Response to the article "Polihexanide – Legal aspects of a risk assessment" by Volker Großkopf and Michael Schanz (published in Wund Management 2016; 10(6):328-29 [34]) A. Kramer*, T. Eberlein, O. Assadian

KEYWORDS
polihexanide, carcinogenicity, benefit-risk assessment

INTRODUCTION

The article by Großkopf and Schanz "Polihexanide – Legal aspects of a risk assessment" was first published in 2015 in the journal Rechtsdepesche [33]. Already at the time of this initial publication, Kramer and Assadian (2015) published a critical response to the article [54]. Given this fact, it is difficult to understand why the identical article by Großkopf and Schanz was reprinted [34] without any response to the argumentation offered by Kramer and Assadian [54].

As we have received inquiries from anxious readers following a further publication of the article by Großkopf and Schanz now in the journal Wundmanagement, we have found it necessary to again comment on this matter. Following up on our 2015 commentary, we now also consider publications on the agent polihexanide (PHMB) that have appeared in the meantime so as to take the most recent state of knowledge into account.

THE PROBLEM

In July 2013 in connection with the European Chemicals Act, the chemical compound PHMB was classified in Category 2 ("may cause cancer"). Products that contain more than 1% PHMB must in consequence be labeled as Class 2 carcinogens. Explicitly exempted from this labeling requirement are medical devices containing PHMB that are used invasively or on the body surface, for example for wound irrigation or as a wound dressing. The reason for this exemption is to be found in the fact that the regulation of hazardous substances and preparations is generally undertaken to ensure occupational and environmental safety and in particular to deal with exposure incidents that could occur in the production of such substances in larger amounts. These regulations should provide suitable measures to protect production employees against critical exposures.

Großkopf and Schanz pose the question in their article [34] whether PHMB, as a result of its classification in Category 2, should not rather be replaced by an equally effective but non-hazardous agent. In doing so, the fact that the classification in Category 2 implies a presumed but not definitive carcinogenicity is overlooked. The question of a suitable alternative is also not addressed. Großkopf and Schanz then come to the conclusion that the use of PHMB should be prohibited if a benefit-risk assessment should result in a negative finding for PHMB. However, the authors neglected to provide the benefit-risk assessment that they themselves demanded.

The legal opinion regarding the replacement of PHMB by a suitable alternative is only relevant when the benefit-risk assessment in fact should result in negative finding for the agent. The reader, however, gets the impression that the use of PHMB is basically questionable from a medical standpoint. For that reason, only a scientifically based benefit-risk assessment can answer the question whether there is a necessity to replace this agent or not. Independent of this, it must be analyzed to what extent the classification by the European Chemicals Agency (ECHA) is scientifically justifiable. Only on this basis, are the legal aspects of the risk classification of any ethical relevance.

CONCLUSIONS BASED ON THE CHEMICAL STRUCTURE OF PHMB IN REGARD TO THE BENEFIT-RISK ANALYSIS

In its chemical structure, PHMB is similar to the chlorhexidine (CHG) molecule with the critical difference that at the terminal C-atoms 4-chloroaniline (CA) is substituted. Following antiseptic rinsing of the oral cavity with CHG, p-chloroaniline (CA) could be detected in the saliva up to 30 minutes following use. Because CA is a known human carcinogen, the release of CA from CHG may have been the reason that CHG in various tests was found to be mutagenic [2,69,83] and in animal experiments to have caused precancerous alterations in the oral mucous membranes after 14 days of use [82]. In contrast, there is no evidence that PHMB has mutagenic effects or that it induces precancerous alterations. This may be a result of the fact that the CA structure is not present in the PHMB molecule.

CONCLUSIONS BASED ON THE MODE OF ACTION OF PHMB IN REGARD TO THE BENEFIT-RISK ANALYSIS

PHMB mainly reacts with negatively charged phospholipids, the principal component of the membrane of gram-negative and gram-positive bacteria. It also reacts with lipopolysaccharides in the outer membrane of gram-negative bacteria. In addition, it reacts with teichoic acids in the cell membrane of gram-positive bacteria and with peptidoglycan elements of the cell wall and the membrane proteins. By contrast, the bonding with the neutral lipopolysaccharides of the cell wall of human cells is less pronounced, which explains the selective antiseptic effect of the agent [42,43,60].

This selective effect is the cause of the favorable biocompatability index, which is well above the value of 1. A value of this level has only been demonstrated additionally for octenidine hydrochloride (OCT) [66]. As a result of PHMB's selective mode of action, bacteria are killed in co-cultures of keratinocytes and S. aureus, while the keratinocytes survive [86]. This phenomenon has only been demonstrated additionally for the antiseptic agent sodium chlorite [16].

The complex mode of action of PHMB makes it unlikely that resistance will develop in the target organisms because the negative surface charge is essential for the totality of vital processes in bacteria, yeasts and fungi and blocking this charge is irreversible. Likewise, fragmentation of the cell membrane is also irreversible. In line with this is the fact that over a period of more than 60 years of use of PHMB, no development in resistance has been observed. By contrast, microbiostatically active agents do display resistance development, including cross-resistance to antibiotics. This applies, for example, to CHG [15,71], triclosan [11,13,14,25] and antiseptics that release silver ions [81]. For this reason, widespread use of these agents is to be regarded critically. Consequently, PHMB is well-suited for use against the increasing number of antibiotic-resistant pathogens, as are hypochlorite [52] and OCT [40].

ANTISEPTIC EFFICACY OF PHMB IN REGARD TO THE BENEFIT-RISK ANALYSIS

The spectrum of efficacy includes all vegetative pathogens, including those with acquired resistance with an exposure time of 1-20 min. in quantitative suspension tests [3,63]. A special feature is PHMB's efficacy against intracellular pathogens such as MRSA, E. coli, S. enterica serovar Typhimurium, M. smegmatis, acanthamoebae and Neisseria. Within keratinocytes, MRSA are killed through direct interaction with PHMB [47]. For other antiseptic agents, an intracellular effect is only relevant for iodophors and certain, specially formulated and prepared mixtures of peroxide and carboxylic acid [89].

With and without organic bioburden, PHMB is more effective than CHG with the same exposure time and also more effective than iodophors with higher blood load. Unlike iodophors and hypochlorite, PHMB has a remanent effect. In specimen tests, PHMB has the same antiseptic efficacy as OCT; in blood load and tests against P. aeruginosa, PHMB is effective in 3 hours as opposed to 10 hours for OCT [77].

Microorganisms in biofilms and in vitro [39] are eliminated as well as in 3D skin models [20] and in animal wounds (pig) [70].

FURTHER EFFECTS RELEVANT FOR WOUND-ANTISEPTIC EFFICACY IN REGARD TO THE BENEFIT-RISK ANALYSIS

Fibrin plaques are significantly reduced by PHMB in in vitro tests [80]. Similarly, the formation of superoxide and peroxynitrite radicals is inhibited [85]. These characteristics, which are important for wound healing, are not known for other antiseptic agents.

The capillary density is increased in the cremaster muscle (in rats) through exposure to PHMB as well as to OCT. The diameter of arterioles, however, is only increased through exposure to PHMB. Likewise the microcirculation in the skin is increased through PHMB, although the functional capillary density and the flow velocity of erythrocytes is significantly reduced [61]. These effects may be principally responsible for PHMB's documented promotion of wound healing,
which has only been found for a few other agents (Table 1).

INFLUENCE ON WOUND HEALING IN REGARD TO THE BENEFIT-RISK ANALYSIS

Until now, increased proliferation of fibroblasts and keratinocytes has only been documented for PHMB (Table 1 [87]). This is an important characteristic in connection with wound healing, which can represent a clinical benefit in the application to wounds. This aspect will be relevant later in the consideration of possible risks of PHMB in other indications in other anatomical regions (see Section 9 in Horner [37]).

Consistent with this, wound healing was also supported in an in vitro wound model [72] as well as in experimental wounds in pigs; in parallel testing, OCT resulted in no promotion of wound healing in respect to increased fibroblast proliferation [40]. In guinea pigs and in rats, wound healing was also accelerated through the use of PHMB, presumably as a result of fibroblast proliferation [9,46]. It appears that there is a multi-factor causal basis for the promotion of wound healing by PHMB. In addition to fibroblast proliferation, the inhibited elastase of P. aeruginosa, which otherwise results in the degradation of wound fluid and tissue proteins, could have an effect in this regard.

LOCAL TOLERANCE AND TOXICITY IN REGARD TO THE BENEFIT-RISK ANALYSIS

PHMB has a classification for acute toxicity of "practically not toxic", based on the oral toxicity of 5 g/kg in rats. In rabbit eyes, a concentration > 25 % is tolerated; in nasal mucous membranes 0.02 % [38].

PHMB is clearly superior to iodophors in tissue tolerance with the exception of cartilage tissue [53,67]. In the HET-CAM test, the irritant effect is not different than that of antibiotic eye drops

[57] and of hypochlorite. The irritant effects of OCT, CHG and Flamazine are higher and much higher (Qasim A, Kramer A, Assadian O, Harnoss J. Screening of selected wound antiseptics for compatibility in the HET-CAM. In prep.).

There is clinical confirmation that PHMB is tolerated on wounds and mucous membranes [4]. PHMB was even better tolerated than Ringer's solution [78]. In mesh grafts, PHMB stimulated reepithelialization while PVP iodine and silver nitrate induced deep necroses and fibrin deposits [21,58]. Following unsuccessful split thickness mesh grafts in pre-treatment with PVP iodine or silver nitrate, pre-treatment and post-treatment with PHMB resulted in complete reepithelialization within 2 months. PHMB is thus histologically and clinically superior to PVP iodine and silver nitrate in pre-treatment and post-treatment of burn wounds with split thickness mesh grafts [21]. With daily application of a PHMB wound gel on the skin graft the new epithelialization was completed after 7 days without the appearance of a postoperative wound infection (surgical site infection, SSI) [48].

In contrast to iodophors, triclosan and OCT, PHMB is not absorbed dermally or from wounds above the detection limit of 10 µm [38]. Consequently, no absorptive-toxic effects including mutagenicity and teratogenicity have been documented in the use of PHMB on skin and wounds. This is also the case for hypochlorite and OCT. For iodophors, however, absorption is a relevant factor due to possible thyroid gland risks. [6]. PHMB is also not harmful in connection with chronic toxicity. The NOEL (no observable effect level) in oral application is 200 mg/kg KM/d. The oral administration of 100 mg/kg KM/d has been tolerated without adverse effects for a period of two years. Even with an oral application of 8 mg/kg KM/d there is no indication of a mutagenic, teratogenic or embryotoxic effect.

ASSESSMENT OF CARCINOGENIC RISK IN REGARD TO THE BENEFIT-RISK ANALYSIS

The supposition of PHMB's possible carcinogenicity is based on two animal studies [37,65]. The relevance of these findings for human as well as veterinary medicine is to be doubted for two reasons. First, in both of these feeding studies, extremely high PHMB concentrations were administered that were far above the NO(A)EL (no-observed-(adverse-) effect level) of 400 ppm for rats and 600 ppm for mice. At 4000 ppm, a significant trend of increased hemangiosarcoma was observed in rats; in particular, after 103 weeks of daily feedings of 162.3 mg/Kg body weight a total of three hemangiosarcoma tumors were found in the livers of the killed animals [37]. In addition, a carcinoma was found.

In the feeding of 0, 400, 1200 and 4000 ppm 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 4000 ppm group was 12 % lower than in the other dosage groups. With feeding of 4000 ppm PHMB (equivalent to 715 mg PHMB/kg KG/d male mice or 855 mg PHMB/ Kg KG/d female mice) the only important clinical difference was an increased incidence of swelling at the anus and anal prolapse. In one male animal in the 4000 ppm PHMB group an adenocarcinoma was found, which the author [65] attributed to chronic inflammation of the colon. Similar to Horner's findings [37], an increasing incidence of hemangiosarcoma of the liver was observed as the PHMB dosage increased (0 ppm PHMB: 4/110 mice; 400 ppm: 2/110; 1200 ppm: 11/110; 4000 ppm: 33/110).

The results of both studies are not surprising and make sense on a prima facie basis when one considers PHMB's the proven capability of promoting fibroblast proliferation The cell proliferation which is desired at the wound can become disadvantageous at the liver and colon with systematic and atypical exposure. With an appropriate clinical indication, however, this cannot occur due to the absence of absorption in wounds and mucous membranes. By contrast, feeding in the NO(A)EL range resulted in no abnormal effects.

The second reason is that no genotoxicity has been found for PHMB [75]. The only explanation for a carcinogenic effect is an epigenetic and not genotoxic alteration of the DNA. In reviewing a possible epigenetic effect, no oxidative stress on the DNA was found to be induced, nor was there demonstrable hydroxylation or hypermethylation of DNA. Significant production of mitogenic cytokines and the transcription factor NF-KB could also not be detected. The status of the GAP junction (GJ1C) was also not significantly affected. Thus, no clear epigenetic effects could be demonstrated either [17].

This study thus supports the assessments of the United States Environmental Protection Agency (EPA) [28-30] and later of the Australian authorities at the OCSEH [68] which interpreted the animal study data of Horner and Milburne [37,65] to reach the conclusion that no relevant health risk for humans is discernible. Much more probable is the explanation that the occurrence of hemangiosarcoma resulted from increased endothelial proliferation, triggered by the exceedingly high feeding dosage. Also to be noted is the fact that the hemangiosarcoma are benign tumors and not a carcinoma. Therefore the labeling "H351 - May cause cancer" is not correct in the sense of the agent being pathohistologically carcinogenic. In the absence of a category for benign tumors, use was made of the classification of possibly carcinogenic effect. If this designation should indicate that tumors in a general sense are meant, then the labeling should include the clarification that this occurs exclusively with oral ingestion of at least 162.3 mg of the agent/kg/KM/d over a period of more than two years.

With proper use of PHMB for wound antisepsis, a carcinogenic risk can be ruled out.

CLINICAL EFFECTIVENESS OF PHMB IN REGARD TO THE BENEFIT-RISK ANALYSIS

For the decolonization of MRSA, PHMB [22,45], CHG [51], OCT [40] and mupirocin [64] are all effective. The use of CHG, however, is limited due to the risk of resistance development and of anaphylactic reactions. The use of mupirocin is also limited due to the risk of resistance development [36]. As the effectiveness of OCT and PHMB has not yet been clinically tested on a comparative basis, no statement can be made regarding a preference for the one or the other agent.

A field of application that is gaining new significance is combining wound treatment with antiseptics with negative pressure wound therapy (NPWT) and with body temperature cold atmospheric pressure plasma (CAP). It has been possible to significantly improve the efficacy of negative pressure wound therapy when treating wounds with a high load of bioburden or biofilm in connection with the instillation of antiseptics [88]. Convincing results have until now been achieved with the agents PHMB [49,84] and hypochlorite.

Wound treatment with cold atmospheric plasma (CAP) at body temperature in human medicine has to date only been able to show that an antiseptic effect can be achieved with good wound tolerance but without actual healing success [10,35,44,50]. In cases with pets, however, combined use of CAP with PHMB has resulted in a complete healing of chronic wounds in 19 of 20 cases where conventional therapy was without success [7]. The cause of this may be that the dormant stage is broken down in chronic wounds through the application of CAP [59], but due to the absence of any remanent antiseptic effect with CAP the healing does not progress. Therefore, parallel application of both treatment principles is required.

In recent years, the prevention of SSI has been opened up as a new and promising area of use for PHMB. Wound irrigation on a PHMB basis has for the first time been shown to result in a significant reduction in the SSI rate in contaminated traumatic wounds following surgical debridement in comparison to Ringer's solution, PVP iodine and hydrogen peroxide [73]. Use of a PHMB antiseptic at the external pin site resulted in a significant reduction in the SSI rate as compared to a placebo in a randomized controlled trial (RCT) [62]. Similarly, there was a significant reduction in the SSI rate at the suture site following cardiac surgery in a placebo controlled cohort study [31]. Until now, however, the application of dressings soaked in PHMB in full-thickness skin grafting could not be shown to have this preventive effect [74].

BENEFIT-RISK ASSESSMENT OF PHMB IN COMPARISON WITH OTHER FREQUENTLY USED ANTISEPTIC AGENTS

In a comparison of all important characteristics for a wound antiseptic, it can be seen that PHMB occupies an outstanding role (Table 1).

PHMB's outstanding position has been confirmed through clinical studies. Table 2 shows the results derived from 33 studies that have been analyzed (18 RCTs, 6 studies with comparison to baseline, 1 case-control study, 1 cohort study, 4 retrospective studies, 2 parallel comparisons on the same wound). Further information can be found in Kramer [52]. In addition, it should be mentioned that there is now a limitation for OCT, which since recently is only recommended for superficial application. This is because in 2016 there were further incidents with edematous swelling and damage to tissue following irrigation of deeper wounds (puncture wounds, bite wounds as well as abscess cavities) with Octenisept®. In some cases, this required surgical revision. Particularly problematic is the irrigation of bite, puncture and incised wounds on the hand or foot as permanent impairment of functionality may be caused. As a result, the German Federal Institute for Drugs and Medical Devices (BfArM) issued the following bulletin in 2016: "To avoid damage to tissue, the preparation must not be applied with a syringe into deep tissue. The preparation is only suitable for superficial use (application with swabs or spray)." [8].

In an updated statement from Scientific Committee on Consumer Safety (SCCS) from 23 December 2016 the following statement was made: "In light of the new absorption studies provided, does the SCCS consider Polyaminopropyl Biguanide (PHMB) safe when used as preservative in all cosmetic products up to a maximum concentration of 0.1 %" (Source: [Scientific Committee on Consumer Safety: SCCS Opinion on Polyaminopropyl Biguanide (PHMB) - Submission III -. SCCS/1581/16. Preliminary version of 23 December 2016]).

This amounts to a moderation of the original risk assessment. This original assessment was based on in vitro data (tear method at the skin) and a dermal absorption of 8.5 % was calculated for PHMB. This technique, however, does not allow for a calculation of the absorption on the other side of the epidermis. Thus it remains relevant that up to the PHMB detection limit of of 10 µg 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 < 10 µg.

CONCLUSIONS FOR THE USE OF PHMB IN CLINICAL PRACTICE

PHMB is to be classified as the agent of first choice for the following indications:

- Treatment of chronic wounds with poor wound healing [23,55,58] 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 can not be covered primarily through plastic surgery
- Therapy of acanthamoebic keratitis [56].

Decolonization of MRSA carriers is effective using PHMB as is the prevention of SSI [27,41]. With the current data available, it cannot be determined whether PHMB is of superior or equivalent value for these application areas as compared to OCT or hypochlorite.

Taking into consideration the unique characteristics of PHMB for antiseptic prevention and therapy on the one hand and the fact that no carcinogenicity has been demonstrated on the other hand, a discontinuation of the use of PHMB with the current state of knowledge is not justifiable [54,55]. In this connection it should be noted that drugs and medical devices usually only contain 0.02 - 0.1 % PHMB and that the agent is not absorbed. Considering the manner of exposure in antiseptic application and that the use on skin, mucous membranes and wounds results in no demonstrable systemic intake, any carcinogenic risk is improbable as is any other sort of systemic danger.

DISCLOSURE

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TABLE 1: COMPARISON OF RELEVANT CHARACTERISTICS FOR WOUND ANTISEPSIS IN SELECTED ANTISEPTIC AGENTS

Agent	Intracellular killing	Development of resistance	Selective antiseptic effect	Wound healing	Cartilage tolerance	Sensitization	Systemic risks
PHMB	Yes	No	+	Positive effect	0.005 %	No	No
OCT	?	No		No inhibition	No	No	No
PVP iodine	Yes	No		Partial inhibition	Yes	Yes	Yes
Hypochlorit	?	No	+		?	No	No
Acetic acid	?	No		0.15 % positive effect	?	No	No
CHG	?	Yes		No inhibition	?	Yes	Possibly
Silver ion	?	Yes		Inhibition	?	No	Yes
Triclosan	?	Yes		No inhibition	?	Yes	Yes

TABLE 2: CONCLUSIONS FROM THE ANALYSIS OF 33 CLINICAL STUDIES (BASED ON KRAMER 2016 [52])

Characteristic	Hypochlorite	OCT	PHMB
Antiseptically effective	Yes	Yes	Yes
Good tolerance	Yes	Yes	Yes
Promotes wound healing	Yes	No inhibition	Yes
Remanent effect	No	Yes	Yes
Peritoneal irrigation in septic peritonitis	Possible	Contraindicated	Contraindicated
Exposure to central nervous system structures	Well tolerated	Contraindicated	?
Superior in comparison to			
Ag+	Possibly	Possibly	Significantly
PVP-I	Significantly	Significantly	Histologically clearly superior
CHG	No studies	No studies	Significantly

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