Re-evaluation of polihexanide use in wound antisepsis in order to clarify ambiguities of two animal studies

Objective: Due to classification of the agent polihexanide (PHMB) in category 2 'may cause cancer' by the Committee for Risk Assessment of the European Chemicals Agency in 2011, the users of wound antiseptics may be highly confused. In 2017, this statement was updated, defining PHMB up to 0.1% as a preservative safe in all cosmetic products. In the interest of patient safety, a scientific clarification of the potential carcinogenicity of PHMB is necessary.
Methods: A multidisciplinary team (MDT) of microbiologists, surgeons, dermatologists and biochemists conducted a benefit-risk assessment to clarify the hazard of antiseptic use of PHMB.
Results: In two animal studies, from which the assessment of a carcinogenic risk was derived, PHMB was administered orally over two years in extremely high concentrations far above the NO(A)EL (no-observed-(adverse-) effect level) in rats and mice. Feeding in the NO(A)EL range resulted in no abnormal effects. In one male in the highest dose group of 4000ppm PHMB, an adenocarcinoma was found, which the author attributed to chronic inflammation of the colon with systemic atypical exposure. The increasing incidence of hemangiosarcomas highly probably resulted from increased endothelial proliferation, triggered by the exceedingly high dosage fed, because PHMB is not genotoxic and there is no evidence for epigenetic effects.
Discussion: It is well known that PHMB is not absorbed when applied topically. Considering the absence of genotoxicity and epigenetic effects together with the interpretation of the animal studies, it is the consensus of the multidisciplinary experts that a carcinogenic risk from PHMB-use for wound antisepsis can be ruled out.
Conclusion: On this basis and considering their effectiveness, tolerability and clinical evidence, the indications for PHMB based wound antiseptics are justified.
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benefit-risk analysis • mode of action • carcinogenicity/tolerability/toxicity • polihexanide (PHMB) • wound antisepsis

The reason for the re-evaluation of PHMB is the confusion of the users of polihexanide (PHMB)-based preparations for wound antisepsis, which are registered as drugs or — for antiseptic wound cleaning — medical devices. The confusion is based on the classification of the active substance PHMB in category 2 'may cause cancer' by the Committee for Risk Assessment of the European Chemicals Agency (ECHA) in 2011.[1] As a consequence, the scientific committee on consumer safety (SCCS) concluded that PHMB is not safe for consumers when used as a preservative in cosmetic spray formulations and in all cosmetic products up to the maximum concentration of 0.3%.[2,3] In the last updated statement from the SCCS (2017), the following revised statement was made: 'Based on the data provided, the SCCS is of the opinion that the use of PHMB as a preservative in all cosmetic products up to 0.1% is safe'.[4]

If the suspected carcinogenic hazard for antiseptic use of PHMB is justified, alternatives for PHMB would have to be considered. If this suspicion proves to be ungrounded, the user must be informed about the negligible risk. Only a scientifically based benefit-risk assessment can answer the ethical question of whether PHMB should be replaced or not.

Methods and approach

A multidisciplinary (MDT) team of microbiologists, surgeons, dermatologists and biochemists carried out a benefit-risk assessment to clarify the hazard of antiseptic use of PHMB with the main focus on carcinogenicity. To characterise the risks, the following properties of PHMB were analysed: local tolerance, cytotoxicity,

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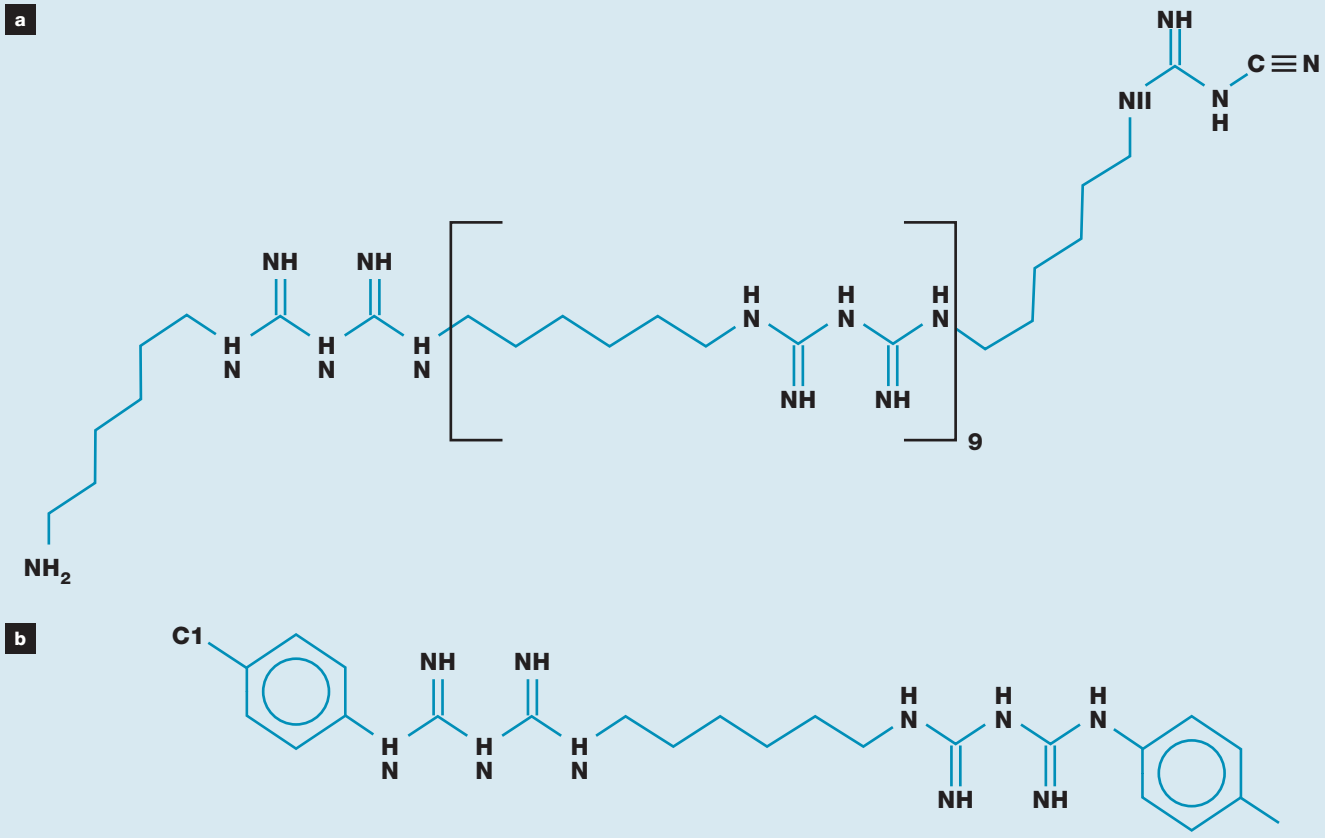
Fig 1. Representative structural formula of PHMB; with nine hexamethylene biguanide units terminated by one amino and cyanoguanidine group, in comparison with chlorhexidine (**a**); 1,1`-Hexamethylene-bis(5-[p-chlorophenyl]biguanide (**b**)



toxicity, absorption, genotoxicity, teratogenicity, undesirable effects, caveats and contraindications. The benefit analysis includes antiseptic efficacy, mode of action, and their consequences for resistance and results of clinical trials.

Results

Risks: chemical structure of PHMB and consequences

The chemical structure of PHMB is similar to that of antimicrobial peptides (AMPs) produced by many cells within the wound, such as keratinocytes and inflammatory neutrophils, where they are thought to help to protect against infection.[5] There are six different PHMB product types identified, possessing combinations of amine, guanidine and cyanoguanidine end-groups.[6] PHMB can be seen as virtually detoxified chlorhexidine (CH), as the molecular structure of PHMB monomers closely resembles the structure of CH molecules, except for the terminal NH-group of CH consisting of 4-chloroaniline (4-CA) (Fig 1). After antiseptic rinsing of the oral cavity with chlorhexidine digluconate (CHG), 4-CA was detected in the saliva up to 30 minutes following use.[7] Because 4-CA is a human carcinogen, the release of 4-CA from CHG may have been the reason that various tests found CHG to be mutagenic or genotoxic,[8–11] capable of inducing DNA damage.[12] In animal studies, CHG has caused precancerous lesions in the oral cavity after 14 days of use.[13] In contrast, there is no evidence that PHMB has mutagenic potency or can induce precancerous alterations.[14] This may be because the 4-CA structure is not present in the PHMB molecule.

Risks: local tolerance and cytotoxicity

In rabbit eye, a concentration of 25% is tolerated and a concentration of 0.02% is tolerated on nasal mucous membrane.[14] The hen's egg test on the chorioallantoic membrane of the egg, is a screening model to determine the tolerability for eyes and wounds, PHMB had an irritant effect not different from commercial antibiotic eye drops.[15] The irritant effect of octenidine dihydrochloride (OCT), CHG and hydrogen peroxide is significantly higher.[16] PHMB is superior to iodophors in terms of tissue tolerance, with the exception of cartilage tissue.[17,18] The cytotoxicity of wound dressings did not differ from that of PHMB-free dressings.[19]

On murine fibroblasts, the rank order of cytotoxicity in relation to the following concentrations of ingredients (w/v) was $AgNO_3$, OCT, silver sulfadiazine,

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benzalkoniumchloride, CHG, triclosan, PHMB and, with the lowest cytotoxicity, PVP iodine (PVP-I).[18]

It is clinically confirmed that PHMB is tolerated on wounds and mucous membranes.[20] In mesh grafts, PHMB stimulates the re-epithelialisation, while PVP iodine and silver nitrate induces deep necroses and fibrin deposits. Following unsuccessful split-thickness mesh grafts in pre-treatment with PVP iodine or silver nitrate, pre- and post-treatment with PHMB resulted in complete re-epithelialisation within two months.[21] In a prospective, multicenter, non-comparative clinical trial with daily application of a PHMB wound gel on skin grafts, except for one graft failure, all patients reached complete re-epithelialisation after one (n=14), two (n=31), or three (n=5) administrations of the gel, without infection or erythema. The median time of seven days to complete graft take was below the average healing time reported in comparable studies.[22]

Risks: toxicity and absorption

Based on the acute oral toxicity of 5g/kg in rats, PHMB is classified as 'practically not toxic',[14] corresponding with the low chronic toxicity. The NOEL (no observable effect level) for oral application is 200 mg/kg body weigth/day (BW/d).[14] An oral dose of 100mg/kg BW/d has been tolerated without adverse effects for a period of two years,[14] a fact underlining the safety of antiseptic applications of PHMB on wounds.

In contrast to iodophors and triclosan, PHMB is not absorbed dermally or from wounds above the detection limit of 10µg.[14] The conclusion of SCCS, that PHMB is safe when used as preservative in cosmetic products up to a maximum concentration of 0.1 %, was revised from the *in vitro* data given in the following section.[4] Using the tear method on the skin, a dermal absorption of 8.5% was calculated. This technique, however, does not allow the calculation of the systemic absorption through the epidermis. Thus, it remains relevant that up to the PHMB detection limit of 10µg there is no basis for assuming that systemic absorption occurs. Given the characteristics of the PHMB molecule, it is also not to be expected that this occurs in amounts <10µg.

Risks: mutagenicity, teratogenicity and carcinogenicity

No indication of mutagenicity or carcinogenicity was found *in vitro* or *in vivo*.[14] Upon oral application of 8mg/kg BW/d, there is no sign of a teratogenic or embryotoxic effect. There is no evidence of relevant adverse effects on the male or female reproductive organs from chronic carcinogenicity studies, or subacute and chronic toxicity studies.[3]

The assumption of ECHA of PHMB's possible carcinogenicity is based on two animal studies.[23,24] The relevance of these findings for human as well as veterinary medicine is to be doubted for two reasons. First, in both feeding studies, extremely high PHMB concentrations far above the NO(A)EL (no-observed-(adverse-) effect level) of 400ppm for rats and 600ppm for mice were administered. At 4000ppm, a significant trend of increased hemangiosarcoma was observed in rats; in particular, after 103 weeks of daily feedings of 162.3mg/kg BW, a total of three hemangiosarcoma tumours were found in the livers of the killed animals.[23] In addition, one carcinoma was found. In the feeding of 0, 400, 1200 and 4000ppm PHMB to mice over two years, the survival rates of male mice in all feeding dosage groups was identical; in female mice, the survival rate in the 4000ppm group was 12% lower than in the other dosage groups. With feeding of 4000ppm PHMB (equivalent to 715mg PHMB/kg BW/d male mice or 855 mg PHMB/kg BW/d female mice), the only clinical difference was an increased incidence of swelling at the anus and anal prolapse. In one male animal in the 4000ppm PHMB group, an adenocarcinoma was found, which the author[24] attributed to chronic inflammation of the colon. Similar to Horner's findings,[23] an increasing incidence of hemangiosarcoma of the liver was observed as the PHMB dosage increased (0ppm PHMB: 4/110 mice; 400 ppm: 2/110; 1200 ppm: 11/110; 4000 ppm: 33/110). Because PHMB promotes fibroblast proliferation,[25] the assumption is obvious that the occurrence of hemangiosarcoma resulted from increased endothelial proliferation, triggered by the exceedingly high feeding dosage. The cell proliferation desired at the wound can become disadvantageous in the liver and colon with systemic atypical exposure. With appropriate clinical use, however, this cannot occur due to the absence of absorption in wounds. This conclusion is underlined by the finding that feeding in the NO(A)EL range resulted in no abnormal effects.

The second reason for a lack of carcinogenicity is that no genotoxicity has been found for PHMB.[14] Therefore, the only explanation for a carcinogenic effect would be an epigenetic, not genotoxic, alteration of the DNA. In an analysis of an epigenetic effect, no oxidative stress on the DNA was induced, nor were hydroxylation or hypermethylation of DNA demonstrable. Significant production of mitogenic cytokines and the transcription factor NF-KB was also not detected. The status of the GAP junction was also not significantly affected. Thus, it was not possible to demonstrate any clear epigenetic effects.[6]

Our interpretation of both animal studies is in accordance with the assessments of the US Environmental Protection Agency (EPA)[26–28] and later of the Australian authorities,[29,30] who interpreted the animal study data as showing no relevant health risk for humans. Therefore, the labelling 'may cause cancer' is not correct for wound application of PHMB. If this designation is intended to mean malignant tumours in a general sense, then the labelling should include the explanation that this would exclusively occur with oral ingestion of at least 162.3mg of the agent/kg BW/d over a period of two years.

Because of the lack of absorption from wounds, the absence of both genotoxicity and epigenetic effects together with the realistic interpretation of the animal studies, it can be ruled out that the use of PHMB for wound antisepsis poses carcinogenic risk.

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Risks: undesirable effects, caveats and contraindications

There are two reported cases of a possible anaphylactic reaction triggered by PHMB, these could not be verified in the skin-prick test,[31] one patient with a grade-III anaphylactic reaction had IgE against both PHMB and CHG. Due to the similar structures, it was postulated that sensitisation was caused by prior treatment with CHG; thus, a known allergy to CHD might be linked to a risk for PHMB anaphylaxis.[32] In the second case, only IgE against PHMB was proven.[33] A further suspected case of anaphylaxis was reported after wound application.[34] Contact allergies are rare, with a frequency of <0.08% in regard to the frequent use of PHMB, especially as a preservative.[35]

Due to the relatively strong binding onto tissue structures, insertion into the skin, canals or body cavities without drainage is to be avoided, although no clinical reports are available yet.[36]

Contraindications are possible allergies and application during the first four months of pregnancy. In later stages, its use should follow strict observance of a benefit-risk assessment.[36]

Benefits: antiseptic efficacy

The spectrum of efficacy includes all vegetative pathogens, including those with acquired resistance with an exposure time of 1–20 minutes in quantitative suspension tests.[37–39] With and without organic bioburden, PHMB is more effective than CHG. Compared to iodophors, PHMB is more effective at blood load. In germ carrier tests, the efficacy of PHMB is comparable to OCT.[40]

A particular advantage is PHMB's efficacy against intracellular pathogens such as *Staphylococcus aureus*, MRSA, *Escherichia coli, Salmonella enterica* serovar Typhimurium, *Mycobacterium smegmatis*, *Acanthamoeba* and *Neisseria*.[41] *Staphylococcus aureus* in infected Mac-T cells[42] as well as MRSA in infected keratinocytes are killed through direct interaction with PHMB.[43] For other antiseptic agents, an intracellular effect is only relevant for iodophors and certain, specially formulated and prepared mixtures of peroxide and carboxylic acid. [44]

PHMB is not only effective against planktonic but also against sessile polymicrobial communities. Microorganisms are eliminated in biofilms *in vitro* as effectively as by CHG.[45] PHMB also reduces biofilms in 3D skin models[46] and in porcine wounds.[47] In comparison with different biocides against differently aged biofilms and planktonic cells of *Escherichia coli* and *Staphylococcus epidermidis*, PHMB was one of the most efficient biocides against biofilms together with peracetic acid.[48] On surfaces, PHMB inactivated the great majority of biofilms, but did not inactivate *Staphylococcus aureus* effectively.[49] In non-healing wounds, continuous application of PHMB reduced biofilm, thereby promoting healing.[50] In an *ex vivo* model, negative pressure wound therapy (NPWT) with instillation of PHMB and other active antimicrobial agents enhanced the reduction of colony forming units (CFUs) by increasing biofilm destruction.[51] In conclusion, there is at present no single antimicrobial agent that completely eradicates biofilms of infected wounds.[52] Therefore, the antiseptic treatment of wounds requires the accompanying debridement of necrosis and/or removal of slough.

Whereas the bactericidal efficacy of PVP-I against *Staphylococcus aureus* and *Pseudomonas aeruginosa* strongly diminished with rising pH, the activity of CHG and OCT was mainly pH independent in a pH range of 5.0–9.0. In contrast, PHMB showed a significant increase in efficacy at higher pH, which could be advantageous for the management of wound infections.[53]

The sustained effect of PHMB[54] should support the antimicrobial efficacy on wounds.

A highly valuable property for antiseptic agents is selective antiseptic action, which means killing bacteria without killing human cells in coculture with bacteria. So far this is only proven for PHMB,[55] acetic acid[56] and NaOCl.[57] Comparable results exist for PHMB adsorbed onto TiAl6V4-surfaces (titanium alloy implant material surfaces). The implant surface was coated with PHMB and artificially contaminated with *Staphylococcus aureus* and it shows antimicrobial properties while inhibiting neither ingrowth behaviour nor proliferation of osteoblasts (MG63-cells).[58] The biocompatibility index (BI) test is described in detail by Müller and Kramer.[18] Antimicrobial BI testing involves the parallel assessment of the *in vitro* cytotoxicity and the antibacterial activity of the agent. This is achieved by determining the IC_{50}, via neutral red and MTT assay, and the RF value, the lowest concentration of an antimicrobial to achieve a $3\log_{10}$ reduction in bacterial CFU/ml. Essentially, the BI is defined as IC_{50}/RF. Under comparable test conditions, the concentration causing a reduction of 3 $\log_{10}$ after 30 minutes exposure of *Escherichia coli* and *Staphylococcus aureus* is lower than the concentration allowing survival of 50% (IC_{50}) of mouse fibroblasts. A value >1 has otherwise only been demonstrated for OCT.[18]

Benefits: mode of action and consequences for resistance

Over a period of more than 60 years of PHMB use, acquired resistance to PHMB has not been reported and appears — due to the complex modes of action — almost unimaginable. PHMB interacts with anionic head groups of the outer layer of the plasma membrane via its cationic biguanide groups and by simultaneously displacing surface-applied Ca^{2+} ions.[59] The hydrophobic hexamethylene units of PHMB are not very flexible and thus cannot be integrated into the hydrophobic membrane double layer. The attachment of the PHMB creates a bridging of anionic head groups of adjacent anionic phospholipids, which is followed by their rearrangement into anionic phospholipid clusters. Due to this, neighbouring anionic phospholipids repel each other and the hydrophobic clustering of phospholipid fatty acid tails of the membrane double layer is

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disintegrated. The membrane integrity is destabilised and its permeability is increased.[60] Anionic glycerophospholipids, such as, phosphatidylglycerol and diphosphatidylglycerol, besides other phospholipids, are the main component of the plasma membrane of Gram-positive and Gram-negative bacteria. Usually, these compounds are not found in the cell membrane of humans or other mammals. This explains the high tolerance of eukaryotic cells to PHMB, since they mainly contain phosphatidylcholine (lecithin) in their cell membrane. PHMB interacts with liposomes and emulsion particles which possess a phosphatidylcholine membrane; the resulting attachment changes neither membrane integrity nor stability.[61,62]

The preferred interaction of PHMB with anionic phospholipids of the plasma membrane does not seem to be the preferred cause for the antimicrobial effect of this agent. Zaki et al.[63] showed that the PHMB-polymer assembles in a compact, ordered, hairpin-like shape that can collapse further into three- or five-folded structures representing a 'snail-like'conformation with intense stacking by the biguanide groups.[58] Derived from self-assembly of biguanide groups, PHMB forms nano-objects which may interact with the phospholipid membrane, in a manner similar to that observed for positively charged nanoparticles[64] or cell penetrating peptides,[65] intracellularly producing an antimicrobial effect. Using fluorescein isothiocyanate (FITC)-marked PHMB and cellular, molecular and biophysical analysis, it was indicated that PHMB is absorbed by bacterial as well as mammalian cells and selectively clogs bacterial chromosomes. The DNA in the nucleus of mammalian cells is not disturbed in this manner; PHMB is stored in endosomes instead.[6] The intracellular antimicrobial effect of PHMB is not associated with DNA degradation, since no DNA-SOS repair system is engaged and no genotoxic or epigenetic effect caused by PHMB has been documented to date. The selective chromosome condensation provides an unanticipated paradigm for antimicrobial action that may not succumb to resistance.[41]

Benefits: physiological and biochemical effects relevant for wound healing

PHMB reduces matrix-metalloproteinase- (MMPs) -induced periwound breakdown.[66,67] Fibrin plaques are significantly reduced by PHMB *in vitro*[68] and slough is reduced in the wound.[69] The formation of superoxide and peroxynitrite radicals is inhibited.[70] The elastase of *Pseudomonas aeruginosa* is inhibited, which otherwise results in degradation of wound fluid and tissue proteins.[67]

The capillary density and the diameter of arterioles are increased in the cremaster muscle in rats through exposure to PHMB. Likewise, microcirculation in the skin is increased through PHMB, although the functional capillary density and the flow velocity of erythrocytes is significantly reduced.[71,72]

The proliferation of fibroblasts and keratinocytes is stimulated by PHMB.[25] Consistent with this, increased formation of granulation tissue[73] and increased wound healing was supported in an *in vitro* wound model[74] as well as in experimental wounds in guinea pigs, rats and pigs.[75–77]

Clinical evidence

PHMB is available as solutions, gels and in wound dressings.[78] In wound antisepsis, PHMB solutions are commonly used at concentrations of 0.01, 0.02 and 0.04%, in a wound cleanser 0.1% PHMB is combined with 0.1% betaine to improve the cleansing efficacy,[79] in gels 0.04 and 0.1%, and in antiseptic dressings (including gauze, biocellulose dressings and foam) 0.2%–0.5%.[78,80–83] In the latter, PHMB impregnated and PHMB-donating dressings must be distinguished.[84]

Clinical indications for PHMB are supportive antisepsis in leg ulcers[85] chronic wounds, infected acute and chronic wounds, burns, decolonisation of wounds colonised with MRSA and prevention of SSI.[36,86]

Although PHMB topical solutions were introduced in wound antisepsis by Willenegger 1973 in Switzerland,[87] research has focused on PHMB wound dressings due to their cost-effectiveness[63,88] preferred for wounds without heavy exudate.[89] PHMB dressings used on acute and chronic wounds reduced pain and inflammation and increased wound healing.[20,50,88,90–92] This can be attributed to the efficacy of PHMB in reducing the bacterial burden in the wound by destroying planktonic cells and biofilm.[50,84] PHMB-impregnated biocellulose dressings for paediatric lacerations were well tolerated and achieved good healing outcome without any local infection.[91] On bacterially contaminated type 2–4 soft tissue wounds, the anti-inflammatory effect and tissue compatibility of PHMB solution were significantly better than that of Ringer solution.[82] Furthermore, PHMB effectively controlled the polymicrobial bioburden of delayed closure surgical wounds.[73,93] Most studies have been done on infected chronic wounds of varying aetiologies. In the consensus guideline on wound antisepsis, seven trials are listed, of which three are RCTs. Improvement of inflammation and wound healing was consistent in all seven studies; in part, significantly faster elimination of microorganisms has been proven.[36]

For second-degree burns[94] and deep partial as well as full-thickness burns,[22] improved re-epithelialisation, significant pain reduction, fewer dressing changes[51] and no infection[94] were reported. Even for newborns and children, the combination of PHMB/undecylenamidopropyl-betain was well tolerated by burns and supported the healing process.[95] Of 198 patients, five AEs (itching, rash and hypergranulating tissue) were reported.[57]

In recent years, the prevention of surgical site infection has opened up a new area for PHMB. Wound irrigation on a PHMB basis has shown significant reduction of SSI rates in contaminated traumatic wounds following surgical debridement, in comparison to Ringer's solution, PVP iodine and hydrogen

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Table 1. Comparison of clinical findings between wound antiseptics, taken from Kramer et al. (2018)[36]

Agent	NaOCl/HOCl	OCT	PHMB	PVP iodine
Silver ions	Tendentially better	Significantly better	Significantly better	Tendentially better
Povidone iodine (PVP iodine)	Significantly better	Tendentially better	Significantly better	n/a
Chlorhexidine digluconate (CHG)	No study	No study	Significantly better	No study

n/a—not applicable

peroxide.[96] Use of PHMB antiseptic gauze at the external pin site resulted in a significant reduction in the SSI rate compared with a placebo.[83] Similarly, there was a significant reduction in the SSI rate at the suture site following cardiac surgery.[97] However, the application of dressings soaked in PHMB in full-thickness skin grafting have not been shown to have this preventive effect.[98]

In combination with NPWT, PHMB can be used for instillation (NPWTi). Results in a porcine model suggest enhanced wound healing and reduced wound bioburden.[99] Clinical results underline results in porcine models.[84,93,100–105] The superiority of NPWTi versus NPWT in a retrospective, historical, cohort, controlled study[106] were not be confirmed in a prospective, multicentre, non-comparative clinical trial by the same author.[107]

Decolonisation of methicillin-resistant *Staphylococcus aureus* (MRSA)-colonised patients with PHMB were successful in 47% of cases; if altered skin was colonised, only 22% had decolonisation success.[108] Only rarely have antiseptics been compared in clinical trials, the results of which are summarised in Table 1.

Conclusion

PHMB's outstanding position for wound antisepsis is based on *in vitro* studies on efficacy and tolerability and has been confirmed through clinical studies.[109] From the analysis of the studies available up to 2012, the Wound Healing and Management Node Group derived the following recommendations for PHMB-based antiseptics:[102]

- Wound dressings could be considered a management option that decreases the patient's wound pain (strong support that merits application)
- Wound dressings could be used for reducing infection and promoting healing in persistent wounds without heavy exudate (moderate support that warrants consideration of application)
- Solutions (up to 2% PHMB) could be used to manage wound infection (moderate support)
- Wound dressings are a cost-effective management option (moderate support).

Taking all studies into consideration, it can be concluded that PHMB is proposed as agent of first choice for the following indications:[36]

- Treatment of chronic wounds with poor wound healing, because wound healing is significantly promoted and a high antiseptic remanence as well as good tissue tolerance are provided
- Treatment of second-degree burns which cannot be covered primarily through plastic surgery.

PHMB is suitable for the following indications, but with the current data available, it cannot be determined whether PHMB is of superior or equivalent value for these application areas compared with other antiseptics:[36]

- Treatment of infected acute wounds
- Prevention of SSI by application pre-, intra- or postoperatively by rinsing or with PHMB impregnated dressings
- Decolonisation of MRSA carriers.

Taking into consideration the unique characteristics of PHMB for wound antisepsis, prevention and therapy in addition to the fact that the data for carcinogenicity are irrelevant, a discontinuation of the use of PHMB with the current state of knowledge is not justifiable. In this context, it should be noted that drugs and medical devices usually contain only 0.02–0.5% PHMB. Considering that PHMB is not absorbed by wounds in detectable quantities, any carcinogenic risk is unlikely as is any other type of systemic hazard. **JWC**

Reflective questions

- Does antiseptic cleansing with PHMB reduce the infection rate of wounds significantly more than with other antiseptics?
- How good is the evidence for PHMB use of in the treatment of chronic wounds?
- Describe the evidence on PHMB tolerability and effectiveness for intra-operative use?

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