Pareva; Rights of Defence**<br><br>Prior to the submission of the classification proposal under Article 37(1) of the CLP, it is understood that France discussed parts of the proposed classification with Arch Chemicals and with Paréva (concerning the proposed CMR 3 classification). However:<br>- It is understood that at no point did it discuss with Arch Chemicals or Paréva the classifications in addition to CMR 3, especially as regards alleged respiratory sensitization effects (T R22; R48/23). | On the third point, a compulsory and systematic consultation of the interested parties before the submission of a harmonized classification proposal is not legally required. Indeed, a public consultation is organized at the European level after the submission of the proposal to give the opportunity to any interested party to present its arguments, in agreement with article 37 (4) of CLP. Pareva has obviously be able to submit its comments during this procedure. The process of the PHMB proposal for harmonized classification therefore fully | |

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| | | **(4) Conclusion and Request**<br><br>Thought the present letter, Pareva expresses its strong reservations about the part concerning inhalation toxicity, the proposal for a harmonized classification of PHMB made by France, and it strongly objects to the lack of consultation in a procedure that ultimately may culminate in a decision adverse to its interests and in which its procedural rights and expectations as a notifier under the BPD have been infringed.<br>In the light of the points raised in this argumentation and its attachment, we, respectfully, but urgently, request that Echa, provisionally suspends the procedure relating to the proposed harmonised classification of PHMB until the review of PHMB under the BPD has been completed and a decision on Annex I listing (or not) of the substance has been taken with due account of the procedural rights and expectation of the notifiers. | complies with legal requirements.<br><br>In conclusion, the French MSCA considers that there is no acceptable justification to suspend the procedure of harmonisation of the classification of PHMB and considers that ECHA can carry on the procedure. | |
| 11/05/2010 | Germany / Wolfgang Pape / Beiersdorf AG / Company-Downstream user | Beiersdorf's comments are:<br>Polyhexamethylene biguanide (PHMB), a polymeric preservative is among other also been used for Cosmetic Products and is regulated in Annex VI of the Council Directive (76/768/EEC). Currently this polymeric chemical is being evaluated under the review programme established by the Biocidal Products Directive (98/8/EC) for existing biocidal active substances. The Rapporteur Member State (RMS) is France and the substance is being supported by Arch Biocides for a variety of applications.<br>As part of the review process, an Annex XV dossier has been accepted by ECHA which proposes the following harmonised Classification & Labelling (CLH) for PHMB (RMS – France, 2010):<br><br>Proposed classification based on Directive 67/548/EEC criteria:<br>Xn; R22<br>T+; R26<br>Xi; R41<br>Xi ; R43<br>T; R48/23 | Noted. Response to Beiersdorf comment is provided in front of Beiersdorf comment in the carcinogenicity section. | Noted |

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| | | Carc. Cat. 3 ; R40<br>N, R50/53<br>Proposed classification based on CLP criteria:<br>Hazard statements:<br>Acute Tox 4 – H302<br>Acute Tox 1 – H330<br>Eye Damage 1 – H318<br>Skin Sens 1 – H317<br>STOT RE 1 – H372 (respiratory tract) (inhalation)<br>Carc 2 – H351 (default)<br>Aquatic Acute 1 - H400<br>Aquatic Chronic 1 - H410<br>Signal word: "Danger"<br>Pictograms: GHS05, GHS 06, GHS08, GHS09.<br><br>The BEIERSDORF AG wishes in particular to comment on one aspects of this proposal, which is:<br>Carc. Cat. 3 ; R40 (category 3 carcinogen). | | |
| 12/05/2010 | France / Lannion-Tregor Agglomeration / Regional or local authority | Our aquatic equipment uses the PHMB for the pool watersdisinfection since March 2008. | Noted | Noted |
| 12/05/2010 | UK / Colin Berry / Individual | I am an independent consultant in toxicology who has advised ARCH on the interpretation of data on the carcinogenicity of PHMB and co-authored an independent review of such data (Mann, P., C. Berry, and P. Greaves. (2009). Scientific Advisory Panel Review of Polyhexamethylene Biguanide (PHMB): Carcinogenicity Studies, Pathology Working Groups, Regulatory Responses, and Mode-of –Action Studies. Scientific Advisory Panel Report. EPL Study Number: 880-001. Experimental Pathology Laboratories, Inc. P. O. Box 169, Sterling, VA 20167). A copy of this review is attached for convenience. Based on my familiarity with the data from this review I believe that the proposed classification as "Carc. Cat. 3 ; R40" is not supported by the evidence referred to in the Annex XV proposal (CLH report). I therefore wish to offer the comments given below and request that they be taken into consideration in the evaluation of the proposed classification for this substance.<br>My experience and expertise are detailed in the attached C.V. | The Scientific Advisory Panel review has been carefully considered and comments are included in the attached document: AdditionalRCOM_FR.docx. We however consider that the overall weight of evidence is consistent with CLP classification Carc 2 – H351. | Agreed |

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| | | Professor Sir Colin Berry<br><br>*[ECHA: Please note that there is still a confidentiality issue under discussion, related to the comments received from prof. Colin Berry and ECHA is waiting for his confirmation. Please do not disclose any information related to this comment, until the issue is clarified.]*<br><br>---<br><br>**Confidentiality claim:**<br>The attached SAP report (Mann, P., C. Berry, and P. Greaves. (2009). Scientific Advisory Panel Review of Polyhexamethylene Biguanide (PHMB): Carcinogenicity Studies, Pathology Working Groups, Regulatory Responses, and Mode-of –Action Studies. Scientific Advisory Panel Report. EPL Study Number: 880-001. Experimental Pathology Laboratories, Inc. P. O. Box 169, Sterling, VA 20167) is the intellectual property of Arch Chemicals and their investment in this report would be seriously prejudiced if it was released into the public domain. The extract above identifies all relevant data needed to make an assessment.<br><br>*[ECHA: Please note that this extract refers to the comment given under the carcinogenicity heading.]* | | |
| 12/05/2010 | Belgium / Evelyn Coelis / COLIPA / Industry or trade association | Colipa, the European Cosmetics association represents the interests of the European cosmetics industry. Colipa's membership consists of 16 international companies and 25 national associations representing also companies based at national level. Furthermore, Colipa has 4 supporting association members and 2 correspondent members. All in all, over 2000 cosmetic companies are directly or indirectly represented by Colipa.<br>Polyhexamethylene biguanide (PHMB) is a substance which is of interest to the cosmetics industry. It is used as an approved preservative in a number of cosmetic products today. Only those substances which are listed in a specific annex of the Cosmetics Directive can be used as preservatives in cosmetic products (Annex VI Part 1 of the European Cosmetics Directive 76/768/EEC: List of preservatives allowed) after a thorough review of their safety file by the Scientific Committee advising the EU Commission. Adequate product | Noted. | Noted |

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| | | preservation is a key aspect of the overall safety of cosmetic products. For this reason and because formulators of personal care products have a limited number of ingredients to choose from when developing preservation systems, industry is very keen on maintaining all preservatives which can be safely used in cosmetic products today, including PHMB.<br>Carcinogenic, Mutagenic and toxic for Reproduction (CMR) classifications that are harmonized under the EU Chemical legislation (67/548/EEC or REACH 1907/2006/EC) are referenced in the European Cosmetics Directive (76/768/EEC) and have thus an impact on the cosmetics industry in Europe. The Cosmetics Directive allows the industry to demonstrate safe use of CMR 3 classified substances in cosmetics through the submission of a complete safety assessment to the European Commission. Nevertheless, Colipa wishes to comment already at ECHA level because we understand that there are discrepancies between different evaluations of the same scientific data.<br><br>Colipa kindly asks to give the comments of Arch Chemicals on the proposal of the French authorities to classify PHMB as a CMR category 3 substance full scientific consideration and to review the raw scientific data on carcinogenicity and inhalation toxicity of PHMB prepared by an expert panel of independent reviewers and submitted by Arch Chemicals. | The Scientific Advisory Panel review and the other documents submitted by Arch Chemicals have been carefully considered and comments are included in the attached document: AdditionalRCOM_FR.docx. We however consider that the overall weight of evidence is consistent with CLP classification Carc 2 – H351. | |
| 12/05/2010 | UK / Jack Poppleton / Arch UK Biocides Ltd / Company-Manufacturer | Polyhexamethylene biguanide (PHMB), a polymeric chemical, is currently being evaluated under the review programme established by the Biocidal Products Directive (98/8/EC) for existing biocidal active substances. The Rapporteur Member State (RMS) is France and the substance is being supported by Arch Biocides for a variety of applications. The function of PHMB is primarily to control bacteria in a variety of disinfection and preservation | Noted | Noted |

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| | | applications. Disinfection applications include hard surface disinfection, water treatment and hand wash applications. Preservative uses include in-can preservation, textile treatments and industrial water system treatments. PHMB is also a preservative for Cosmetic Products and appears in Annex VI of the Cosmetics Directive.<br>As part of the review process, an Annex XV dossier has been accepted by ECHA which proposes the following harmonised Classification and Labelling (CLH) for PHMB:<br><br>Proposed classification based on Directive 67/548/EEC criteria:<br>Xn; R22<br>T+; R26<br>Xi; R41<br>Xi ; R43<br>T; R48/23<br>Carc. Cat. 3 ; R40<br>N, R50/53<br><br>Proposed classification based on CLP criteria:<br>Hazard statements:<br>Acute Tox 4 – H302<br>Acute Tox 1 – H330<br>Eye Damage 1 – H318<br>Skin Sens 1 – H317<br>STOT RE 1 – H372 (respiratory tract) (inhalation)<br>Carc 2 – H351 (default)<br>Aquatic Acute 1 - H400<br>Aquatic Chronic 1 - H410<br>Signal word: "Danger"<br>Pictograms: GHS05, GHS 06, GHS08, GHS09.<br><br>Arch wishes to comment on two aspects of this proposal. These are:<br>a) Carc. Cat. 3 ; R40 (category 3 carcinogen)<br>b) T+; R26 and T; R48/23 (long term risk from inhalation)<br><br>Arch believes that the carcinogenicity risk is not supported by the evidence and | | |

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| | | that the inhalation risk stems from irritation -not from toxicity. Accordingly, Arch proposes, that the correct classification for the substance would be:<br><br>Proposed classification based on Directive 67/548/EEC criteria:<br><br>• Xn; R22<br>• Xi; R37<br>• Xi; R41<br>• Xi ; R43<br>• N, R50/53<br><br>Proposed classification based on CLP criteria:<br>• Hazard statements:<br>• Acute Tox 4 – H302<br>• Eye Damage 1 – H318<br>• Skin Sens 1 – H317<br>• STOT SE 3 – H335 (respiratory tract)<br>• Aquatic Acute 1 - H400<br>• Aquatic Chronic 1 - H410<br>• Signal word: "Danger"<br>• Pictograms: GHS05, GHS07, GHS09.<br><br>Detailed reasoning for these changes is made in the relevant sections below.<br>Two independent reviews of the information have been conducted by world class experts in the field of carcinogenicity, one requested by the US Environmental Protection Agency and the other requested by Arch Chemicals. Both reviews have been supplied to RMS France. Arch also submits a series of documents supporting these views in the upload attachments area of this commenting page.<br>----<br><br>**Confidentiality claim:**<br>Two of the 4 documents attached are the intellectual property of Arch Chemicals and their investment in these reports would be seriously prejudiced if they were released into the public domain. The two reports in question are: | Responses to comments are provided in the respective sections. | |

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| | | a)Busey WM, 1996,Polyhexamethylene Biguanide: Two Year Feeding Study in Rats.Pathology Working Group Peer Review of Proliferative Vascular Lesions in Male & Female Rats. Central Toxicological Laboratory, Macclesfield, UK. CTL/C/3172. Unpublished.<br><br>b)Kamendulis, L. M. 2008. Studies to Elucidate the Potential Involvement of the Kupffer Cell in PHMB Mouse Liver Hemangiosarcomas. Department of Pharmacology and Toxicology. Indiana University School of Medicine. Indianapolis, Indiana. Unpublished.<br><br>The extract above and the attached summary document (RESPONSE BY ARCH UK BIOCIDES LTD., TO CLH REPORT – PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING – POLYHEXAMETHYLENE BIGUANIDE. April 30, 2010) identify all relevant data needed to make an assessment. | | |
| 13/05/2010 | Netherlands / Unilever / Company-Downstream user | Unilever, which is one of the world's leading fast moving consumer goods companies, produces notably a large number cosmetic and household care products under well-known brand names such as Lux, Dove, Domestos, Lysoform and Klinex.<br>Polyhexamethylene biguanide (PHMB) is a biocidal active substance substance of which the primary function is to control bacteria in a variety of disinfection and preservation applications. Disinfection applications include hard surface disinfection, and hand wash applications. Preservative uses include in-can preservation, and as a preservative for Cosmetic Products, which is a key aspect of the overall safety of cosmetic products.<br>Unilever would like to comment at ECHA level because we are convinced that the response of Arch Chemicals to the proposal of the French authorities to classify PHMB as a CMR category 3 substance should be given full scientific consideration.<br>Unilever kindly asks to review the raw scientific data on carcinogenicity of PHMB prepared by an expert panel of independent reviewers and submitted by Arch Chemicals. | Noted<br><br>The Scientific Advisory Panel review and the other documents submitted by Arch Chemicals have been carefully considered and comments are included in | Noted |

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| | | | the attached document: AdditionalRCOM_FR.docx. We however consider that the overall weight of evidence is consistent with CLP classification Carc 2 – H351. | |
| 13/05/2010 | France / Le Nautile / Centre AQUATIQUE/ Swimmingpool / Company-Downstream user | All staff is satisfied with the P.H.M.B. product:general atmosphere around the pool is pleasant, not-toxic and kind for the customers<br>For the technicial expert, the product is easy to handle and not dangerous. Since we have treated the playful pool with the P.H.M.B product,we have found the solution concerning the chloramines. | Noted. PHMB is however used at very low concentration (application dose of 10 ppm recommended by manufacturer) in pools and absence of discomfort in this context does not preclude existence of toxic properties relevant for classification. | Noted |
| 14/05/2010 | UK / Christopher Flower / The Cosmetic Toiletry and Perfumery Association / Industry or trade association | The Cosmetic, Toiletry and Perfumery Association (CTPA) is the trade association that represents the cosmetics industry in the United Kingdom. Our members are manufacturers and brand owners of cosmetic and personal care products as well as ingredient suppliers and comprise both multinational companies and SMEs. CTPA is a member association of Colipa, the European Cosmetics Association.<br><br>The basic premise of the European Cosmetics Directive (76/768/EEC) is that a cosmetic product must not cause harm to human health when applied under normal or reasonably foreseeable conditions of use. In the EU, it is the responsibility of the manufacturer / importer to assure the safety of cosmetic products and their ingredients. A key element of the EU approach is a thorough safety assessment of each cosmetic product that is put on the EU market. The safety assessment has to be carried out by a duly qualified person and is based on the safety profile of the final cosmetic product as well as its ingredients.<br><br>CTPA is aware of the proposal for the classification of polyhexamethylene biguanide (PHMB) under the CLP Regulation (EC) No 1272/2008 and is | Noted. | No additional comment. |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | thankful to ECHA for the opportunity to respond to this public consultation on the proposal.<br><br>Polyhexamethylene biguanide (International Nomenclature of Cosmetic Ingredients (INCI) name: polyaminopropyl biguanide) is used by a number of our members as a preservative in cosmetic products.<br><br>Preservatives are essential components of the majority of cosmetic products. They act to protect against contamination by microorganisms during storage and to ensure continued safe use by the consumer. Without preservation cosmetic products can become contaminated, leading to product spoilage and possibly even irritations or infections.<br><br>Only those preservatives that have been assessed by the European Commission's independent expert scientific committee as safe and approved by the member states can be used in cosmetic products. These preservatives are listed in Annex VI to the Cosmetics Directive along with the maximum permitted levels. Under entry 28 of Annex VI to the Cosmetics Directive, poly(1-hexamethylenebiguanide hydrochloride) (CAS 32289-58-0) is permitted for use as a preservative in cosmetics up to a maximum concentration of 0.3% in the finished product.<br><br>We are aware that several of our members have been liaising with the raw materials supplier Arch Chemicals which has taken the lead in providing a submission to the ECHA consultation, commenting in particular upon certain aspects of the proposal, namely the Carc. Cat. 3; R40 (Category 3 carcinogen) and T+; R26 and T; R48/23 (long term risk from inhalation) classifications (based on Directive 67/548/EEC criteria).<br><br>As representative of approximately 85% of the UK cosmetics market by value, CTPA is making this comment in support of the submission by Arch Chemicals and requests that the Risk Assessment Committee take due consideration of the argumentation provided in that submission. This submission does not just represent the interests of one company but many of our members, both raw material suppliers and down-stream users. We also understand that a similar support is being expressed at the European level by Colipa. | It should be noted that a classification of PHMB Carc 2 – H351 would imply that mixtures containing PHMB would be considered carcinogenic according to classification only at concentration exceeding 1%.<br><br>The Scientific Advisory Panel review and the other documents submitted by Arch Chemicals have been carefully considered and | |

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| | | | comments are included in the attached document: AdditionalRCOM_FR.docx. We however consider that the overall weight of evidence is consistent with CLP classification Carc 2 – H351. | |
| 14/05/2010 | France / Bernard Rosso / Iget Chimie - Laboratoires Aci / Company-Downstream user | Our company uses PHMB as an active substance in formulations used for veterinary hygiene purposes including products used in areas in which animals are housed (PT3 of directive 98/8/CE, known as the « BPD »), disinfection products of drinking water for animals (PT5 of directive 98/8/CE).<br>Our comments deal with your following labelling proposals :<br>- Carc.Cat3 R40 (pages 3-4 then 34-44)<br>- T+ R26 and T R48/23 (pages 3-4 then 14-15 and 29-33 and 44 and )<br>Please, see our comments in the respective specific part here under. | Responses to comments are provided in the respective sections. | Noted |
| 14/05/2010 | Germany / B. Braun Melsungen AG / Company-Downstream user | PHMB (INN: Polihexanide) is currently being evaluated under the review programme established by the Biocidal Products Directive (98/8/EC) for existing biocidal active substances.<br>The function of PHMB is primarily to control bacteria in a variety of disinfection and preservation applications. Disinfection applications include hard surface disinfection, water treatment, hand wash applications. Preservative uses include in-can preservation, textile treatments and industrial water system treatments. PHMB is also a preservative for Cosmetic Products and appears in Annex VI of the Cosmetics Directive.<br>As part of the review process, an Annex XV dossier has been accepted by ECHA which proposes the following harmonised Classification and Labelling (CLH) for PHMB (RMS – France, 2010):<br><br>Proposed classification based on Directive 67/548/EEC criteria:<br>Xn; R22<br>T+; R26<br>Xi; R41<br>Xi ; R43<br>T; R48/23<br>Carc. Cat. 3 ; R40<br>N, R50/53 | Noted. | Noted |

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| | | Proposed classification based on CLP criteria:<br>Hazard statements:<br>Acute Tox 4 – H302<br>Acute Tox 1 – H330<br>Eye Damage 1 – H318<br>Skin Sens 1 – H317<br>STOT RE 1 – H372 (respiratory tract) (inhalation)<br>Carc 2 – H351 (default)<br>Aquatic Acute 1 - H400<br>Aquatic Chronic 1 - H410<br>Signal word: "Danger"<br>Pictograms: GHS05, GHS 06, GHS08, GHS09.<br><br>We wish to comment on two aspects of this proposal:<br>a) Carc. Cat. 3 ; R40 (category 3 carcinogen)<br>b) T+; R26 and T; R48/23 (long term risk from inhalation)<br><br>We believe that the carcinogenicity risk is not supported by the data set and that the inhalation risk stems from irritation -not from toxicity. Accordingly, we propose that the correct classification for the substance would be:<br><br>Proposed classification based on Directive 67/548/EEC criteria:<br><br>• Xn; R22<br>• Xi; R37<br>• Xi; R41<br>• Xi ; R43<br>• N, R50/53 Proposed classification based on CLP criteria:<br>• Hazard statements:<br>• Acute Tox 4 – H302<br>• Eye Damage 1 – H318<br>• Skin Sens 1 – H317<br>• STOT SE 3 – H335 (respiratory tract)<br>• Aquatic Acute 1 - H400<br>• Aquatic Chronic 1 - H410<br>• Signal word: "Danger" | Responses to comments are provided in the respective sections | Rapporteurs and RAC do not consider R37 as appropriate. |

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| | | • Pictograms: GHS05, GHS07, GHS09.<br><br>Detailed reasoning for these changes is made in the relevant sections below. | | |
| 14/05/2010 | Portugal / Member State | Considering the present proposal, we agree to establish a harmonised classification & labelling for PHMB.<br>The proposed Classification and Labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive (health and environment).Therefore, we support this proposal.<br>Nevertheless there seems to be a minor inconsistency with the NOEC value for sediment organisms, for which were presented two different results, 196 mg.kg-1 wet weight in section 7.1.1.4 and 391 mg.kg-1 wet weight in table 26. Therefore, it should be verified which value is correct.<br>We also consider that it should be mentioned if the relevant tests were performed under GLP conditions. | Thank you for your support and your careful reading. The correct value NOEC for sediments organism is 196 $mg.kg^{-1}$ wet weight. The document has been amended.<br>GLP statements have been added in table 26 of the revised CLH report. | No additional comment |
| 14/05/2010 | France / Cecile Bourquet / MAREVA / Company-Downstream user | We are very surprised of the proposed labelling for the product PHMB, and more particularly for the classifications "Toxic" or "Very Toxic" by inhalation ("skull" logo with the sentences R26 and R48/23) or Carc. Cat 3 (with the sentence R40). | Noted | Noted |

**Carcinogenicity**

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| 10/05/2010 | US / Samuel Cohen / Individual | I am writing with respect to the findings in rats and mice regarding polyhexamethylene biguanide (PHMB). I am relying on the report entitled, "Scientific Advisory Panel Review of Polyhexamethylene Biguanide (PHMB); Carcinogenecity Studies, Pathology Working Group, Regulatory Response of Mode-of-Action Studies." The major issues are the finding of hemangiosarcomas in rats and mice. Based on my review of this material as well as my background knowledge of this particular tumor type, I concur with the interpretation of the Pathology Working Group indicating that the results in the rats are not related to treatment and that the finding in the mice are most likely related to the administration of a dose well in excess of the maximum tolerated dose (MTD), leading to tumors associated with the severe toxicity engendered at this dose, the carcinogenicity not due to the chemical itself. | This comment was also submitted as an attached document submitted by Arch Chemicals "Letter from Dr S Cohen.pdf" and included in the document "ARCH RESPONSE 30 April 2010.pdf". Responses to this comment are therefore included in the attached document: AdditionalRCOM_FR.docx. | Noted |

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| | | First, I would like to comment on the composition of the Pathology Working Group and Science Advisory Panel. This panel consisted of Dr. Peter C. Mann, Professor Sir Colin Berry, and Dr. Peter Greaves. This is a highly distinguished group of individuals who are not only highly capable in their abilities in histopathology, but in the interpretation of the studies with respect to biology and human relevance. In particular, Dr. Greaves and Dr. Berry are M.D. pathologists with a long and distinguished record regarding the evaluation of animal studies and interpreting the implications with respect to humans.<br><br>The results in rats I believe are as stated by this panel, and are not treatment related. Based on the results of the investigation of the Pathology Working Group, the tumor incidence consisted of two hemangiomas in the high dose group in both males and females and one hemangiosarcoma in the low dose group in the females. Importantly, one hemangiosarcoma was present in the low dose female group and one with the high dose, with none with the mid-dose. Importantly, the finding of hemangiomas in the high dose group in both males and females is not relevant to the interpretation of the results with respect to hemangiosarcomas. This is clearly delineated by the Pathology Working Group, but I would highlight this by the recent conclusion of a broad panel of experts from academia, government and industry in the publication by Cohen et al. (Toxicological Sciences, 111:4-18, 2009) which concluded that there truly are not precursor lesions for hemangiosarcomas that are known in either animals or in humans. Hemangiomas are common in mice, rats, as well as humans, whereas hemangiosarcomas are common in mice, uncommon in rats, and exceedingly rare in humans. In fact, as described in the Expert Panel Report, there is considerable evidence that hemangiomas do not actually represent a neoplastic response, but rather, represent a hamartomatous lesion. Hamartomas are not preneoplastic and represent merely an accumulation of normal types of tissues into a distinctive nodule or mass. Hemangiomas are common in humans, not only in childhood, but increasingly in adults as we age. The small skin lesions in adults have the unfortunate title of being called senile hemangiomas. The important conclusion is that the hemangiomas should not be included in the overall assessment of hemangiosarcomas in these rats. The evidence strongly | | The comment is conflicting to the CLH report with respect to the following point: The hemangiosarcoma in a low dose female was not considered in the CLH dossier (see Table 19 of BD). Instead it is reported that there is one hemangiosarcoma in a high dose females. |

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| | | supports the conclusion of the Pathology Working Group that hemangiosarcomas were not treatment related in the rat study, and represent neither a carcinogenic hazard or risk for humans.<br><br>The results in mice are quite different from those in the rat. There is unquestionably a treatment related effect at the high dose in both males and females. At the lower doses, the incidences of hemangiosarcomas were essentially the same as the controls. The Pathology Working Group came to the conclusion of slightly different incidences compared to the Study Pathologists, but nevertheless, there is unquestionably a treatment related effect at the high dose. The Pathology Working Group deals more than adequately with the issue of counting animals with these lesions rather than individual organs, such as liver and spleen. Also, they deal quite readily with the issue of classification of hemangiosarcoma and hemangioma and the lack of relationship of these two diagnoses. An important consideration is the high background incidence of hemangiosarcomas in male and female mice, greater than 10%. As the Pathology Working Group notes, and has been extensively commented in the literature, mice have a very high background incidence of hemangiosarcomas, predominantly in the liver, but also commonly in spleen, bone marrow, and subcutaneous adipose tissue. I do not know the historical control incidences from this particular laboratory, but I am certain that the concurrent control was well within the range seen in the historical controls. Thus, the incidences at the 400 and 1200 ppm doses are within these control ranges, and thus are below an effect level.<br><br>The incidences of hemangiosarcomas at 4000 ppm are increased in both the males (12 of 55 mice) and females (10 of 55 mice). The important issue for interpretation of this study, however, has nothing to do with this particular diagnosis, per se, but with the fact that the animals were administered a dose that turned out to be severely toxic and well above the maximum tolerated dose (MTD). The findings at 4000 ppm should thus be completely disregarded in the overall risk assessment.<br><br>Treatments at doses well in excess of the MTD are well known to be unrelated to potential risk of carcinogenesis, or for that matter, toxicology, for humans. The most notorious example is the finding of liver tumors in | | |

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| | | mice administered acetaminophen (paracetamol), the commonly used analgesic. In a large number of studies which have been reported utilizing doses within the MTD, there was no evidence of hepatocarcinogenesis, or for that matter, any evidence of carcinogenicity. However, in the one publication (Flaks and Flaks, Carcinogenesis, 4: 363-638, 1983) in which an increased incidence of liver tumors was detected in mice involved administration of a dose that was well in excess of the MTD. Actually, in the Flaks and Flaks study, the extent of decreased body weight gain was comparable to that seen in the present experiment with 4000 ppm PHMB. There clearly is no concern about carcinogenicity risk to humans related to paracetamol. On the same basis, there should be no concern about human carcinogenic risk from PHMB.<br><br>Mode of action analysis actually sheds some light on a potential mechanism that might be involved with the tumors at this high, toxic dose. At the highest dose level there was intestinal toxicity, which resulted in an increase in plasma endotoxin levels in studies after 14 and 28 days. This was associated with hepatic endothelial cell proliferation. Endotoxin is well known to have as one of its effects an increase in endothelial proliferation. Since the endotoxin would be arising from the damaged gastrointestinal tract, its first site of contact internally would be through the portal vein and possibly lymphatics, reaching the liver. This would be handled primarily by the reticuloendothelial system in the liver, the endothelial cells and the Kupffer cells. The findings in the short term mode of action examinations are entirely consistent with this postulated mode of action. Most importantly, the short term studies demonstrate that there is an increase in endothelial cell proliferation in the liver following administration of the high dose of the chemical. Since the chemical is nongenotoxic, increased cancer incidence is induced by increased cell proliferation, in this case, endothelial cells, either directly or indirectly. The evidence for PHMD strongly supports an indirect induction of endothelial cell proliferation occurring secondary to the extreme toxicity in the mice.<br><br>Regardless of the findings in the mode of action analysis, however, the overriding concern with the findings at 4000 ppm is that this dose is in excess the MTD and should not be considered further in the risk assessment evaluation. Thus, the critical determinant value are the results at 1200 ppm. | | |

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| | | These are clearly negative. Thus, at acceptable dosages for a carcinogenicity study, there is not a carcinogenic effect in the mice.<br><br>In the mouse carcinogenicity study, at the dose exceeding the MTD, the hypothesized mode of action would consist of gastrointestinal irritation leading to gastrointestinal inflammation and the release of endotoxin into the portal blood, leading to endothelial cell proliferation and ultimately hemangiosarcomas. This mode of action is unrelated to the effect by the chemical, but rather, is due to the toxicity occurring at a dose that is excessive. A dose of 1200 ppm meets the criteria of an MTD, and is without the carcinogenic effect.<br><br>The findings with the mouse skin painting study unfortunately also are severely compromised. An extensive number of the animals were found to have hepatitis, possibly related to infection with Helicobacter hepaticus. Although there were some vascular tumors in the livers of these animals, these would most likely have been related to the inflammation in the liver and unrelated to the treatment with the chemical.<br><br>Several chemicals have been identified over the past decade as producing an increased incidence of hemangiosarcomas in mice. A small number have been identified that also increase the incidence of hemangiosarcomas in rats. However, the chemicals which are known to produce the hemangiosarcomas in rats (as well as in humans) are well known to be genotoxic, such as vinyl chloride and thorotrast. In contrast, the chemicals which appear to increase the incidences of hemangiosarcomas only in mice appear to be those that are classified as non-genotoxic, such as PHMB. These include compounds such as pregabalin, retinoids, 2-butoxyethanol, and PPARγ and dual PPARα/γ agonists. Although the details of the mode of action for these chemicals has not yet been ascertained in detail, considerable data has accumulated in the past decade suggest that the commonality for all of them is an increase in endothelial cell proliferation leading to the development of these tumors, and that the mouse for some reason is uniquely susceptible to these non-genotoxic effects. Similar effects in rats and humans do not appear to lead to hemangiosarcomas. | | |

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| | | The increase in endothelial cell proliferation appears to be due to either hypoxia and oxidative damage or due to a direct mitogenic effect on the endothelial cells by the chemical itself of by an indirect effect on endothelial growth factors (Cohen et al., Toxicol. Sci., 111: 4-18, 2009). The mouse has numerous differences compared to the rat and humans that might explain its unique susceptibility. The susceptibility appears to be common in many strains of mice, including the CD1 and B6C3F1 strains commonly used in bioassays. Mice have a higher background proliferation rate for endothelial cells compared to either rats or humans. Furthermore, the antioxidant protective mechanisms in mouse endothelial cells are considerably weaker than either in rats or in humans. For some of the known non-genotoxic hemangiosarcomagens, co-administration with vitamin E, which provides protection against the oxidative damage, protects against the development of the increased endothelial cell proliferation. This has been demonstrated for 2-butoxyethanol in greatest detail, including striking differences between the mouse and rat. There is also evidence that the mouse is considerably more susceptible to tissue hypoxia than either rats or humans, possibly due to striking differences in respiratory controls of acid base balance in response to decreases in oxygen saturation in the peripheral blood. In combination, the large number of differences between mice and rats, and also with respect to humans, likely contribute to the significant differences in susceptibility to background incidences of hemangiosarcomas in the different strains of mice compared to other species, such as rats and humans. Genetic susceptibility also likely plays a role. In contrast, many of these same effects have been identified in humans and not associated with the development of hemangiosarcomas, as is well described in the expert report of the Pathology Working Group.<br><br>In summary, I concur with the conclusion of the expert panel that the administration of PHMB was not treatment related to the development of hemangiosarcomas in rats. In mice, the induction of hemangiosarcomas by PHMB was not due to the chemical itself but rather the extreme toxicity with doses well in excess of the MTD, which led to increased endothelial cell proliferation and ultimately development of the hemangiosarcomas. Administration of a dose that is approximately at the MTD had no effect on the incidences of hemangiosarcomas or other tumors. Thus, I concur with the conclusion that PHMB is not carcinogenic in either rats or mice, | | |

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| | | specifically it does not induce hemangiosarcomas in these species at doses acceptable for long-term bioassays. | | |
| 06/05/2010 | Germany / Jan Averbeck / Member State | Against the background of haemangiosarcomas in the liver, which are uncommon in rats the German CA could follow the recommendation of France for a classification into cat 2 (CLP-regulation).<br><br>Page 41; 44<br>Relevant tumors after application of PHMB seem to be the haemangiomas and haemangiosarcomas of the liver in different testing animals (rat and mouse). However, the incidences were increased at doses near the MTD or above the MTD. Concerning the mid dose of the rat study from Horner (1996), quantitative data regarding the treatment-related reductions in bodyweight and the "slightly reduced survival" in females would be helpful for the discussion. Additionally more precise information concerning the statistical significance and the historical controls could facilitate the discussion. | Your support is noted.<br><br>In Horner 1996 body weights were approximately 4-6% lower in high dose males compared to male controls throughout the majority of the study period and 10% lower in high dose females compared to female controls by week 91 with divergence from controls from week 35. Kaplan-Meier survival rate were 0.92 in high dose females vs 1.0 in female controls on week 52, 0.82 vs 0.90 on week 76 and 0.39 vs 0.52 on week 104. This information has been added in the CLH report. The report from the Pathology Working Group (Busey 1996) does not report any statistical analysis of the data and all information available on historical controls are | Noted |

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| | | Although the German CA supports the proposed classification with H351, the discussed secondary MOA (endothelial cell proliferation after Kupffer cell activation due to endotoxin release from gram-negative bacteria from the GI tract) does not seem to be consistent with the observation that haemangiosarcomas were observed not only in oral studies but also in a dermal study. Since the dermal absorption of PHMB is very low (~0.2 %) and the excretion via bile is very low (~0.2 %) it is not convincing that extensive endotoxin release could be triggered by dermal exposure unless the major exposure in this study was oral due to ingestion by licking.<br><br>Thus, if this secondary mechanism of action cannot be used to support Carc 2-H351 instead of Carc1B-H350, a justification for the choice of Carc 2-H351 should be given discussing the weight of evidence including the MTD, tumours in two species, different organs and after exposure via two different routes of exposure. | already included in the CLH report.<br><br>We consider that no evidence is available to support that endotoxin release and Kupffer cell activation is the mode of action for induction of liver vascular tumours. Induction of vascular tumours in the dermal study tends to go against this hypothesis however as mentioned by Germany oral exposure by licking cannot be excluded in this study and the hypothesis may not be overruled on this basis.<br><br>In the weight of evidence, although vascular tumours are induced in two species, we consider that lack of mutagenicity, induction of a single type of tumours and induction of tumours at high doses (clear induction above MTD and more equivocal induction at doses below MTD) justifies that classification Carc 1B is not appropriate for PHMB. | |
| 10/05/2010 | France / Daniel Cros / Laboratoire PAREVA / Company- | (pp 42-44):<br>Laboratoire PAREVA has a Combined Chronic Toxicity\Carcinogenicity study (OECD 453) pending. | The classification proposal is based on the available data, which already consist | Agreed. |

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| | Manufacturer | Results (final report) will be available in September 2011.<br>Laboratoire PAREVA does not agree to classify PHMB as Carc. Cat. 3 until this study is not available. | in a large database especially for carcinogenicity and which justify classification.<br>Evaluation of the new data will be performed by France as Rapporteur Member State when available and a revision of classification will be considered if appropriate.<br>CLP regulation states that a revision of classification can be submitted by any Member State Competent Authority based on new data if considered appropriate. | |
| 11/05/2010 | Germany / Wolfgang Pape / Beiersdorf AG / Company-Downstream user | Beiersdorf's comennt is:<br>Derived mainly from the argumentation given in the CLH Report, we believe that the carcinogenicity risk is not supported by the evidence of available data. There have been performed over the time three carcinogenicity studies: i) one oral life-time feeding study in the mouse (CLH 5.7.1.), ii) one combined oral study in rats that has been conducted according to US EPA Guideline 83-5 carcinogenicity and chronic toxicity feeding study, and iii) finally the oldest a dermal 80-weeks skin painting study on mice (CLH 5.7.3.), which was performed in a time "prior to the development of any published and internationally accepted guidelines". Furthermore there exists an evaluation prepared by expert pathologists on the validity of the existing animal test data. According to the experts' opinion either the experimental data are of limited value or showing unequivocal results that do not allow to make scientifically sound conclusions concerning carcinogenicity of animal data (Mann et al. 2009).<br><br>The basis for our argumentation is the following:<br>• As expected for a polymeric substance PHMB is not absorbed through the skin in toxicologically significant amounts (CLH 5.1). This questionable study and its results show only slight increase in tumor incidences at dose | The comparison of doses inducing vascular tumours | No additional comment |

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| | | levels of 30 mg PHMB/mouse/d (or 750 mg/kg bw/d) which was according to the remarks made in the CLH Report clearly beyond the Maximum Tolerated Dose (MTD) showing excessive mortality (> 75%) and reduced body weight gain in both sexes. Furthermore, chronic irritancy was remarked directly after applications in the high level group, whereas in the 6 mg group (= 150 mg/kg bw/d) these effects were only transient and disappear during the study time. Up to this concentration there appeared to be no difference in incidences of animals with vascular tumors. We believe that the results of this "old" painting study using ethanol as vehicle should not be part of the judgment of the carcinogenic potential from PHMB. The proposed classification as an R40 carcinogen category 3 (Carc 2 – H351 [default]) is not appropriate.<br>• In the "Scientific Advisory Panel Report" on this study it was concluded "that PHMB was "not carcinogenic to mouse skin when applied at doses up to 30 mg/mouse/day for a period of 80 weeks." Both non-neoplastic and neoplastic changes in the liver were noted in the report as "variable degrees of hepatic inflammation which was especially manifest in Group 4 animals as a severe form of hepatitis. These changes appear to have been responsible for increased deaths in this group during the 52-79 week period. Although no specific infectious agent was identified in the liver microscopically, the possibility of such an occurrence cannot be excluded. It would appear that the long standing inflammatory liver changes seen in this study were responsible for the slightly increased incidence of liver tumors." | in mice in the oral and dermal studies, considering lower dermal absorption, shows a discrepancy. The more likely explanation is that oral exposure due to licking may have significantly contributed to the systemic exposure of animals in the dermal study.<br>It is noted that the high dose in the mice dermal study clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria. Section 3.6.2.3.2(j) of ECHA guidance on CLP regulation states that "If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification." Some evidence of induction of vascular tumours also available at doses below | |

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| | | | MTD in rats at the high dose and in mice by oral route at the mid-dose. Considered altogether these elements therefore points to a classification in Category 2, as proposed.<br>The SAP review emphasize on the hypothesis that tumours may be caused by an Helicobacter infection. Helicobacter have been associated with induction of hepatitis and of hepatocellular tumours (Mahler 1997). However, in this study no increase in hepatocellular carcinomas was observed and incidence of hepato-adenoma is 2/100, 1/100, 2/100 and 4/100, respectively at 0, 15, 150 and 750 mg/kg in males and females combined so that an increase is not clear. Besides, males are generally more sensitive than females and this is not consistent with what is seen in the dermal mice study. It is also surprising that Helicobacter infection occurred in the high dose group only. Therefore, it is considered that this hypothesis cannot be confirmed. | |

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| | | • The findings in mice in the oral feeding study show weaknesses and positive results only at concentrations which clearly exceed the MTD. It was concluded that "there was clear evidence of a treatment-related increase in the incidence of animals with either haemangioma or haemangiosarcoma in the high-dose of both sexes. This increase was largely due to the increased number of vascular tumors in the liver. In all other dose levels, there was no significant difference between the number of vascular tumor-bearing animals and controls. The small difference in incidence of haemangiosarcomas in the liver between control and mid-dose males was considered a chance event because it did not attain statistical significance and approximates the historical control range of haemangiosarcomas of the liver from CTL [the study laboratory]. In thirteen studies conducted at CTL from 1985 to 1994, the range of haemangiosarcomas in male mice ranged from 1.8% to 18.3%, with an average of 9.16%. In females, the range of haemangiosarcomas ranged from 0% to 9.1%, with an average of 4.2%. The six haemangiosarcomas in the liver of the mid-dose males constitutes a 10.9% incidence, which is within the range of historical controls at CTL. Up to the MTD no statistically relevant increase in tumor incidences could be observed. The findings of the dosing in excess to the MTD should not be used for concluding on any carcinogenic potential of PHMB. | It is noted that the high dose clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria, as discussed above.<br>At mid-dose in the oral mice study, no statistical analysis was shown on liver vascular tumours either in the study report, the PWG report or in the USEPA evaluation. It is therefore not possible to state that it is or it is not statistically significant. Besides, historical controls provided are historical incidences of haemangiosarcomas at any sites and no data is available for vascular tumours in liver only. It is therefore not possible to state that it is or it is not within historical controls.<br>A moderate increase of liver haemangiosarcomas is observed at mid-dose in males and considering the same carcinogenic response at the highest dose, these tumours are considered biologically significant and not incidental. | |

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| | | | It is noted that the high doses in the mice studies clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria, as discussed above. | |
| | | • In the two mouse studies the highest test concentration was fairly beyond the MTD. As a consequence it cannot be concluded that the experimental data are clearly related to carcinogenic effects of the test substance. | It is considered that the comparison of PHMB with strong carcinogenic compounds may not relevant as mode of action can be different and it does not provide an evidence of absence of a carcinogenic effect of PHMB. Besides, quinoline actually induces liver haemangiosarcomas and preneoplastic lesions in the liver such as nodular hyperplasia. However, quinoline also induces hepatocellular carcinomas and liver lesions are more likely precursor lesions for hepatocellular carcinomas and not for haemangiosarcomas. Besides, the absence of pre-neoplastic lesions does not negate the observation of liver vascular tumours above historical controls at the high dose. Finally, contrary | |
| | | • The rat study (1996) was peer reviewed as well by an Pathology Working Group (PWG) [EPL Report, 2009] where it was noted that "equivocal or marginal results in carcinogenicity tests in animals are often difficult to interpret, especially with neoplasms which occur at low frequency. This is primarily due to the variability of background or spontaneous tumor incidences among laboratory animals used in these tests. In a weight of evidence approach suggested by Squire in 1989, he noted that many observations of biological and pathological change can provide a more comprehensive basis on which to interpret equivocal or marginal test findings. These observations included damage in potential target tissue, increase in pre-neoplastic lesions in potential target tissue, increased neoplastic progression, tumor multiplicity or decreased latency, cell proliferation, evidence of genetic damage or receptor effects in potential target tissue and the biological plausibility of a result.<br>The PWG further noted that "spontaneous vascular neoplasms in the liver are rare in laboratory rats of all strains, including the Alpk:APfSD (Wistar- | | |

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| | | derived) rats. In 18 chronic toxicity and carcinogenicity studies conducted at CTL with the Alpk:APfSD strain of Wistar rat, one haemangiosarcoma has been reported in the liver of control males." No haemangiomas were reported in the livers of control rats of either sex, nor were haemangiosarcomas reported in the liver of control females.<br>Haemangiosarcomas were induced in the liver by several strongly carcinogenic chemicals including quinoline (Hirao et al., 1976), terafluorethylene (NTP, 1995) and vinyl fluoride, vinyl chloride and vinyl bromide (Bodganffy et al., 1995). In these cases, there was an associated increase in the incidence of non-neoplastic vascular changes considered to be probably pre-neoplastic precursors of vascular neoplasms in the liver. No such precursor lesions were noted in the liver in this study. Furthermore, "the incidence of vascular neoplasms in the liver in this study is low and predominantly benign. Only one of the five neoplasms was malignant."<br>The PWG noted that the "incidence of vascular neoplasms in the liver was much lower than that reported by the Study Pathologist at other sites such as the mesenteric lymph node" and that "the incidence of vascular neoplasms at these sites was not treatment related. Furthermore, the incidence of animals having vascular neoplasms at any site was not increased with treatment."<br>Based on the above observations, the PWG concluded that "the overall weight of evidence indicates that the slightly higher number of Group 4 (2000 ppm) male and female rats having vascular neoplasms of the liver is not associated with the dietary administration of PHMB. In the unanimous opinion of the PWG, these neoplasms were considered to be incidental."<br>• As a matter of fact the CHL report seems to be based on an inaccurate evaluation of the frequency and nature of the findings in the animal studies resulting in a misled assessment. Furthermore the CLH report has mixed up in an inappropriate manner the findings of haemangiomas with haemangiosarcomas in order to identify levels of statistical significance.<br>• Haemangiosarcomas are considered to be clearly depending on genotoxic effects, whereas PHMB has been demonstrated through a number of studies to be non-genotoxic. This hold true in particular humans, therefore the PHMB-induced tumor genesis is considered to have no relevance to humans.<br><br>Major References:<br>Mann, P., C. Berry, and P. Greaves. (2009). Scientific Advisory Panel | to what is mentioned in the SAP review, the incidence of vascular tumours at any site was statistically significantly increased at the highest dose in females with Peto's prevalence test according to USEPA analysis (USEPA 2003). Besides, the incidence of vascular tumours in the liver at the high dose exceeds the historical controls in both males and females, although statistical significance of liver combined vascular tumours is unknown. | |

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| | | Review of Polyhexamethylene Biguanide (PHMB): Carcinogenicity Studies, Pathology Working Groups, Regulatory Responses, and Mode-of –Action Studies. Scientific Advisory Panel Report. EPL Study Number: 880-001. Experimental Pathology Laboratories, Inc. P. O. Box 169, Sterling, VA 20167 | | |
| 12/05/2010 | Belgium / Frederic Denauw / Member State | Table 23 p 42: there is an inversion between the Horner and Milburn studies.<br><br>Given:<br>- the small increase of neoplasms at 2000 ppm in an oral study in the rats,<br>- the non-neoplastic changes in the liver at 1200ppm in a feeding study in mice and<br>- the higher incidence of haemangiosarcomas above the MTD in oral and dermal studies in mice;<br>The classification as carcinogenic 3 R40 may be supported. | Thank you. The inversion has been corrected.<br><br>Your support is noted. | Noted |
| 12/05/2010 | UK / Colin Berry / Individual | Page 34 to 46:<br>The tumour (type and location) which forms the basis for the proposed classification of carcinogenicity in the CLH report is that of haemangiosarcoma found predominately in the liver of rats and mice. Because of concerns about tumour incidence, Pathology Working Groups (PWGs) were convened to examine vascular lesions of the liver from both the 2-year feeding study in rats (Busey, 1996) and the 2-year feeding in mice (Mann, 2002). In addition, a series of experiments designed to further elucidate the Mechanism of Action for the proliferative effects from PHMB were conducted at Indiana University School of Medicine (Kamendulis, 2008). In 2009 an independent Scientific Advisory Panel (SAP) (Mann, Berry, and Greaves, 2009) was convened to review the data from these studies and to discuss the relevance of these findings to humans. The members of this SAP have extensive experience in the microscopic evaluation and interpretation of lesions observed in chronic toxicity and carcinogenicity bioassay studies in rodents as well as vascular neoplasia in humans. These reports from the various study groups have been further evaluated by Samuel M. Cohen, M.D., Ph.D., Professor, Department of Pathology and Microbiology, Havlik-Wall Professor of Oncology, at the Univeristy of Nebraska. Dr. Cohen's report is a useful overview of the studies and the prior expert reviews of their result. He concurs with the conclusion of the prior independent expert reviewers that the administration of PHMB was not treatment related to the development of | The arguments presented in these documents have been carefully considered and comments are included in the attached document: AdditionalRCOM_FR.docx. We however consider that the overall weight of evidence is consistent with CLP classification Carc 2 – H351. | No additional comment |

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| | | haemangiosarcomas in rats.<br>In mice, he concludes that the induction of haemangiosarcomas by PHMB was not due to the chemical itself but rather the extreme toxicity with doses well in excess of the MTD, which led to integrity of the gut wall being compromised which may have led to a series of cascading events resulting in endothelial cell proliferation and ultimately development of the hemangiosarcomas. Administration of a dose that is approximately at the MTD had no effect on the incidences of haemangiosarcomas or other tumours. He therefore concurs with the conclusion that PHMB is not carcinogenic in either rats or mice. Specifically PHMB does not induce haemangiosarcomas in these species at doses acceptable for long-term bioassays.Similarly, the SAP reviewed the 3 rodent bioassays and the PWG report for the 2-year rat oral study and the 2-year mouse oral study. | It is noted that high doses in the mice studies clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria. Section 3.6.2.3.2(j) of ECHA guidance on CLP regulation states that "If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification." Some evidence of induction of vascular tumours also available at doses below MTD in rats at the high dose and in mice by oral route at the mid-dose. Considered altogether these elements therefore points to a classification in Category 2, as proposed. | |

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| | | Based on this review, the SAP determined that:<br>1. PHMB shows no evidence of mutagenic activity. The CLH report makes this same conclusion.<br><br>2. All group differences in vascular tumour incidence in rats and mice except those in the high-dose group in the mouse feeding study (4000 ppm PHMB) are incidental and therefore do not indicate carcinogenic activity.<br><br>3. The incidence of vascular tumours in the high-dose group in the mouse feeding study compared with controls is not evidence of a carcinogenic effect because:<br>1. Dosing at 4000 ppm was well above the maximum tolerated dose (MTD) which together with the mode of action analysis indicated they are not relevant to lower doses. | The French authorities consider that:<br>1. Absence of mutagenity of PHMB is acknowledged and this element has been considered in the weight of evidence.<br>2. A statistical increase in liver haemangiosarcomas in female mice by dermal route at 750 mg/kg, a statistical increase in haemangiosarcomas at any site in male and in female mice by oral route at 4000 ppm and a statistical increase in haemangiosarcomas and haemangiomas at any site in female rats by oral route at 2000 ppm are observed. These increases were generally further supported by consideration of historical controls and are not considered incidental.<br><br>3. In mice by oral route:<br><br>a. High dose clearly exceed the MTD and this | |

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| | | 2. The difference in incidence of haemangiomas and haemangiosarcomas in mice in the 4000 ppm PHMB group compared with controls is modest.<br><br>3. These haemangiomas and haemangiosarcomas occur at an age where mice develop these tumours spontaneously. There is no evidence of their development occurring at an earlier age.<br><br>4. The tumours show no evidence of a shift to a less well-differentiated phenotype.<br><br>5. This pattern of a modest increase in incidence of vascular tumours in mice at two years, morphologically identical to those observed in controls, is similar to other agents that are considered non-carcinogenic. Notable examples include troglitazone and pregabalin which have been or are used as long-term therapy in humans (Anon, 2005; Duddy et al., 1999a and 1999b). | element has been considered in the weight of evidence and in accordance with classification criteria.<br>b. The increase of vascular tumours in the liver increase from 7% in male controls to 36% in high-dose males and from 2% in female controls to 22% in high-dose females.<br>c. Although vascular tumours spontaneously occur quite commonly, incidence of haemangiosarcomas at any site exceed historical controls for both males and females at the high dose. Historical control data for vascular tumours in the liver only are not available and no comparison can be made for this site specifically.<br>d. Absence of evidence of a shift to a less well-differentiated phenotype does not rule out the identification of tumours.<br>e. The carcinogenicity profiles of troglitazone or pregabalin drugs are not known but the French authorities are not aware | |

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| | | 6. A plausible explanation has been advanced for the higher incidence of haemangioma and haemangiosarcoma in the mouse at the 4000 ppm dose group compared with controls. The data suggests that there is an underlying process of sustained cytotoxicity and increased DNA synthesis in hepatic endothelial cells in mice given high doses of PHMB. As these effects do not occur at lower doses vascular tumours are unlikely to occur at low exposures. As a consequence the mouse liver tumour findings are irrelevant to use of PHMB as proposed where exposure to humans will be low.<br><br>7. Haemangiomas and haemangiosarcomas found in humans are biologically very different from those that occur in mice. In humans haemangiomas are common but bear no relationship to haemangiosarcomas. Haemangiosarcomas are rare in humans and most of the known causes are dependent on genotoxic effects.<br><br>8. In humans, angiogenesis and endothelial cell proliferation is well regulated and vascular proliferation as a result of prolonged injury or overproduction of angiogenic factors is not associated with vascular tumour development.<br><br>The PHMB CLH document states that this chemical increases the incidence of benign and malignant vascular tumours in female rats by the oral route | of any discussion on carcinogenic classification on these compounds. Their use as drug does not preclude that they would not justify a classification if evaluated according to CLP regulation.<br>f. No experimental evidence is available to support the proposed mode of action. Besides, discussion of potential implications in terms of carcinogenic risk for human, in particular at low doses is not in the scope of a classification dossier and is not further discussed here.<br>g. The carcinogenesis mechanism could be different depending of the chemical. Besides, haemangiosarcomas are observed in human although rarely.<br>h. In absence of evidence on the mode of action of induction of vascular tumours in animals its relevance for human cannot be discussed further.<br><br>These comments were also | |

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| | | and in male and female mice by the oral and dermal route. However, the CLH report does not address the SAP's conclusion that, although there was an increase in haemangiomas in rats at the top dose of 2000 ppm, haemangiomas are common in humans and bear no relationship to haemangiosarcomas. Therefore, the observation of haemangiomas in rats is not relevant to the determination of the carcinogenicity classification of PHMB. This is a critical omission.Thus the interpretation of the data by a number of independent, experts (who are world renowned in their chosen field of expertise) indicates that the conclusion of an increase in haemangiosarcomas in rats at the top dose is not valid. Based on the correct interpretation of all the available data, it is apparent that PHMB does not warrant classification for carcinogenicity.Each of the key studies and their interpretation by these independent experts is discussed sections (i) to (iv) below<br>.i) Rat Oral Feeding Study (Horner, 1996)The CLH report indicates that PHMB induced an increase in haemangiosarcomas at the top dose of 2000 ppm PHMB in the diet. In this study, no haemangiosarcomas were observed in the liver of male rats and only 1 haemangiosarcoma was observed in the liver of female rats at this dose. The historical control data shows that only 1 haemangiosarcoma in the liver of males and none in the liver of females was observed in 18 studies at the laboratory which conducted the work. Haemangiosarcoma is not a sex specific tumour type, and the incidence could have been easily reversed. Therefore, one haemangiosarcoma in a high dose female is an incidental finding and is not related to treatment. This conclusion was presented by the PWG, and it is also the conclusion of the SAP which reviewed the data from this study. Haemangiosarcoma has been induced by chemicals such as quinoline (Hirao et al., 1976), tetrafluorethylene (NTP, 1997), vinyl chloride, and vinyl bromide (Bogdanffy et al., 1995). The data from these studies indicate that non-neoplastic vascular lesions considered precursors of vascular neoplasms were noted. No such lesions were noted in the PHMB rat study. Also, the above chemicals are genotoxic, a toxicological effect not associated with PHMB. Furthermore, the incidence of animals having vascular neoplasms at any site was not increased with treatment.Based on the above observations, the PWG, and the SAP concluded that the overall weight of evidence indicate that the incidence of vascular neoplasms in the liver from the rat study is not associated with the dietary administration of PHMB, and | included in their entirety in the attached document "ARCH RESPONSE 30 April 2010.pdf"submitted by Arch Ltd and response to comments are provided in the attached document: AdditionalRCOM_FR.docx. | |

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| | | is in fact an incidental finding.<br>ii) Mouse Oral Feeding Study (Milburn, 1996)An increase in the incidence of haemangiosarcoma and haemangioma was noted in the liver and also at any site at the top dose (4000 ppm) in this study. This dose was greatly in excess of the maximum tolerated dose (MTD), a fact acknowledged in the CLH report which states, "The significance of this increased incidence is very uncertain in the presence of such marked toxicity." Indeed, there is consensus within the scientific community that it is not appropriate to use data from a dose which exceeds the MTD to judge the potential for chemically-induced carcinogenicity. Beck et al. (2007) note that dosing above the MTD may result in tumour production secondary to tissue changes rather than a direct carcinogenic influence of the agent tested. Therefore, the data from the top dose in this study in invalid and should not be used to assess carcinogenic potential. Notwithstanding the transcendence of the MTD at the top dose in the mouse oral study, the CLH report uses the data at this dose to consider the biological significance of the incidence of haemangiosarcoma in the liver of males at the mid dose (1200 ppm). The CLH report states, "in light of the clear increase of haemangiosarcomas in the liver at the high dose in males, the increase at mid-dose is considered as treatment-related and biologically significant." This conclusion is invalid. As explained above, it is not scientifically appropriate to use data generated at a dose above the MTD to evaluate carcinogenic potential of a compound at doses below the MTD. More importantly, 1) the increase in haemangiosarcoma in the liver of male mice at the mid-dose is not statistically significant, and2) the incidence of haemangiosarcoma (6/55 (11%)) in the liver of males at the middle (1200 ppm) dose is within the historical control incidence (1.8% - 18.3%) for this tumour type at any site.Vascular tumours in rodents are multicentric, so that it is most appropriate to consider the total number of animals with vascular neoplasms, rather than individual organs with either primary or metastatic lesions (Mann, Berry, and Greaves, 2009). When the total number of tumour-bearing animals is calculated, it appears that only the high-dose group is significant in either sex. It has been noted that the use of data from the high dose should be excluded from consideration of the potential for carcinogenicity from PHMB. In individual mice, tumours are often seen in more than one organ when the pattern of growth is consistent with a multi-centric origin rather than a single primary tumour with metastatic spread to | | |

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| | | other sites. Hence the number of haemangiosarcoma-bearing mice provides the most reliable basis for assessment. The incidence of haemangiosarcomas in this study is 5, 4 and 6 in males and 6, 4, and 4 in females in controls, 400 ppm, and 1200 ppm, respectively. The incidence of haemangiomas is 2, 3 and 4 in males and 6, 2, and 5 in females in controls, 400 ppm, and 1200 ppm, respectively. The data from this oral mouse study clearly indicates that the incidence of haemangiosarcoma and haemangioma is not related to treatment with PHMB.<br>iii) Mouse Dermal Study (Clapp, 1977)In contrast to the opinion expressed in the CLH report, this study indicates that the incidence of haemangiosarcoma and haemangioma, as well as any other tumour type, is not related to treatment with PHMB. The top dose in this study (750 mg/kg/day) exceeded the MTD based on excessive mortality (76-78% of animals dying prior to study termination) and reduced bodyweight gain in both sexes (up to 50%). Therefore, the data generated from animals at this dose is not valid for use in consideration of carcinogenic potential. Beck et al. (2007) note that dosing above the MTD may result in tumour production secondary to tissue changes rather than a direct carcinogenic influence of the agent tested. There was no increase in either haemangiosarcoma or haemangioma at the mid-dose (150 mg/kg/day) or the low dose (15 mg/kg/day). Both non-neoplastic and neoplastic changes in the liver were noted as "variable degrees of hepatic inflammation which was especially manifest in high dose animals as a severe form of hepatitis. These changes appear to have been responsible for increased deaths in this group during the 52-79 week period. It would appear that the long standing inflammatory liver changes observed in this study were responsible for the slightly increased incidence of liver tumours." Since this study was completed, it has been discovered that a number of mice in carcinogenicity studies had been infected by the bacterium Helicobacter hepaticus. Helicobacter infections have been shown to be associated with an increased incidence of hepatitis and hepatocellular neoplasms. Specifically, incidence of both neoplasms of the liver (both hepatocellular and haemangiosarcoma) was increased in affected studies. There were no similar increases in other organs (Haley et al., 1998). The conclusion by the authors was that "interpretation of carcinogenic effects in the liver of mice may be confounded if there is H. hepaticus-associated hepatitis." In this study the range of hepatic tumours in control mice from the historical data are equal or | | |

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| | | greater than the incidence of hepatic tumours in the mice at the high dose. The issue of PHMB-induced carcinogenicity from dermal exposure is essentially of academic quality because the dermal absorption is so low. Even at the top dose of 750 mg/kg/day applied dermally, the absorbed dose is approximately 0.05 mg/kg based on the results from absorption in vitro through human epidermis (Clowes, 1998). This is approximately 50 times lower than the threshold (400 ppm in the diet or approximately 60 mg/kg) for an increase in DNA synthesis (Kamendulis, 2008) from oral exposure of PHMB to the mouse based on an absorption rate of 4% from oral exposure (Lythgoe, 1995a and 1995b), and roughly 150 times lower than the no-observed-effect level (NOEL) for PHMB-induced carcinogenicity in the mouse.Based on the amount of PHMB that enters the body of the mouse from dermal exposure, it is probable that an insufficient amount is absorbed to produce any systemic toxicological event. The data from this dermal mouse study clearly indicates that the incidence of haemangiosarcoma and haemangioma is not related to treatment with PHMB.<br>iv) Studies to Determine Mechanism of Action (Kamendulis, 2008)Recent mechanism of action studies have shown that PHMB does not directly stimulate endothelial cell DNA synthesis but rather functions through an indirect mechanism, potentially involving endotoxin-mediated Kupffer cell activation and growth of liver endothelial cells, which ultimately leads to hepatic haemangiosarcomas. PHMB causes gastrointestinal irritation and inflammation which would allow the leakage of bacterial endotoxin into the hepatic portal circulation. The dose levels in these studies (up to 4000 ppm) were chosen to mimic the animal studies. Increased endotoxin has been shown to activate Kupffer cells resulting in increased oxidative stress and increased DNA synthesis of endothelial cells in the liver. The NOEL for increased DNA synthesis has been shown to be 400 ppm. There was no increase in haemangiosarcomas at doses which did not increase DNA synthesis. The proposed mechanism for PHMB-induced carcinogenicity has been criticized because of the increase in serum endotoxins at doses below doses which induce an increase in DNA synthesis and cell proliferation. An increase in endotoxin was noted following a dose of 100 or 200 ppm for 14 days. This is likely due to the lack of sufficient time of the presence of endotoxin in the system to produce an increase in DNA synthesis. However, no increase was observed in DNA synthesis following exposure to PHMB for 28 days at dose levels up to and including 400 ppm. | | |

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| | | v) Report from Professor S M CohenDr Cohen reviews the report from the SAP and the PWG, and relates those findings to the latest information available on the incidence of Haemangiomas and hemangiosarcomas. In his report, Dr Cohen states: "The results in rats I believe are as stated by this panel, and are not treatment related. Based on the results of the investigation of the Pathology Working Group, the tumor incidence consisted of two Hemangiomas in the high dose group in both males and females and one haemangiosarcoma in the low dose group in the females. Importantly, one haemangiosarcoma was present in the low dose female group and one with the high dose, with none with the mid-dose. Importantly, the finding of haemangiomas in the high dose group in both males and females is not relevant to the interpretation of the results with respect to hemangiosarcomas. This is clearly delineated by the Pathology Working Group, but I would highlight this by the recent conclusion of a broad panel of experts in the publication by Cohen et al. (Toxicological Sciences, 111:4-18, 2009) which concluded that there truly are not precursor lesions for hemangiosarcomas that are known in either animals or in humans. Hemangiomas are common in mice, rats, as well as humans, whereas hemangiosarcomas are common in mice, uncommon in rats, and exceedingly rare in humans. In fact, as described in the Expert Panel Report, there is considerable evidence that haemangiomas do not actually represent a neoplastic response, but rather, represent a hamartomatous lesion. Hamartomas are not preneoplastic and represent merely an accumulation of normal types of tissues into a distinctive nodule or mass. Hemangiomas are common in humans, not only in childhood, but increasingly in adults as we age. The small skin lesions in adults have the unfortunate title of being called senile haemangiomas. The important conclusion is that the haemangiomas should not be included in the overall assessment of hemangiosarcomas in these rats. The evidence strongly supports the conclusion of the Pathology Working Group that hemangiosarcomas were not treatment related in the rat study, and represent neither a carcinogenic hazard or risk for humans. The results in mice are quite different from those in the rat. There is unquestionably a treatment related effect at the high dose in both males and females. At the lower doses, the incidences of hemangiosarcomas were essentially the same as the controls. The Pathology Working Group came to the conclusion of slightly different incidences compared to the Study Pathologists, but nevertheless, | | |

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| | | there is unquestionably a treatment related effect at the high dose. The Pathology Working Group deals more than adequately with the issue of counting animals with these lesions rather than individual organs, such as liver and spleen. Also, they deal quite readily with the issue of classification of haemangiosarcoma and haemangioma and the lack of relationship of these two diagnoses. An important consideration is the high background incidence of hemangiosarcomas in male and female mice, greater than 10%. As the Pathology Working Group notes, and has been extensively commented in the literature, mice have a very high background incidence of hemangiosarcomas, predominantly in the liver, but also commonly in spleen, bone marrow, and subcutaneous adipose tissue. I do not know the historical control incidences from this particular laboratory, but I am certain that the concurrent control was well within the range seen in the historical controls. Thus, the incidences at the 400 and 1200 ppm doses are within these control ranges, and thus are below an effect level. The incidences of hemangiosarcomas at 4000 ppm are increased in both the males (12 of 55 mice) and females (10 of 55 mice). The important issue for interpretation of this study, however, has nothing to do with this particular diagnosis, per se, but with the fact that the animals were administered a dose that turned out to be severely toxic and well above the maximum tolerated dose. The findings at 4000 ppm should thus be completely disregarded in the overall risk assessment. Treatments at doses well in excess of the MTD are well known to be unrelated to potential risk of carcinogenesis, or for that matter, toxicology, for humans. The most notorious example is the finding of liver tumors in mice administered acetaminophen (paracetamol), the commonly used analgesic. In a large number of studies which have been reported utilizing doses within the MTD, there was no evidence of hepatocarcinogenesis, or for that matter, any evidence of carcinogenicity. However, in the one publication (Flaks and Flaks, Carcinogenesis, 4: 363-638, 1983) in which an increased incidence of liver tumors was detected in mice involved administration of a dose that was well in excess of the MTD. Actually, in the Flaks and Flaks study, the extent of decreased body weight gain was comparable to that seen in the present experiment with 4000 ppm PHMB. There clearly is no concern about carcinogenicity risk related to paracetamol. On the same basis, there should be no concern about human carcinogenic risk from PHMB. Mode of action analysis actually shed some light on a potential mechanism that might be involved with the tumors at this | | |

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| | | high dose. At the highest dose level there was intestinal toxicity, which resulted in an increase in plasma endotoxin levels in studies after 14 and 28 days. This was associated with hepatic endothelial cell proliferation. Endotoxin is well known to have as one of its effects an increase in endothelial proliferation. Since the endotoxin would be arising from the damaged gastrointestinal tract, its first site of contact internally would be through the portal vein and possibly lymphatics, reaching the liver. This would be handled primarily by the reticuloendothelial system in the liver, the endothelial cells and the Kupffer cells. The findings in the short term mode of action examinations are entirely consistent with this postulated mode of action. Most importantly, the short term studies demonstrate that there is an increase in endothelial cell proliferation in the liver following administration of the high dose of the chemical. Regardless of the findings in the mode of action analysis, however, the overriding concern with the findings at 4000 ppm is that this dose is in excess the MTD and should not be considered further in the risk assessment evaluation. Thus, the critical determinant value is the results at 1200 ppm. These are clearly negative. Thus, at acceptable dosages for a carcinogenicity study, there is not a carcinogenic effect in the mice. In the mouse carcinogenicity study, at the dose exceeding the MTD, the hypothesized mode of action would consist of gastrointestinal irritation leading to gastrointestinal inflammation and the release of endotoxin into the portal blood, leading to endothelial cell proliferation and ultimately hemangiosarcomas. This mode of action is unrelated to the effect by the chemical, but rather, is due to the toxicity occurring at a dose that is excessive. A dose of 1200 ppm meets the criteria of an MTD, and is without the carcinogenic effect. The findings with the mouse skin painting study unfortunately also are severely compromised. An extensive number of the animals were found to have hepatitis, possibly related to infection with Helicobacter hepaticus. Although there were some vascular tumors in the livers of these animals, these would most likely have been related to the inflammation in the liver and unrelated to the treatment with the chemical. Several chemicals have been identified over the past decade as producing an increased incidence of hemangiosarcomas in mice. A small number have been identified that also increase the incidence of hemangiosarcomas in rats. However, the chemicals which are known to produce the hemangiosarcomas in rats (as well as in humans) are well known to be genotoxic, such as vinyl chloride and thorotrast. In contrast, | | |

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| | | the chemicals which appear to increase the incidences of hemangiosarcomas only in mice appear to be those that are classified as non-genotoxic, such as PHMB. These include compounds such as pregabalin, retinoids, 2-butoxyethanol, and PPARγ and dual PPARα/γ agonists. Although the details of the mode of action for these chemicals has not yet been ascertained in detail, considerable data has accumulated in the past decade suggest that the commonality for all of them is an increase in endothelial cell proliferation leading to the development of these tumors, and that the mouse for some reason is uniquely susceptible to these non-genotoxic effects. Similar effects in rats and humans do not appear to lead to hemangiosarcomas. The increase in endothelial cell proliferation appears to be due to either hypoxia and oxidative damage or due to a direct mitogenic effect on the endothelial cells by the chemical itself of by an indirect effect on endothelial growth factors. The mouse has numerous differences compared to the rat and humans that might explain its unique susceptibility. The susceptibility appears to be common in many strains of mice, including the CD1 and B6C3F1 strains commonly used in bioassays. Mice have a higher background proliferation rate for endothelial cells compared to either rats or humans. Furthermore, the antioxidant protective mechanisms in mouse endothelial cells are considerably weaker than either in rats or in humans. For some of the known non-genotoxic hemangiosarcomagens, co-administration with vitamin E, which provides protection against the oxidative damage, protects against the development of the increased endothelial cell proliferation. This has been demonstrated for 2-butoxyethanol in greatest detail, including striking differences between the mouse and rat. There is also evidence that the mouse is considerably more susceptible to tissue hypoxia than either rats or humans, possibly due to striking differences in respiratory controls of acid base balance in response to decreases in oxygen saturation in the peripheral blood. In combination, the large number of differences between mice and rats, and also with respect to humans, likely contribute to the significant differences in susceptibility to background incidences of hemangiosarcomas in the different strains of mice compared to other species, such as rats and humans. Genetic susceptibility also likely plays a role. In contrast, many of these same effects have been identified in humans and not associated with the development of hemangiosarcomas, as is well described in the expert report of the Pathology Working Group. In summary, I concur with the conclusion of the expert | | |

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| | | panel that the administration of PHMB was not treatment related to the development of hemangiosarcomas in rats. In mice, the induction of hemangiosarcomas by PHMB was not due to the chemical itself but rather the extreme toxicity with doses well in excess of the MTD, which led to increased endothelial cell proliferation and ultimately development of the hemangiosarcomas. Administration of a dose that is approximately at the MTD had no effect on the incidences of hemangiosarcomas or other tumors. Thus, I concur with the conclusion that PHMB is not carcinogenic in either rats or mice, specifically it does not induce hemangiosarcomas in these species at doses acceptable for long-term bioassays."<br>Conclusions<br>In summary, PHMB is not carcinogenic in rodents based on the following reasons:<br>1. Any findings in mice were at doses which exceeded the MTD and were a result of extreme toxicity which led to integrity of the gut wall being compromised which may have led to a series of cascading events resulting to increased endothelial cell proliferation and ultimately development of the hemangiosarcomas. These findings cannot therefore be properly used to conclude any carcinogenic potential for PHMB.<br>2. The mouse oral study demonstrates the absence of a statistical increase in haemangiosarcoma at the mid dose in the mouse oral study. The incidence of haemangiosarcoma at the mid-dose in the mouse oral study was within the range of historical control incidence for this tumour type at the laboratory which conducted the study.<br>3. The single incidence of haemangiosarcoma in female rats is an incidental finding. The historical control incidence, from 18 studies at the laboratory which conducted the study, for this tumour type in rats is one in males and none in females. However, this tumour type is not sex specific, and the historical control incidence could just as easily have been reversed between males and females.<br>4. PHMB is not absorbed through the skin in toxicologically significant amounts, and the effects observed in the mouse dermal study are not due to this chemical. The low rate of skin absorption of PHMB has been acknowledged in the CLH report in section 5.1. Further, it appears that the mice in the study had been infected with heliobacter, therefore compromising its findings. It follows that the mouse dermal study from 1977 should not be considered in an assessment of carcinogenic potential | | |

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| | | from PHMB. The proposed classification of PHMB as carcinogen category 3; R40 (CLP Carc 2 – H351) is not appropriate and is inconsistent with an independent scientific evaluation of the data from the cancer studies. A thorough consideration of the biological and toxicological factors associated with these studies leads to the logical conclusion that PHMB is not carcinogenic in rodents<br>5. The CLH report mistakenly amalgamates findings of haemangiomas with haemangiosarcomas to identify levels of significance for haemangiosarcomas. Haemangiomas and haemangiosarcomas found in humans are biologically very different from those that occur in mice. In humans haemangiomas are common but bear no relationship to haemangiosarcomas.<br>6. The known causes of human haemangiosarcoma are clearly dependant on genotoxic effects. PHMB has been demonstrated through a number of studies to be non-genotoxic. Therefore, it is reasonable to conclude that PHMB-induced tumourigenesis has no relevance to humans.<br><br>**Confidentiality claim:**<br>The attached SAP report (Mann, P., C. Berry, and P. Greaves. (2009). Scientific Advisory Panel Review of Polyhexamethylene Biguanide (PHMB): Carcinogenicity Studies, Pathology Working Groups, Regulatory Responses, and Mode-of –Action Studies. Scientific Advisory Panel Report. EPL Study Number: 880-001. Experimental Pathology Laboratories, Inc. P. O. Box 169, Sterling, VA 20167) is the intellectual property of Arch Chemicals and their investment in this report would be seriously prejudiced if it was released into the public domain. The extract above identifies all relevant data needed to make an assessment. | | |
| 12/05/2010 | Belgium / Evelyn Coelis / COLIPA / Industry or trade association | Colipa kindly asks to review the raw scientific data on carcinogenicity of PHMB, prepared by an expert panel of independent reviewers and submitted by Arch Chemicals. | The Scientific Advisory Panel review and the other documents submitted by Arch Chemicals have been carefully considered and comments are included in the attached document: AdditionalRCOM_FR.docx. We however consider that the overall weight of | Noted |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | | evidence is consistent with CLP classification Carc 2 – H351. | |
| 12/05/2010 | UK / Jack Poppleton / Arch UK Biocides Ltd / Company-Manufacturer | Pages 34 to 44:<br>Arch believes that the CLH report is an inaccurate assessment of the frequency and nature of findings in the animal studies. The interpretation of the information supplied by Arch is believed to be inaccurate for the following reasons:<br><br>1. Any findings in mice were at doses which exceeded the maximum tolerated dose (MTD). It is not reasonable to extrapolate from findings at doses exceeding the MTD to low rates of exposure.<br>2. The mouse oral study demonstrates the absence of a statistical increase in haemangiosarcoma at the mid dose. The incidence of haemangiosarcoma at the mid-dose in the mouse oral study was within the range of historical control incidence for this tumour type at the laboratory which conducted the study. This group therefore provides no evidence of carcinogenicity.<br>3. The single incidence of haemangiosarcoma in rat females is an incidental finding. The historical control incidence, from 18 studies at the laboratory which conducted the study, for this tumour type in rats is one in males and none in females. However, this tumour type is not sex specific, and the historical control incidence could just as easily have been reversed between males and females. Therefore, the single manifestation is not a study-specific effect.<br>4. PHMB is not absorbed through the skin in toxicologically significant amounts, and the effects observed in the mouse dermal study are not due to this chemical. The low rate of skin absorption of PHMB is acknowledged in the CLH report in section 5.1. Further, it appears that the mice in the study had been infected with heliobacter, compromising its findings. It follows that the mouse dermal study from 1977 should not be considered in an assessment of carcinogenic potential from PHMB. The proposed classification of PHMB as carcinogen category 3; R40 (CLP Carc 2 – H351) is not appropriate and is inconsistent with an independent scientific evaluation of the data from the cancer studies. A thorough consideration of the biological and toxicological factors associated with these studies leads to the logical conclusion that PHMB is not carcinogenic in rodents.<br>5. The CLH report mistakenly amalgamates findings of haemangiomas with | It is considered that:<br>1. High doses in mice studies clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria<br>2. In mice by oral route, a statistically significant increase in the incidence of haemangiosarcomas at any site is observed in males and females at the high dose of 4000ppm, with incidence of haemangiosarcomas above historical control data. This dose is considered to exceed the MTD. A moderate increase of liver haemangiosarcomas is also observed at mid-dose in males. Although statistical analysis is unknown and historical control data are not available for this value, this increase is considered biologically significant compared to controls and can be attributed to treatment. | Noted |

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| | | haemangiosarcomas to identify levels of significance for haemangiosarcomas. Haemangiomas and haemangiosarcomas found in humans are biologically very different from those that occur in mice. In humans haemangiomas are common but bear no relationship to haemangiosarcomas. Haemangiosarcomas are rare in humans and most of the known causes are dependent on genotoxic effects.<br>6. The known causes of human haemangiosarcoma are clearly dependant on genotoxic effects. PHMB has been demonstrated through a number of studies to be non-genotoxic. Therefore, it is reasonable to conclude that PHMB-induced tumourigenesis has no relevance to humans.<br><br>This reasoning is fully supported by indpendent reviews of the animal studies and interpretations made in other regulatory regimes worldwide.<br><br>**Confidentiality claim:**<br>Two of the 4 documents attached are the intellectual property of Arch Chemicals and their investment in these reports would be seriously prejudiced if they were released into the public domain. The two reports in question are:<br><br>a)Busey WM, 1996,Polyhexamethylene Biguanide: Two Year Feeding Study in Rats.Pathology Working Group Peer Review of Proliferative Vascular Lesions in Male & Female Rats. Central Toxicological Laboratory, Macclesfield, UK. CTL/C/3172. Unpublished.<br><br>b)Kamendulis, L. M. 2008. Studies to Elucidate the Potential Involvement of the Kupffer Cell in PHMB Mouse Liver Hemangiosarcomas. Department of Pharmacology and Toxicology. Indiana University School of Medicine. Indianapolis, Indiana. Unpublished.<br><br>The extract above and the attached summary document (RESPONSE BY ARCH UK BIOCIDES LTD., TO CLH REPORT – PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING – POLYHEXAMETHYLENE BIGUANIDE. April 30, 2010) identify all relevant data needed to make an assessment. | 3. In the rat oral study, a statistically significant increase in the incidence of combined hemangiomas and hemangiosarcomas at any site is observed in females at the high dose of 2000ppm. This kind of tumors is rare in rats and the incidence of vascular tumours in the liver at the high dose exceeds the historical controls in both males and females, although statistical significance of liver combined vascular tumours is unknown.<br>4. In the mice dermal study, the hypothesis of an Helicobacter infection cannot be confirmed. Besides, oral exposure due to licking may have significantly contributed to the systemic exposure of animals in this study and may explain the apparent discrepancy in doses that induce vascular tumours in mice in the oral study and in the dermal study considering lower dermal absorption.<br>5. Haemangiosarcomas are observed in human | |

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| | | | although rarely.<br>6. In absence of evidence on the mode of action of induction of vascular tumours in animals its relevance for human cannot be discussed further. | |
| 13/05/2010 | Netherlands / Unilever / Company-Downstream user | Unilever believes that the interpretation of the information supplied by Arch Chemicals is inaccurate for the reasons listed below. In addition, the rationale below is fully supported by indpendent reviews of the animal studies and interpretations made in other regulatory regimes worldwide.<br>• The CLH report is an inaccurate assessment and evaluation of the frequency and nature of findings in the animal studies<br>• Any findings in mice were at doses which exceeded the MTD and were a result of extreme toxicity which led to integrity of the gut wall being compromised which may have led to a series of cascading events resulting to increased endothelial cell proliferation and ultimately development of the hemangiosarcomas. These findings should not therefore be used to conclude any carcinogenic potential for PHMB.<br>• The lack of a statistical increase in haemangiosarcoma at the mid dose in the mouse oral study. The incidence of haemangiosarcoma at the mid-dose in the mouse oral study was within the range of historical control incidence for this tumour type at the laboratory which conducted the study.<br>• The judgment in rats that the single incidence of haemangiosarcoma in females is an incidental finding. The historical control incidence, from 18 studies at the laboratory which conducted the study, for this tumour type in rats is one in males and none in females. However, this tumour type is not sex specific, and the historical control incidence could just as easily have been reversed between males and females.<br>• PHMB is not absorbed through the skin in toxicologically significant amounts, and the effects observed in the mouse dermal study are not due to this chemical. The low rate of skin absorption of PHMB has been acknowledged in the CLH report in section 5.1. Further, it is believed that the mice had been infected with heliobacter which compromises the findings of this study. Therefore, the mouse dermal study from 1977 should not be | The arguments provided here are identical than those of the previous comment. Please see our response above. | Noted |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | considered in the judgment of carcinogenic potential from PHMB. The proposed classification of PHMB as carcinogen category 3; R40 (CLP Carc 2 – H351) is not appropriate and is inconsistent with an independent scientific evaluation of the data from the cancer studies. A meaningful consideration of the biological and toxicological factors associated with these studies leads to the logical conclusion that PHMB is not carcinogenic in rodents.<br>• The CLH report mistakenly amalgamates findings of haemangiomas with haemangiosarcomas to identify levels of significance for haemangiosarcomas. Haemangiomas and haemangiosarcomas found in humans are biologically very different from those that occur in mice. In humans haemangiomas are common but bear no relationship to haemangiosarcomas. Haemangiosarcomas are rare in humans and most of the known causes are dependent on genotoxic effects.<br>• The known causes of human haemangiosarcoma are clearly dependant on genotoxic effects. PHMB has been demonstrated through a number of studies to be non-genotoxic. Therefore, it is reasonable to conclude that PHMB-induced tumourigenesis has no relevance to humans."<br><br>• The discussion of the significance of the angiosarcomas in the RMS France proposal clearly states; 'It is however noted that PHMB is not considered genotoxic and the mechanistic study establishes a NOEL for liver endothelial cell proliferation at 400 ppm after 28 days of dietary exposure in mice, which is consistent with the NOAEL for tumour induction in the oral mouse carcinogenicity study'.<br>This indicates that the Rapporteur accept the principle that the mode of action for inducing these liver tumours, based on evidence of increased cell proliferation, is supported by the mode of action studies carried out to investigate this. An increase in cell proliferation is plausibly driving the tumour formation at the mid dose in the same way that they agree it does at the high dose, where the maximum tolerated dose is exceeded.<br><br>In view of this, together with confirmation that the tumour incidence at the mid dose is statistically equivocal and that the exposure to PHMB in this study is far in excess of any human exposure, it seems like a case for careful consideration as to whether classification for carcinogenicity is really warranted. | It is considered that PHMB induces vascular tumours at high dose, although not necessarily excessive. A non-genotoxic mode of action is accepted and induction of tumours could be linked with the increase in endothelial cell proliferation in the liver. However, the link with GI tract irritation and/or endotoxin release is not clearly established. | |

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| | | In this case the evidence is that the process (increased vascular endothelial cell proliferation) at the level of human exposure to PHMB would not exceed the threshold for the mode of action of PHMB induced tumour induction in animals to be relevant (i.e.extrapolated) to man. | These considerations relate to carcinogenic risk assessment and are not relevant for classification purpose. | |
| 13/05/2010 | Ireland / Health & Safety Authority / National Authority | The Irish CA is in agreement with the proposed classification of PHMB as Carc. Cat 3 (Dir 67/548/EEC) or Carc 2 H351 (CLP Regulation) | Noted. | Noted |
| 14/05/2010 | France / Bernard Rosso / Iget Chimie - Laboratoires Aci / Company-Downstream user | We well understood that the cancer assessment is based on 3 different studies :<br>- A 80-week skin painting study on mouse using a 20% aqueous formulation of PHMB (Clapp, 1977).<br>- An oral life-time feeding study in the mouse (Milburn, 1996)<br>- An oral combining carcinogenicity and chronic toxicity study in the rat (Horner, 1996)<br><br>It seems that these 3 studies, if studied separately, do not show an absolute certainty that the PHMB is generating cancer in the animals.<br>It seems that you built your conviction on the exceptional cases of cancer noted during each of these studies (like a "beam of assumption").<br><br>Regarding the "skin painting study" :<br>This study should not be used anymore for the following reasons :<br>a) it's a very old study (1977) performed at a date prior to the GLP guidelines (as indicated in 5.7.3, page 40)<br>b) it is not logical that a "skin painting study " is taken into account when it is stated in the same report that "in vitro, a low dermal absorption of PHMB has been measured on human epidermis"<br>c) the applied dose "clearly exceeded the Maximum Tolerated Dose (MTD)" (as also indicated in 5.7.3, page 40) | The classification is proposed based on a weight of evidence assessment in accordance with section 3.6.2.2.2 of Annex VI of CLP.<br><br>The skin painting is an old study but was considered valid by the applicants and the RMS under the BPD review process.<br>The studies by all physiological routes of exposure are relevant for | Noted |

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| | | Regarding the "oral studies" :<br>Except when the MTD was exceeded, it is not so clear that the statistics demonstrate a PHMB-related occurrence of the observed cancer in these studies (this is written several times in pages 36 to 39).<br>More, the statistical observation of the hemangiomas and hemangiosarcoma seem to be not-dose-dependants (tables 20 and 21 page 39).<br><br>This is just as if another (uncontrolled) parameter, having no link with PHMB, was of importance in the test. | evaluation of carcinogenicity in agreement with section 3.6.2.3.2(h) of ECHA guidance on CLP regulation. It is noted that the high dose clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria, as discussed above.<br><br>In the rat oral study, a statistically significant increase in the incidence of combined hemangiomas and hemangiosarcomas at any site is observed in females at the high dose of 2000ppm not exceeding MTD. This kind of tumors is rare in rats and the incidence of vascular tumours in the liver at the high dose exceeds the historical controls in both males and females, although statistical significance of liver combined vascular tumours is unknown. In the mouse oral study, a moderate increase of liver haemangiosarcomas is also observed at mid-dose (not exceeding MTD) in males. Although statistical | |

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| | | | analysis is unknown and historical control data are not available for this value, this increase is considered biologically significant compared to controls and can be attributed to treatment. | |
| | | Another possible parameter is the following :<br>When studies are performed on rodents, it is better to apply the tested substance in the drinking water.<br>In this case, the dose is cumulated by the animals during a longer period of time. At the opposite, when the substance to be tested is included in food, there are at least 2 uncontrolled parameters :<br>- the rats are stuffing themselves quite until no more food is available, so the main substance quantity is ingested in a very short time, and make a false figure as the intake is calculated as a "Daily average dose".<br>- the remaining part of prepared mixture (of food and substance to be tested) can partially degrade and imply uncontrolled drifts in the protocols. | Administration of the test substance through diet is one of the mode of administration recommended in OECD guideline 451 and is relevant for the assessment of the carcinogenic potential of PHMB. | |
| | | Again in these oral route studies you mention that "administration of 4000ppm PHMB was greatly in excess of a maximum tolerated dose (MTD) based on bodyweight" (part 5.7.1: oral carcinogenicity, page 35).<br>Our supplier, Laboratoire Pareva, indicated that they have a study is pending on this toxicity property (OECD 453) started in 2008, and which result are scheduled for September 2011.<br>Why being so fast in labelling a substance which is used since more than 40 year in a numerous fields of applications, without waiting until 2011 to remove any doubt ?<br><br>In our experience, PHMB is used in the drinking water of animals in several industrial breeding, and at the opposite of the conclusions of the "CLH report", users reported a decrease of the juvenile mortality during their weaning period. | The classification proposal is based on the available data, which already consist in a large database especially for carcinogenicity and justify classification.<br>Evaluation of the new data will be performed by France as Rapporteur Member State when available and a revision of classification will be considered if appropriate. | |

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| | | | CLP regulation states that a revision of classification can be submitted by any Member State Competent Authority based on new data if considered appropriate. | |
| 14/05/2010 | Germany / B. Braun Melsungen AG / Company-Downstream user | p. 34-44<br>We believe that the carcinogenicity risk of PHMB (INN: Polihexanide) is not supported by the data disclosed in the CHL-report. It has to be mentioned that the identical set of toxicological data was already subject of a profound evaluation by the EPA (US Environmental Protection Agency) in 2003. The EPA experts recognized PHMB as not cancerogenic for use in humans. Since the date of the report, no new criteria were developed for the assessment of toxicological data regarding carcinogenicity, and there is no reason to believe that the EPA underestimated the risk of carcinogenicity.<br><br>Accordingly, in 2006 the BfArM (German Federal Institute for Medicinal Products and Medical Devices) granted two Marketing Authorisations for wound antiseptics containing PHMB as active substances (Zul.-Nr. 57861.00.00 and 57862.00.00 dated 30.11.2006, invented names Serasept 1 and Serasept 2) which are currently marketed in Germany. In case of any concern with respect to the carcinogenicity of the substance, the Applications for Marketing Authorisations securely would have been rejected.<br><br>With respect to the evaluation presented in the CHL-report, we have the following objections:<br><br>1. We feel that the mouse dermal study from 1977 should not be considered in the judgment of carcinogenic potential from PHMB. Since PHMB is not significantly absorbed by skin, it is not systemically available after dermal | The purpose of classification is to identify hazard and considerations on risks or uses are not relevant in this context. The evaluation of USEPA made in 2003 has been considered in the CLH report and is attached to the present RCOM. They concluded that "PHMB showed evidence of carcinogenicity", which is not, in our opinion, in contradiction with CLP classification Carc 2 – H351.<br>No further information is available on the BfArM evaluation and their position on carcinogenic hazard of PHMB.<br><br>The comparison of doses inducing vascular tumours in mice in the oral and dermal studies, considering lower dermal absorption | Noted |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | application. From that any occurrence of vascular tumors in the liver is highly unlikely to be caused by PHMB. As provided in the CHL-report, the quality of this study is poor and one should be careful to draw negative conclusions from it. The French Agency states: "The study was conducted pre-GLP and prior to the development of any published guidelines. ….. It was clear that the dose level of 30 mg PHMB/mouse/day exceeded the Maximum Tolerated Dose (MTD) based on excessive mortality (76-78% of animals dying prior to study termination) and reduced bodyweight gain in both sexes (up to 50% reduction). Furthermore, noticeable irritation was seen immediately following application. This high incidence of irritation was exaggerated during week 76 when the undiluted PHMB solution was applied to the skin by error. ….."<br>Supporting the argument that topically applied PHMB is not absorbed and thus cannot cause tumors in the liver, we present the results of an absorption study on wounds in 18 patients. Being absolutely in line with the known results for intact skin, no systemic absorption of PHMB was detected (LOD 10 ppm) when PHMB 0.02% and 0.04%, respectively, was used as rinsing solution under continuous moistening of big wounds in surgery and under antiseptic treatment of granulating wounds for several weeks duration. Absorption was observed only in one patient in which 120 µg/ml PHMB was detected in one serum sample. In this patient the relatively high total volume of 1,800 ml PHMB 0.02% was applied intraabdominally for 1 hour and 5 minutes as rinsing solution during cholecystectomy and appendectomy. In this case the (anyhow very low) systemic uptake of PHMB most likely resulted from absorption through the peritoneum (Martinoni B. ETH-Zentrum Zürich, Schweiz, 1988).<br><br>2. The conclusions drawn by the French Agency from the oral studies in rodents are doubtful:<br><br>• Any findings in mice were at doses which exceeded the MTD. These findings cannot be used to conclude any carcinogenic potential for PHMB since the toxic effects of the substance may itself cause increased endothelial cell proliferation and ultimately development of the hemangiosarcomas observed. | show a discrepancy. The more likely explanation is that oral exposure due to licking may have significantly contributed to the systemic exposure of animals in the dermal study. The skin painting is an old study but was considered valid by the applicants and the RMS under the BPD review process.<br>It is noted that the high dose clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria, as discussed above.<br><br>It is noted that the high dose in the mice oral study clearly exceed the MTD and this element has been considered in the weight of evidence and in accordance with classification criteria, as discussed above. Section | |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | • Summarising findings of haemangiomas and haemangiosarcomas to identify levels of significance for haemangiosarcomas is scientifically not justified. This approach cannot be used to conclude carcinogenicity of PHMB in man, since haemangiomas and haemangiosarcomas found in humans are biologically very different from those that occur in rodents.<br><br>Therefore, the proposed classification of PHMB as carcinogen category 3; R40 (CLP Carc 2 – H351) is not appropriate. | 3.6.2.3.2(j) of ECHA guidance on CLP regulation states that "If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification."<br><br>Summarising findings of haemangiomas and haemangiosarcomas is considered relevant as they emerge from the same tissue.<br><br>Although haemangiomas observed at birth in man do not evolve to malignancy, the haemangiomas observed in the animal studies with PHMB were not present at birth. They are considered induced by the treatment and observation of haemangiosarcomas shows that an evolution to malignancy may occur. As | |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | | mentioned in the SAP report haemangiosarcomas are observed in human although rarely and there is no available evidence to show that the vascular tumours observed in the animals may not be relevant for humans. | |

**Mutagenicity**

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| 10/05/2010 | France / Daniel Cros / Laboratoire Pareva / Company-Manufacturer | Not concerned. | Noted | |
| 11/05/2010 | Germany / Wolfgang Pape / Beiersdorf AG / Company-Downstream user | Beiersdorf's comment is:<br>We agree with the CHL dossier proposal for no classification for this endpoint. | Noted | |
| 12/05/2010 | Belgium / Evelyn Coelis / COLIPA / Industry or trade association | Colipa agrees with the proposal in the submiited Dossier for Harmonised Classification and Labelling, namely for no classification for this end-point. | Noted | |
| 12/05/2010 | UK / Jack Poppleton / Arch UK Biocides Ltd / Company-Manufacturer | Page 44:<br>Arch agrees with the CLH dossier proposal for no classification for this end-point. | Noted | |
| 13/05/2010 | Netherlands / Unilever / Company-Downstream user | Unilever agrees with the CLH dossier proposal for no classification for this end-point. | Noted | |
| 14/05/2010 | Germany / B. Braun Melsungen AG / Company-Downstream | We agree with the CLH dossier proposal (no classification for this end-point) | Noted | |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | user | | | |

**Toxicity to reproduction**

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| 07/05/2010 | France / Picot Alexandre / Individual | It's not toxic !! all analysis of the DASS are good since November 2007.<br>Opening date of the aquatic center cote saint-andre in the Isere in France. | Noted. However, DASS evaluations focus on efficacy of the products and not on its toxicity. | |
| 10/05/2010 | France / Daniel Cros / Laboratoire Pareva / Company-Manufacturer | Not concerned. | Noted | |
| 10/05/2010 | France / Xavier Debrenne / Individual | la manipulation du PHMB est sans commune mesure plus agréable et sans danger pour les exploitants. | Noted | |
| 11/05/2010 | Germany / Wolfgang Pape / Beiersdorf AG / Company-Downstream user | Beiersdorf's comment is:<br>We agree with the CHL dossier proposal for no classification for this endpoint. | Noted | |
| 12/05/2010 | Belgium / Evelyn Coelis / COLIPA / Industry or trade association | Colipa agrees with the proposal in the submiited Dossier for Harmonised Classification and Labelling, namely for no classification for this end-point. | Noted | |
| 12/05/2010 | UK / Jack Poppleton / Arch UK Biocides Ltd / Company-Manufacturer | Page 44 to 45:<br>Arch agrees with the CLH dossier proposal for no classification for this end-point. | Noted | |
| 13/05/2010 | Netherlands / Unilever / Company - Downstream user | Unilever agrees with the CLH dossier proposal for no classification for this end-point. | Noted | |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
|---|---|---|---|---|
| 14/05/2010 | Germany / B. Braun Melsungen AG / Company-Downstream user | We agree with the CLH dossier proposal (no classification for this end-point) | Noted | |

**Respiratory sensitisation**

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
|---|---|---|---|---|
| 07/05/2010 | France / Christophe Morice / Lannion-Tregor Agglomeration / Regional or local authority | Nous n'avons constaté à ce jour aucun désagrément au niveau des voies respiratoire de la part des baigneurs ni des personnels travaillant dans l'établissement (éducateurs sportifs, personnels technique, baigneurs...). | Noted. No classification is proposed for respiratory sensitisation. | |
| 07/05/2010 | France / Picot Alexandre / Individual | there is no respiratory difficulties precisely because there is no mine-chlorination. | Noted. No classification is proposed for respiratory sensitisation. | |
| 07/05/2010 | France / Gerald Rioual / Communauté de communes de Kaysersberg / Regional or local authority | Unique alternative<br>Le phmb dans nos bassin n'a provoqué aucun problème a signaler et apporte au contraire un confort respiratoire largement meilleur que notre précédent traitement au chlore. L'ambiance au bord des bassins est moins oppréssante, moins de fatigue en fin de journée, moins d'irritation, moins de maladie type sinusite, bronchite pour les agent... | Noted. No classification is proposed for respiratory sensitisation. | |
| 09/05/2010 | France / Olivier Dutrieux / Communaute de communes pays de bievre liers / Regional or local authority | tres bon produit<br>aucune allergies ni irritation<br>pas de nocivite<br>aucun probleme respiratoire<br>bien meilleur que le chlore<br>aucun danger a manipuler<br>pas d incompatibilite avec d autres produits<br>analyses faciles<br>pas de mousse ni de turbite<br>eau tres claire et tres limpide<br>pas d odeurs<br>pas d emanations quelconques toxique ou autre<br>tres facile d usage et sans danger | Noted. No classification is proposed for respiratory sensitisation. | |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | eau douce et non irritante pour la peau<br>pas d iritation des yeux<br>tres bon produit pour l homme<br>tres bonne qualite<br>utilisation parfaite pour les baigneurs<br>ques des avantages<br>pas d inconvenients connus<br>bien meilleur que le chlore<br>parfait en piscine publique<br>produit respectant les usagers et le personnel<br>un veritable progres au vu du chlore qui lui est tres toxique | | |
| 10/05/2010 | France / Xavier Debrenne / Individual | le bien être et une sensation nouvelle de nos MNS qui surveillent et sont très sensibles aux odeurs de chlore puisque tournant sur d'autres équipements de la collectivité | Noted. No classification is proposed for respiratory sensitisation. | |
| 10/05/2010 | France / Daniel Cros / Laboratoire PAREVA / Company-Manufacturer | Respiratory (pp 14 and 31-33):<br>In the Inhalation toxicity study, there is a confusion between the observed effects due to the physico-chemical properties of PHMB (which should have been sufficient to exempt PHMB from this studies) and what has been assessed as being a systemic toxicity (which was NOT systemic toxicity).<br>For this confusion, please, see our attached file " 2010 05 06 - 1 - Scient Devel against T+ Classif (inhal) -en.pdf " (ZIP file). | Noted. No classification is proposed for respiratory sensitisation. Responses to comments on acute inhalation toxicity submitted in the attached file are included in the attached document: AdditionalRCOM_FR.docx | |
| 11/05/2010 | Germany / Wolfgang Pape / Beiersdorf AG / Company-Downstream user | Beiersdorf's comment is:<br>We agree with the CHL dossier proposal for no classification for this endpoint. | Noted | |
| 12/05/2010 | France / Lannion-Tregor Agglomeration / Regional or local authority | Regarding the effetcts on respiratory tracts:<br>Up to today, we noticed no inconvenience indicated by our technical employees working in the establishment (sports, teachers, technicians...), nor any complains from the users (adult swimmers, teenagers, sports clubs,...), nor from parents coming to our course for "swimming-babies". We find it very strange the labelling proposition of this product as "very toxic by inhalation". The only "inhalation impact" of the PHMB we use, is a pleasant lavander smell when the can is openned, or when we add it into injection tanks. | Noted. No classification is proposed for respiratory sensitisation. Concerning acute toxicity by inhalation it should be noted that PHMB is used at very low concentration (application dose of 10 ppm recommended by manufacturer) in pools and | |

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| | | We also appreciate the advantages linked to the use of PHMB:<br>- notably lower risks in the handeling<br>- safer to the storage (compared to the previous chlorinated products used in swimming pool. | absence of discomfort in this context does not preclude existence of toxic properties relevant for classification. | |
| 12/05/2010 | Belgium / Evelyn Coelis / COLIPA / Industry or trade association | Not relevant for this substance | Noted | |
| 12/05/2010 | UK / Jack Poppleton / Arch UK Biocides Ltd / Company-Manufacturer | Page na:<br>Not relevant for this substance | Noted | |
| 13/05/2010 | Netherlands / Unilever / Company-Downstream user | Not relevant for this substance | Noted | |
| 14/05/2010 | France / MIMNRE DU HAUT CONSEIL DE LA SANTE PUBLIQUE member of the higt council of the' Public Health / National Authority | I have studied the project of harmonised classification of the substance activate biocide Polyhexamethylene biguanide or PHMB proposed by RMS France, in its "CLH report" available on-line.<br><br>I am very surprised that the toxicity by inhalation of a polymer under its ionised form in aqueous solution – and thus not volatile – was retained. In these conditions, the evaluation of the exposure by the respiratory route would need some explanations of the context in which a human being could be exposed because, except with a nebulisation of the product, we hardly understand how such an exposure could be justified. | No classification is proposed for respiratory sensitisation.<br><br>Concerning acute toxicity by inhalation it should be noted that inhalation of a substance is not restricted to inhalation of its vapours but may also occur via inhalation of aerosols. Hence, OCDE guidelines for inhalation studies states that animals may be exposed to the test article as a gas, vapour, aerosol, or a mixture thereof. Classification criteria for acute toxicity provide cut-off for each type of | Noted |

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| | | Moreover the irritating character for respiratory tracts stated in the text has never been observed during the years PHMB has been used in public swimming pools (29 years in the oldest one). At the opposite, while chlorine (through the nitrogen trichloride (NCl3), the by-product of its action on the nitrogenous compounds) attracts attention of the hygienists and toxicologists due to complaints and observations coming from the pool staffs (especially in indoors' swimming pools) it is the breathing comfort that is evoked by these same pool staffs when chlorine is replaced by the PHMB. This point had been specially underlined as a main advantage when the CSHPF(1) (in which I was designated as the reporter) examined the authorisation demand for the use of PHMB as a water sanitiser in public swimming pools in France.<br><br>I think that the protocol and the results of the study published in 1976 ( Carney) would need, as usually done by the authorities in charge of the Risk Assessment, to be submitted to an experts' committee in toxicology and chemical contaminants (because the dosage and more generally the analysis of the PHMB at low level is particularly complex and difficult) to assess whether (i) the assays are relevant, (ii) the protocol is robust and (iii) the results are reliable respectiing the nowadays standards, before being potentially accepted in order to be discussed and also taking into account the whole set of already existing results from the scientific literature about the same subject.<br><br>(1) Conseil Supérieur d'Hygiène Publique de France = French Public Health Superior Council | exposure, gases, vapours, dust or mists and the data available on inhalation toxicity of liquid aerosol of PHMB is therefore relevant for identification of a hazard by inhalation and its classification.<br><br>PHMB is used at very low concentration (application dose of 10 ppm recommended by manufacturer) in pools and absence of discomfort in this context does not preclude existence of toxic properties relevant for classification.<br><br>The study by Carney 1976 has been carefully reviewed. This study is old and was therefore not conducted according to guideline of according to GLP that was not compulsory at that time. Compared with current guidelines for acute toxicity, the main issue is indeed the absence of reporting that actual exposure concentrations have been controlled. It | |

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| | | | was however specified that the atmospheres were analysed using an Anderson Cascade Impactor which gave the percentage of respirable particules, as requested in the guidelines. Besides, the results of Carney 1976 for repeated toxicity at lower doses are consistent with another study performed according to OECD guideline and GLP (Noakes 2006) in terms of NOAEL and LOAEL. This further supports the reliability of Carney 1976. In Noakes 2006, the two highest doses tested in Carney 1976 were not included and the results of Carney 1976 can therefore not be confirmed or contradicted. They are considered as relevant for acute toxicity classification and support classification Acute 1 – H330. | |
| 14/05/2010 | France / Complexe sportif de Gérardmer (F-88) (public Pool) / Company – Downstream user | Commentaire proposé pour la piscine collective de Gérardmer (88)<br><br>Our comment deals with your proposition of labelling of the PHMB as " very toxic by inhalation " (pages 3 and 4 of the " CLH report ", among others pages).<br>This proposition seems to us completely out of scope with regard to our use of this product.<br>Indeed, we use the PHMB as disinfectant for the swimming pool water treatment (instead of chlorine-based products) since 1982. Since this time, we were supplied either by ICI or Maréva. Thus, we have been we using this product for our pools' | Noted. No classification is proposed for respiratory sensitisation.<br>Concerning acute toxicity by inhalation it should be noted that PHMB is used at very low concentration (application dose of 10 ppm recommended by | Noted |

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| | | water treatment, 24 hours a day and 7j / 7 since 28 years this year.<br><br>And since these 28 years of use, we NEVER had any problems which would justify the apposition of logos and sentences proposed for the risk by inhalation. Nevertheless, besides the "standard" use, our technicians also use it for the disinfection of surfaces (tiles around the pools, accesses and neighbourhoods...) with a sprayers ! (the kind of agricultural sprayer, used for gardening).<br><br>We do not know how to consider if the cited studies (Carney and Noakes) are made in representative conditions or not (adapted protocols? Rats' sensitivity compared to the man's? ....), but it is obvious that there is a gap between their results and the reality of the experience of a 28-year use...<br>Furthermore, on a common sense point of view, it seems to us unthinkable to inject a product with a "skull" logo in a water destined for public bathing.<br>And, following our idea, we do not intend to have one day to treat our pools with chlorine-based products. One have just to see the physical state of the covered swimming pools treated with chlorine-based products (even after less than 5 years of use) to imagine the impact of these same products on the human health.<br>On the other hand, we invite you to come and see on the spot that our 28-year old installations are as new as on the 1st day (no rust, no concrete's degradation, green plants in good health, ...).<br><br>To conclude, we ask you to make this proposition be examined again by experts to avoid this product to disappear, because PHMB is a product:<br>(i) which showed its ability/efficacy in the applications described above,<br>(ii) which is today the only "chlorine free" and "not oxidizing" solution existing for an effective treatment of (covered) public swimming pools waters,<br>(iii) which is the only hope of numerous staffs working in these establishments and who won't have other choice than to undergo the effects of the by-products of a chlorine-based disinfection. You must know that, in France, this exposure has been recognised as an occupational disease. | manufacturer) in pools and absence of discomfort in this context does not preclude existence of toxic properties relevant for classification.<br>Besides, the classification presented in the CLH dossier is proposed for the active substance PHMB and may not be relevant for all products containing PHMB depending on their concentration in PHMB. E.g., a mixture containing 1% of PHMB ($CL_{50}$=0.03 mg/l) and 99% of other ingredients not classified for acute toxicity will be classified only in category 4 for acute toxicity. | |
| 14/05/2010 | France / Bernard Rosso / Iget Chimie - Laboratoires Aci / Company-Downstream user | For this part, we are very surprised of such a severe labelling of the product.<br>Anyway, our field of application do not correspond to such exposure risk.<br>But there's a point which is very surprising for us : at the dates of the studies (Carney 1976 and Noakes 2006), it is accepted that rats were exposed to such low doses of PHMB (0.025 to 26 µg/L). Indeed, up to today, our most precise level of | Noted. No classification is proposed for respiratory sensitisation.<br>Besides, the analysed level of PHMB in the pool is | Noted |

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| | | analysis of PHMB is 0.5 mg/L, in water !<br>This represents a 20 to 20000-fold ratio between both analytical level !<br>It is very likely that the doses indicated in these reports are not 100% sure.<br><br>One last remark : nowhere in your "CLH report" is indicated if PHMB has been detected (qualitatively and quantitatively) in blood (or other body fluids), to show that animal died because of an actual systemic toxicity. Indeed, at the higher doses (supposed to be 26 and 12.5 µg/L) the so very short time between the exposure of animals to PHMB and their death let us think that PHMB has no time to have any toxic effect. | very surprising considering that the application dose recommended by PHMB manufacturers is 10 ppm (0.01 mg/l).<br><br>When they induce mortality, the local toxic effects on the respiratory tract are as relevant as systemic effects for classification for acute toxicity by inhalation.<br>Besides, the conditions of exposure in the high-dose animals in Carney 1976 are consistent with OECD guidelines for assessment of acute inhalation toxicity. | |
| 14/05/2010 | Germany / B. Braun Melsungen AG / Company-Downstream user | Not relevant for this substance | Noted | |
| 14/05/2010 | France / Public Pool of Sélestat (F-67) / Company-Downstream user | I am the manager of the "Piscine des Remparts", the Public pool of Sélestat (F-67)<br>We use PHMB as a swimming pool water treatment since July 4th, 2009, first opening date of this town equipment.<br>We were very surprised to learn that you intend to classify and label PHMB as a "product with high risks for the health in case of exposure by inhalation".<br>These are my remarks on the use of PHMB as disinfectant in our swimming pool of Sélestat :<br>from the technical staff, in charge of water treatment :<br>no incident nor inconvenience was noticed. The product is easy to handle without danger. Its storage is easy and without danger also. The packaging is satisfactory, and allow us to avoid any over-exposure. | PHMB is used at very low concentration (application dose of 10 ppm recommended by manufacturer) in pools and absence of discomfort in this context does not preclude existence of toxic properties relevant for classification. | Noted |

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| | | From the customers (bathers and visitors) :<br>they give us very satisfactory returns since the swimming pool is opened. As regards the clarity of the water but also the about its skin contact : no irritation and no allergy were noticed on skin or on eyes (compared to chlorine in other pools)<br>An important part of bathers are comes yo our swimming pool for the sweetness and the quality of the water, in comparison with other swimming pools of our country in which the water treatment is more "traditional" (with chlorine products). As a sum up, we don't understand why a product like PHMB should wear a so repulsive label with a "dead head" sign, when it has been used during so much time without any incident, relative to an inhalation risk! | | |
| 14/05/2010 | France / Cecile Bourquet / MAREVA / Company-Downstream user | Respiratory :<br>The PHMB is a product which Maréva supplies since 1983 as disinfectant for private or public pool water treatment.<br><br>Private swimming pools :<br>We have been supplying PHMB in France, but also in Italy, in Switzerland, in Germany, in Austria and in England. This application represents approximately 10 000 swimming pools treated with PHMB.<br>In none of these European countries, we were informed about incidents linked to the proposed classification of "toxic by inhalation", even if an important part of the German private pools are indoors' pools.<br><br>Since 1998, we also supply PHMB in the United States, mainly for the same private pools water treatment.<br>For that purpose, it was necessary to supply a complete dossier to the Environment Protection Agency (EPA) which approved our PHMB, what is worth an authorisation of sale on the territory of the USA.<br><br>The mandatory labelling of the PHMB in the USA is as follows:<br>- "WARNING" => equivalent to that of the regulation 1272-2008-CE says "CLP regulation"<br>- Causes substantial temporary eye injury purpose => as our R41<br>- Harmful yew, swallowed => as our R22<br>- KEEP OUT OF REACH OF CHILDREN => as our S2<br>- Do not get concentrate in eyes now one clothing => as our S25 and S27 | Noted. No classification is proposed for respiratory sensitisation.<br><br>Concerning acute toxicity by inhalation it should be noted that PHMB is used at very low concentration (application dose of 10 ppm recommended by manufacturer) in pools and absence of discomfort in this context does not preclude existence of toxic properties relevant for classification.<br><br>The present classification proposal has been established based on classification criteria of the CLP regulation (EC 1272/2008) and on the criteria of the Directive | Noted |

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| | | - Avoid contact with skin => as our S24<br>- Avoid breathing vapour or mist => as our S23<br>- Wash thoroughly with soap and water handling => as our S28<br>- Wear goggles or shield when handling concentrate => as our S39<br>- Keep container closed => no equivalence<br><br>The main applications in the USA is the disinfection of swimming pools and SPA waters.<br>The experience feedback in the USA shows a lower risk (see annex 1) than the one proposed in the CLH report : since 1982, 118 persons were exposed to PHMB in the USA amongst which 7% were exposed by inhalation route. In these 7% exposed by inhalation, the most common symptoms were respiratory irritation (75%) and coughing/choking (38%). No death have been reported.<br>We are far from a "very toxic" substance by inhalation route.<br><br>Public swimming pools :<br>We supplied PHMB in about 35 swimming pools since March, 2007.<br><br>The demand of approval made with the French authorities was the object of an attentive study, preceded by periods of tests in several experimental swimming pools.<br>The CSHPF(1) expressed a first positive opinion in 1989.<br>This experts' committee had in hands a part of the toxicological studies which are also today in the PHMB dossier.<br>The product was used since 1989 in some collective swimming pools, the most known being the Gérardmer's ( F-88).<br>Then, a new file was passed on in the same French authorities in May 2004 with the aim of confirming the PHMB approval for its use as a disinfecting agent for Public pool water.<br>For the second time, in December 2005, the CSHPF(1) expressed a favourable opinion for the use of the PHMB in in Public pools. This opinion led, after some technical exchanges, to a new authorisation, in March 2007.<br>The reason for which the public pools managers ask for PHMB is the replacement of the chlorine-based products.<br>The main advantage they find is to obtain a (non-irritating) non-aggressive atmosphere of the swimming pool hall (see newspapers extracts). | 67/548/EEC that are the two texts legally applicable at the European level.<br><br>PHMB is used at very low concentration (application dose of 10 ppm recommended by manufacturer) in pools and absence of adverse effects in this context does not preclude existence of toxic properties relevant for classification.<br><br>Noted. However, approval of the French authorities for use in public pools and CSHPF evaluation do not aim to give an opinion on hazard identification relevant for classification. | |

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| | | This practical advantage is a general remark of all the staff (usually exposed to the chlorine by-products) who approves by a large majority the PHMB for that reason.<br>This systematic observation "on the ground" is in total opposition with the conclusions extrapolated by the studies taken into account for the proposition of labelling of the PHMB !<br>More, new generations of public pools are now equipped with 2 parts : a sporting pool and a "relaxation" pool.<br>The "relaxation" part can include equipments such as: slides, bubbles baths, fountains, SPA, water jets...<br>All these devices generate a very important movements of water, facilitating the generation of fogs.<br>But this never led to any complaints about inhalation problems.<br>It is even the opposite: bathers can stay longer in this water games without irritation or any other respiratory problems!<br><br>To date, PHMB is the only chlorine-free and oxidiser-free solution allowing an effective treatment of public or private pool waters.<br>Indeed, since February 2003, the exposure to chlorine by-products is recognised in France as an occupational disease !<br><br>To end, let's compare the VLE (Limit Exposure Values)(2) of some toxic gases with the deducted CL50 of PHMB (CLH report part 5.2.2, page 14):<br>- HCl(gas) : 7.5 µg / L => labelling = T, R23 (Toxic by inhalation) AND C,R35 (corrosive)<br>- Cl2 (gas) : 3 µg / L => labelling = T, R23 (Toxic by inhalation) AND Xi, R36/37/38<br>- PHMB : < 26 µg / L => labelling = T+,R26 (very toxic by inhalation) AND T, R48 / 23 (Risk of grave effects for the health in case of prolonged exposure by inhalation)<br>There must be a mistake somewhere...<br><br>(1) CHSPF = Conseil Supérieur de l'Hygiène Publique de France = French Public Health High Council<br>(2) VLE is the maximum accepted value or at least the values measured on duration not exceeding 15 min | Classification of each substance is made based on relevant data as specified in the classification criteria. It does not include VLE. These values do not correspond to direct toxicological results only but are consensual management values, including also technical feasibility issues and other non scientific parameters. | |

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| | | ---------- <br><br> Annex 1 <br><br> Polyhexamethylene biguanide, also known as PHMB, is a group of polymers used as an antimicrobial agent in a wide variety of applications including oil-in-water and water-in-oil emulsions, industrial reagents, silicone systems, cellulose solutions and oil recovery systems. PHMB is primarily used as a non-chlorinated antimicrobial agent in swimming pool and spa facilities. The evidence of health effects in humans resulting from exposure to PHMB is reviewed here. In particular, the acute and chronic toxicity, teratogenic/ reproductive effects, and carcinogenicity are discussed. Two approaches are used: <br>• The potential health effects of PHMB in humans, reported as incident reports from different sources, are summarised. <br>• A literature search of chronic health effects associated with PHMB exposure, including results of epidemiological studies, is summarised. <br><br> The information presented in this review is limited to EPA assessments of US data sources. <br><br> 1. INCIDENT REPORT DATA ASSOCIATED WITH HEALTH EFFECTS OF PHMB EXPOSURE <br> The following databases were consulted for the poisoning incident data on the active ingredient PHMB (PC Code: 11180) <br><br> a. OPP Incident Data System (IDS) - The Incident Data System of The Office of Pesticide Programs (OPP) of the Environmental Protection Agency (EPA) contains reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested. | Inhalation studies available on PHMB are consistent with classification criteria for T+; R26 and T; R48/23. | |

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| | | b. Poison Control Centers - as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1996 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System, which obtains data from about 65-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.<br><br>c. California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.<br><br>d. National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive, has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.<br><br>e. Published Incident Reports - Some incident reports associated with PHMB related human health hazard are published in the scientific literature.<br><br>OPP's Incident Data System (IDS)<br>A total of 118 individual incident cases submitted to the EPA Office of Pesticide Programs involving use of PHMB-containing swimming pool products were reviewed to determine the effects of exposure to PHMB (CAS No. 27083-27-8). All of the incident reports reviewed were for residential use of the products by consumers. In 14% (17 cases) out of the 118 individual incident cases reviewed, it was determined that the exposure effects were the result of not using the product as intended by the manufacturer. They included not following the instructions on the label, accidental ingestion of the product, or splashing the concentrated product onto the skin or into the eyes. | Noted. However, in absence of additional information on the condition of exposure and | |

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| | | The reported routes for exposure of the 118 incident cases were dermal (58%), ocular (30%), ingestion (9%), inhalation (7%) and unknown (<1%). In some cases more than one route of exposure applied for a individual incident case (e.g., both dermal and ocular exposure). The most common symptoms reported for each exposure route are as follows:<br>• The most common symptoms reported for cases of dermal exposure were skin irritation/burning (80%), rash (50%), hives/welts (19%), itching (16%), skin discoloration/redness (9%), allergic reaction (7%), and blistering (7%).<br>• The most common symptoms reported for cases of ocular exposure were eye irritation/burning (100%), eye pain (69%), loss of vision (17%), swelling of eyes (6%), and allergic reactions (6%).<br>• The most common symptoms reported for cases of exposure via ingestion were vomiting/nausea/abdominal pain (46%), irritation to the mouth/throat (46%), respiratory irritation including coughing/choking (18%) and diarrhoea (9%).<br>• THE MOST COMMON SYMPTOMS FOR CASES OF EXPOSURE VIA INHALATION WERE RESPIRATORY IRRITATION (75%) AND COUGHING/CHOKING (38%).<br><br>Poison Control Center<br>All the incidences reported in the Poison Control Center data base are included above in the OPP's IDS. No additional data were reported in the Poison Control Center database covering the years 1993 through 1996.<br><br>California Data - 1982 through 1996<br>There are no incidence reports submitted to the California Pesticide Illness Surveillance Program (1982-1996)database related to PHMB exposure.<br><br>National Pesticide Telecommunications Network (NPTN)<br>There are no incidences reported in the NPTN database related to PHMB exposure.<br><br>Incident Reports Associated with Acute Toxic Effects of PHMB Published in Scientific Literature.<br>There is no incident report associated with acute toxic effects of PHMB published in Scientific literature reviewed. | in particular the concentration of PHMB in the products that caused the incidents, no conclusion can be drawn. | |

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| | | 2. EPIDEMIOLOGIC STUDIES ASSOCIATED WITH HEALTH EFFECTS OF PHMB IN HUMANS<br>There are no chronic health effects associated with PHMB exposure, (including results of epidemiological study reported in scientific literature).<br><br>3. Conclusion<br>There are incidences reported associated with exposure to end-use products containing PHMB. Dermal and ocular routes are the primary means of exposure. Most of the incidences are related to irritation and/or allergic type reaction. There are no chronic health effects associated with PHMB exposure, (including results of epidemiological study reported in scientific literature). | The information presented here is noted. No information is given on the concentration in PHMB in the products on the market and their conditions of use. It is not known whether potential respiratory exposure during use is expected and at which level. In absence of this information, the data presented here are not sufficient to dismiss effects identified in animals. | |

**Other hazard classes**

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| 30/04/2010 | UK / Stephen Dungey / Member State | - We agree with the proposed environmental classification and labelling. However, as well as the M factor, specific concentration limits should be added. | Noted. SCL have been added | Noted |

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| | | | in the revised CLH report. | |
| | | - Table 1: The water solubility is only expressed as a weight percentage. Could it also be given in units of 'mg/l'? | The calculation of the water solubility gives a result of about 700 g/L. This value will be included in the CLH report. | No additional comments |
| | | - Section 4.1.3: The description of the O'Malley et al. (2006) study should be placed before the summary section, and it would be helpful if further details could be provided since this appears to be a key study in the argument on degradation. Data should also be compared to the classification criteria, rather than the substance being described as "not easily and weakly biodegradable". | Section 4.1.3: Considering the classification criteria, we believe that the key study is the 301 B one (Long and Roberts, 1994). The other studies support the biodegradation behaviour of the substance. | The following clarification has been added to the BD: "According to the criteria for degradation in the guidance to regulation EC n° 1272/2008 on CLP …" |
| | | - Section 4.2.1: Although not part of the classification criteria, information on adsorption is relevant for the interpretation of other studies, and we think it is useful to include it (reference is made to strong adsorption in the description of the WWTP simulation test in Section 4.1.2.3). | Section 4.2.1: Considering that the key study for classification criteria is OECD 301 B, data on adsorption are not deemed essential. | No additional comments |

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| | | - Section 7.2: There is no need to include terrestrial toxicity data since they are not used for classification purposes. | Section 7.2: Noted. We acknowledge that this part is not mandatory considering classification criteria; it is however kept in the CLH dossier for information. | The results of this test are not used for C&L purposes and are left out of the BD. |
| 06/05/2010 | Germany / Jan Averbeck / Member State | Physico-Chemical Properties<br>The evaluation and classification of physico-chemical hazards for the endpoints<br>- Explosivity<br>- Flammability<br>- Oxidising properties<br>is not possible because information on physico-chemical studies (Schofield, 2007) is not available in IUCLID dataset.<br><br>Environment<br>In general the German CA agrees with the proposed classification and labelling. | The IUCLID 5 was not filled because it is not compulsory to complete the robust study summaries for the biocide substances at present. Further information about these studies has been added in the CLH report in order to allow the evaluation.<br><br>Noted. | Noted |

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| | | But we would like to point out that the assessment of this substance (CA-Report) is not yet terminated and there is currently no approved final Assessment Report available.<br><br>Page 4:<br>We recommend adding the proposed labelling (with wording of the hazard statements and precautionary statements) according to CLP Regulation. | Labelling elements such as precautionary statements according to CLP are not harmonised. Relevant harmonised elements are given in the classification section. | |
| 07/05/2010 | France / Christophe Morice / Lannion-Tregor Agglomeration / Regional or local authority | Nous apprécions également les avantages liés à la manipulation du PHMB dont les risques sont nettement inférieurs au dangers liés au stockage et à l'utilisation d'autre produits utilisés en piscine (chlore par exemple). | Noted. | Noted |
| 11/05/2010 | Germany / Wolfgang Pape / Beiersdorf AG / Company-Downstream user | Beiersdorf's comment is:<br>With respect to inhalation toxicity we offer the following comment. PHMB has a strong instrinsic irritation potential as shown for mucouse membranes identified by OECD TG 405 for ocular irritancy. Therefore we are convinced that the effects noted in the inhalation studies were clearly a result of irritation and not from systemic toxicity. Like the ARCH Chemical Company, we declare that PHMB should therefore correctly be identified as a respiratory irritant and not as being toxic by inhalation, i.e. correctly as R37 instead of: T+; R26 and T;R48/23(long term risk from inhalation). | We agree that effects may be related to local toxicity of PHMB in the respiratory tract. However, we consider that local effects are as relevant as systemic effects for classification for acute toxicity. | The rapporteurs agree with the dossier submitter. |
| 12/05/2010 | Belgium / Frederic Denauw / Member | Based on the results of the aquatic acute toxicity test on the most sensitive species (72hEC50algae = 0.015 mg/L), the fact that the substance is not readily biodegradable and | | Noted |

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| | State | that the substance shows no potential to bioaccumulate (log Kow = -2.3), it is justified to classify as Aquatic Acute 1 and Aquatic Chronic 1.<br><br>Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, PHMB should be classified as N, R50/53.<br><br>In view of the proposed classification and the toxicity band between 0.01 and 0.1 mg/l, a M-facotr of 10 could be assigned.<br><br>In conclusion : we agree with the proposed environmental classification (based on CLP criteria) by the FR MSCA : Aquatic Acute 1, H400<br>Aquatic Chronic 1, H410<br><br>Some comments:<br>4.3.1.1 Bioaccumulation estimation<br>It would be useful to mention the value (result) of the calculated aquatic BCF.<br><br>7.2.1.1 Toxicity to soil micro organisms<br>"… reliability factor = 240 worms …" should be "… reliability factor = 2; 40 worms …" | Your support is noted.<br><br>4.3.1.1 Bioaccumulation estimation: Considering that PHMB is<br>-a polymer<br>-electrically charged<br>-outside the domain of application (log kow < 2), we thus believe that it would be false to calculate an aquatic BCF from log kow for PHMB<br><br>7.2.1.1: thank you, this sentence has | The indication in the CLH report : "…and the existed linear relationship used to estimate the aquatic BCF" has not been included in the BD. |

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| | | 7.4.3 Conclusion on the environmental classification and labelling<br>* Three criteria are used to decide on the environmental classification of a substance (aquatic toxicity, biodegradability and bioaccumulation) : the first two criteria are resumed but no conclusion is mentioned concerning the last criterion "bioaccumulation". Please add this info even if the substance shows no potential to bio accumulate<br>* last sentence :<br>"In addition, as the 96h-EC50 value for algae …" should be "In addition, as the 72h-EC50 value for algae…" | been corrected<br><br>7.4.3: thank you the document has been amended. | Noted<br><br>Noted |
| 12/05/2010 | Belgium / Evelyn Coelis / COLIPA / Industry or trade association | Colipa kindly asks to review the raw scientific data on inhalation toxicity of PHMB, prepared by an expert panel of independent reviewers and submitted by Arch Chemicals, which support the classification of PHMB as a a respiratory irritant and not as being toxic by inhalation. | The data has been considered and responses to their comments are provided in front of the respective comments. | Noted |
| 12/05/2010 | UK / Jack Poppleton / Arch UK Biocides Ltd / Company-Manufacturer | Page 31 to 33:<br>With respect to inhalational toxicity Arch offers the following comment.<br>The effects noted in the inhalation studies were clearly a result of irritation and not from systemic toxicity for the following reasons:<br><br>1. PHMB causes local irritation in the lung with no signs of systemic toxicity with a NOAEL of 0.0239 µg/l for local irritation and 2.47 µg/l for systemic toxicity (highest dose tested).<br>2. The only study which can substantiate any classification for inhalation effects is the 2006 Noakes study which supports a classification of R37 Irritating to respiratory system. This study does not support classification as R26 Very Toxic via Inhalation.<br><br>PHMB should therefore correctly be identified as a respiratory irritant and not as being toxic by inhalation. | We agree that effects may be related to local toxicity of PHMB in the respiratory tract. However, we consider that local effects are as relevant as systemic effects for classification for inhalation toxicity. | The rapporteurs agree with the dossier submitter. |
| 13/05/2010 | Ireland / Health & Safety Authority / | Human Health:<br>The Irish CA agrees with the proposed additional classification for human health: | HH: your support is noted | Noted |

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| | National Authority | T+: R22, R26, R41, R43, R48/23 (Directive 67/548/EEC) or Acute Tox 4 H302, Acute Tox 1 H330, Eye damage 1 H318, Skin Sens 1 H317, STOT RE 1 H372 (CLP Regulation.<br><br>Environment:<br>The Irish CA agrees with the proposed classification for the environment: N, R50/53 (Directive 67/548/EEC) or Aquatic Acute 1 H400 Aquatic Chronic 1 H410 (CLP) based on the justification provided by France.<br><br>Environmental Hazard Assessment:<br>The Irish CA suggests the following changes to the LOEC values:<br>• Long-term toxicity to fish (page 49): NOEC was 10 µg/l and the LOEC was > 10 µg/l. We suggest the LOEC should be reported as, LOEC was 17µg/l.<br>• Long-term toxicity to aquatic invertebrates (page 50): NOEC was 8.4µg/l and the LOEC was `x> 8.4µg/l. We suggest the LOEC should be reported as, LOEC was 24 µg/l. | Environment: your support is noted<br><br>Environmental Hazard Assessment: thank you for your suggestion, however the range of concentration tested doesn't permit to establish a clear LOEC value between the NOEC and the values you propose. The LOEC values you propose could therefore overestimate the LOECs. That's why we prefer to express the LOEC as" >" | In the RAC BD, $LOEC_{fish}$ is reported to be 17µg/l and the $LOEC_{invertebrate}$ is reported to be 24µg/l based on mean measured concentrations. |
| 14/05/2010 | Germany / B. Braun Melsungen AG / Company-Downstream user | p. 27-33<br>With respect to inhalational toxicity we offer the following comment:<br>We believe that the risk of systemic toxic effects via of PHMB is not supported by the data disclosed in the CHL-report, whereas PHMB is shown to be irritating if inhaled. | | Noted |

| Date | Country/ Person/Organisation/ MSCA | Comment | Response | Rapporteur's comment |
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| | | 1. We feel that the rat inhalation study from 1976 should not be considered. As provided in the CHL-report, the quality of the 1976 study is poor. The French Agency states: "The study was performed before adoption of guidelines and its interpretation was limited by poor reporting. Differences with the actual guidelines were noted: lower number of animals (5/sex/group required in guidelines), no information on monitoring of atmosphere, housing conditions and extent of haematological examinations, limited biochemical analysis and organs for histological examination". Since a well conducted GLP study of 2006 is available, the 1976 study should be disregarded. | These statements on the limitation of the study are relevant to consider the validity of the study compared to guideline for repeated toxicity. However, considering acute toxicity guideline, the only issue is indeed the absence of reporting that actual exposure concentrations have been controlled. It was however specified that the atmospheres were analysed using an Anderson Cascade Impactor which gave the percentage of respirable particules as required in the | |

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| | | | guideline. Besides, the results of Carney 1976 for repeated toxicity at lower doses are consistent with another study performed according to OECD guideline and GLP (Noakes 2006) in terms of NOAEL and LOAEL. This further supports the reliability of Carney 1976. In Noakes 2006, the two highest doses tested in Carney 1976 were not included and the results of Carney 1976 can therefore not be confirmed or contradicted. They are considered as relevant for acute toxicity classification and support classification | |

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| | | 2. Toxic effects observed in the 2006 study are "judged to be the result of a primary irritant response" (statement in the CHL-report). No systemic toxic effects were observed. The data from this study support a classification of R37 Irritating to respiratory system but do not support classification as R26 Very Toxic via Inhalation. | Acute 1 – H330.<br><br>We agree that effects may be related to local toxicity of PHMB in the respiratory tract. However, we consider that local effects are as relevant as systemic effects for classification for acute toxicity. | |