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A perspective on the safety of parabens as preservatives in wound care products

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Abstract

Antimicrobial and/or preservative ingredients incorporated in wound care products are subjected to certain safety restrictions. However, several of those agents, and paraben preservatives in particular, have been criticised. Conflicting reports on the potential of parabens to induce allergic contact dermatitis, and their assumed oestrogen-like activity, raised public health concerns about their overall safety. Here, we seek to provide a balanced perspective on the most significant purported adverse health effects, and thereby allay the many misconceptions regarding the safety of parabens. Extensive and long-term monitoring of paraben allergy frequencies illustrate that allergic reactions are quite uncommon, especially when compared with other antimicrobial and preservative agents. The estrogenic potential of parabens was illustrated to be far less potent than that of natural oestrogen receptor ligands, and the etiological significance of their presence in human tissue has not been established. The general consensus based on investigations by both the scientific community and regulatory agencies indicates that, with current safety regulations regarding their use in place, this effective and well-documented group of preservatives should not warrant drastic measures to replace them. As such, despite the ongoing concern, it is indicated that, when used at typical concentrations, parabens are unlikely to affect human health.

KEYWORDS

allergic contact dermatitis, endocrine disrupting, estrogenic activity, parabens, preservatives

List of Abbreviations: ACDS, American Contact Dermatitis Society; ASEAN, Association of Southeast Asian Nations; CIR, Cosmetic Ingredient Review; ECHA, European Chemicals Agency; EECDRG, European Environmental and Contact Dermatitis Research Group; ESSCA, European Surveillance System on Contact Allergies; FDA, Food and Drug Administration; GRAS, Generally Recognized as Safe; IVDK, Information Network of Departments of Dermatology; NACDG, North American Contact Dermatitis Group; PHMB, polyhexanide; SCCS, Scientific Committee on Consumer Safety; SEQ, sensitisation exposure quotient.

1 | INTRODUCTION

Wounds of various aetiologies have a significant impact on global health, affecting approximately 1.5 to 2.0 million people in Europe (acute and chronic wounds) and about 6.5 million people in the United States (chronic wounds) alone.[1] Living with a wound can not only have a profound effect on quality of life, but the management of wounds also accounts for health care costs of up to millions of dollars per year in developed countries.[2,3] Consequently, the efficient and safe management of both minor and major wounds is of vital importance. To this end, various topical wound care products are available that provide a moist wound-healing environment, promote autolytic debridement, demonstrate anti-inflammatory activity and/or antimicrobial properties, and thereby promote an improved and rapid healing.[4] As wound healing can be delayed by microbial infection, topical antiseptics and antibiotic agents, including cadexomer and povidone iodine, chlorhexidine, polyhexanide (PHMB), octenidine, silver, and bacitracin, may be present to control microbial colonisation.[2,3,5] To prevent contamination of the dressing itself with mould, fungi, and/or bacteria and to protect consumers against an undesired increase in the risk of infection, preservation of such wound care formulations can be an additional prerequisite.[6] Similar to cosmetics and other personal care products, preservative ingredients, such as urea derivatives (imidazolidinyl and diazolidinyl urea), isothiazolinones (methylisothiazolinone and methylchloroisothiazolinone), halogen-organic actives (iodopropynyl butylcarbamate and methyldibromo glutaronitrile), formaldehyde, Quaternium 15 (ie, formaldehyde-releaser), silver salts, organic acids (potassium sorbate, sodium benzoate), phenoxyethanol (alone or in combination with methyldibromo glutaronitrile), and parabens, can be indispensable.[4,6-9]

Although the use of antimicrobial and preservative ingredients is, in turn, subjected to certain restrictions in order to safeguard both product and consumer safety, consumer awareness regarding their skin sensitisation potential has increased. Several agents, and paraben preservatives in particular, have been criticised in this regard. The homologous *p*-hydroxybenzoate esters, generally known as parabens or paraben esters, have been, for more than 70 years, among the most commonly used types of preservatives (biocides) in food, cosmetics, medical devices, and pharmaceutical products.[1-5] Methyl- and propyl-paraben are by far the most regularly used preservatives in topical formulations for skin and wound care because of their broad spectrum of activity against moulds, fungi, and bacteria; low cost; chemical inertness; minimal toxicity; and worldwide acceptance.[6,7,10,11] Nevertheless, initial public health concern regarding paraben safety related to peri-wound allergic dermatitis was further exacerbated by the publication of a study on laboratory animals indicating the potential oestrogen-like activity of paraben esters, including methyl-, ethyl-, propyl-, and butyl-paraben.[12] In 2004, Darbre et al[13] further fuelled the controversy by identifying the presence of different paraben esters in human breast tumour tissue samples.

In response to these alleged adverse effects and the resulting media-driven consumer fear, manufacturers were sometimes pressured to replace parabens in their products with other preservative systems.[14] However, the medical and scientific community has been evaluating and will continue to evaluate the available data in order to determine the significance, if any, of these findings towards

Key Messages

- Topical antimicrobial agents and/or preservative ingredients are important to safeguard wound care products from deterioration and protect the consumer from unwanted infections. However, the safety of such agents, and the widely used paraben preservatives in particular, has been questioned.
- In this review, we seek to provide a balanced perspective on the most significant purported adverse health effects, and thereby allay the many misconceptions regarding the safety of parabens.
- The capacity of parabens to act as skin sensitisers and cause allergic contact dermatitis has remained remarkably uncommon, especially when compared with other frequently used topical antimicrobial agents and preservative ingredients.
- Claims related to the assumed oestrogen-like and carcinogenic activity of parabens should be put into perspective. Notably, generally accepted standards are in place to ensure that these preservatives are used in such levels they do not pose a risk to the recipients.
- Despite the ongoing concern for paraben preservatives, current scientific knowledge and regulatory agencies indicate that, with standard safety regulations regarding their use in place, the paraben preservatives should not warrant drastic measures to replace them.

public health. Moreover, objective safety assessments, conducted by the United States Food and Drug Administration (FDA) and the independent Cosmetic Ingredient Review (CIR) programme, as well as by regulatory agencies of the European Union and Association of Southeast Asian Nations (ASEAN), did not lead to the modification of current guidelines for the use of paraben esters in cosmetics and personal care products, including those for wound management.[15-18] Paraben esters are even labelled by the FDA and Cosmetic Act as Generally Recognized as Safe (GRAS), which means the substance is generally recognised, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use. Other examples of compounds that are considered GRAS include vitamin A and sugar.[19,20]

Because many misconceptions have arisen around this extensively used class of effective preservatives, we attempted to provide a balanced perspective on the most significant purported adverse health effects and, thus, the safety of paraben esters.

2 | SKIN SENSITISATION POTENTIAL

Patients suspected of having allergic contact dermatitis can be diagnosed by patch testing with a standard or baseline series of potential ingredients of interest. For parabens, commercial patch test systems with a 16% paraben mix, comprised of the four most commonly marketed paraben esters, that is, methyl-, ethyl-, propyl- and butyl-paraben, each at a concentration of 4%, are used in Europe and many other parts of the world since 1994. The North American Contact Dermatitis Group (NACDG), that is, the largest contact dermatitis study group in North America, applied a 15% concentration mix with methyl-, ethyl-, propyl-, butyl-, and benzyl-paraben (each at 3%) until 1996. Thereafter, the paraben mix patch test concentration was lowered to 12% by excluding benzyl-paraben from the test mixture.[21,22] Notably, these patch test concentrations are significantly higher than the maximum total paraben ester concentration allowed in skin care products, that is, 0.8% per product, with no single paraben ester having a concentration higher than 0.4%. For products containing propyl- and butyl-paraben, the maximal total limit concentration has been set at 0.19%.[23] For other topically used antimicrobials and preservative ingredients, patch test systems with appropriate test concentrations are available as well, either as part of a standard series or for individual testing purposes.

The epidemiological evaluation of the allergy frequency of potential skin sensitisers, including paraben esters, is largely based on regular retrospective analyses of patch test data stemming from dermatology centres collaborating in large (often international) surveillance working groups. Epidemiological prevalence data on paraben mix skin sensitisation from the North American associations NACDG and Mayo Clinic indicate a rather stable and low prevalence rate of contact allergy to parabens over 24-year (1992–2016) and 17-year time periods (1998–2015), respectively (Table 1). During these test periods, patch test positivity rates reported by the NACDG ranged between 0.6% and 2.3%,[24-26,28,30,33,35,38,41,43,45,47] whereas those reported by the Mayo Clinic ranged between 0.8% and 1.7%.[29,31,37,44] For the NACDG, the highest allergy prevalence rates were reported for test cycles before and until 1996.[24-26] Interestingly, these higher-prevalence frequencies were mainly observed when benzyl-paraben was still included in the patch test mixture (ie, 15% paraben mix). Thereafter, positive patch test rates (using a 12% paraben mix) were remarkably lower, ranging between 0.6% and 1.0%.[28,30,33,35,38,41,43,45,47] Despite the fact that, currently, the majority of diagnoses is performed using patch test screening systems including a 16% paraben mix, there has been controversy over which concentrations are more sensitive and/or more specific. Patch tests with higher paraben mix concentrations, approaching the irritation threshold, are prone to lead to false-positive reactions.[22,48] In contrast, patch tests applying lower paraben mix concentrations and inadequately reaching elicitation thresholds could lead to more false-negative reactions.[22,49,50] Notably, discussions regarding the ideal patch test concentrations in order to avoid both false-positive and -negative results are also ongoing for other frequently used preservatives, such as the potent sensitisers methylchloroisothiazolinone/methylisothiazolinone and methyldibromoglutaronitrile (alone or in combination with phenoxyethanol).[51-54] The observed decrease in paraben contact allergy prevalence rates might thus be partly explained by differences in paraben mix concentrations, as well as by the exclusion of the less frequently used, and possibly more sensitising, benzyl-paraben from the patch test mixture.

Similar sensitisation rates were observed by European surveillance groups. Both the European Surveillance System on Contact Allergies (ESSCA) and the Information Network of Departments of Dermatology (IVDK), two European working groups linking dermatology departments in 12 and 3 different countries, respectively, periodically reported paraben allergy prevalence rates ranging between 0.5% and 1.2%[32,34,36,39,42,46] and 0.8% and 1.3%,[27,40] respectively, over a total test period of 22 years (1996–2018) (Table 1). For the first retrospective test cycle reported by the IVDK (1996–2008), the authors specifically stated that a substantial proportion of the total positivity rate might be because of false-positive

TABLE 1 Paraben mix allergy frequencies reported by the largest contact dermatitis surveillance working groups in North America and Europe (1992 - 2019).

	Percentage positivity rate (no. of patch-tests)					
Test cycles	**NACDG[a]**		**Mayo Clinic**	**ESSCA[b]**	**IVDK[c]**	
1992 – 1993	2.3 (3 508)(24)					
1993 – 1994						
1994 – 1995		1.8 (3 086)(25)				
1995 – 1996						
1996 – 1997	1.7 (4 096)(28)				1.3 (121 247)(53)	
1997 – 1998						
1998 – 1999		1.0 (5 803)(29)	1.6 (1 318)(36)			
1999 – 2000						
2000 – 2001						
2001 – 2002	0.6 (4 898)(30)		1.7 (3 841)(37)			
2002 – 2003				1.2 (8 857)(47)		
2003 – 2004	1.1 (5 142)(31)					
2004 – 2005				1.0 (9 166)(48)		
2005 – 2006	1.2 (4 439)(32)			1.0 (17 197)(49)		
2006 – 2007			1.7 (3 090)(38)			
2007 - 2008	1.1 (5 082)(33)			1.0 (23 331)(50)		0.9 (43 029)(54)
2008 – 2009						
2009 – 2010	0.8 (4 304)(34)			0.7 (52 586)(51)		
2010 – 2011						
2011 – 2012	1.4 (4 231)(35)		0.8 (2 576)(39)		0.6 (44 366)(54)	
2012 – 2013						
2013 – 2014	0.6 (4 859)(26)			0.5 (28 569)(52)		
2014 – 2015						
2015 – 2016	0.6 (5 593)(27)				0.8 (36 983)(54)	
2016 – 2017						
2017 – 2018						
2018 - 2019						

[a]North American Contact Dermatitis Group.
[b]European Surveillance System on Contact Allergies.
[c]Information Network of Departments of Dermatology.

reactions. From the 1.3% positive patch tests, only 0.2% of the patients reacted with a strong, unequivocal allergic reaction, while the remainder could have been explained by irritation rather than a true allergic reaction.[27] Nevertheless, patch test positivity rates continued to be low and apparently stable up to and including the IVDK's most recent report (2015–2018).

In addition, the European Environmental and Contact Dermatitis Research Group (EECDRG) studied the evolution of average annual contact allergy rates for a series of preservatives (including paraben mix) between 1991 to 2000 (16 centres in 11 countries)[55] and 2001 to 2008 (12 centres in 8 countries).[56] Stable annual allergy frequency rates between 0.5% and 1.0% were reported over this 17-year period.[55,56] The low allergy prevalence rates reported by larger surveillance groups are also confirmed by worldwide data derived from individual patch test studies. Individual studies published in the last 10 years (2010–2020) report paraben mix allergy positivity rates of 0.3% and 2.6% (Table 2).[57-65] The highest rate was derived from a study in Singapore (2.6%),[61] and the lowest from studies conducted in Lithuania[62] and The

TABLE 2 Paraben mix patch test data derived from other allergy frequency screening studies published between 2010 and 2020 (this year inclusive)

Test Cycle	Country	Percentage Positivity Rate (No. of Patch Tests)
1985–2008	Denmark	0.5 (18 178)[57]
2007–2008	Norway	1.2 (2089)[58]
2004–2009	China	0.5 (2758)[59]
1993–2006	Australia	1.1 (6845)[60]
2006–2011	Singapore	2.6 (3177)[61]
2014–2015	Lithuania	0.3 (297)[62]
1994–2013	The Netherlands	0.3 (8029)[63]
2006–2018	Thailand	2.1 (2803)[64]
2017–2018	Laos	0.7 (150)[65]

Netherlands[63] (0.3%). Overall, these paraben sensitisation rates correlate well to those reported in larger North American and European epidemiological studies.

With an average allergy rate of approximately 1.0%, the skin sensitisation potential of the paraben mix is rather low, especially when compared with those of other frequently used topical antimicrobial and preservative ingredients. Paraben mix allergy rates in the NACDG and the Mayo Clinic's most recent retrospective reports (ie, 0.8% and 0.6%, respectively) were remarkably lower than those of commonly used preservatives, including urea derivatives, isothiazolinones, halogen-organic actives (alone or in combination with phenoxyethanol), formaldehyde, and Quaternium 15 (with allergy prevalence rates ranging between 0.9% and 13.6%).[44,47] In addition, higher allergy rates between 0.8% and 7.8% were reported for antiseptics and antimicrobials, such as chlorhexidine, bacitracin, and neomycin.[44,47] Similarly, parabens were shown to have the lowest rate of positive patch tests among a series of preservatives, such as the urea derivatives imidazolidinyl and diazolidinyl urea, the isothiazolinones, methyldibromo glutaronitrile, formaldehyde, and the formaldehyde-releaser Quaternium 15, included in the annual allergy frequency reports by the ECCDRG.[55,56] In the ESSCA's most recent retrospective report,[46] paraben mix even ranked the third lowest of 29 allergens tested (including both preservative and non-preservative potential allergens) in terms of allergic contact dermatitis prevalence. Only the topical antimicrobial clioquinol and the plant allergen primin, which currently no longer warrant inclusion in the European baseline series, scored better with patch test positivity rates of 0.3% and 0.2%, respectively.[46,66] In contrast, the highest allergen prevalence rates included a metal (nickel sulphate), another preservative (methylisothiazolinone, tested at different concentrations), and a fragrance (fragrance mix I) with patch test positivity rates of 18.1%, 7.3% to 10.2%, and 7.3%, respectively.[46] Allergic contact dermatitis reports are not as numerous for some other commonly used topical antimicrobial and preservative ingredients, such as povidone iodide, octenidine, and silver salts, as these are not routinely mentioned in standard series of larger surveillance patch tests. Yet, an individual patch test study for povidone iodine indicated an allergenic prevalence rate of 0.4% (among 500 patients) and is therefore, similar to paraben mix, considered a rare allergen.[5] For octenidine and silver salts, further reports are needed to define their allergenicity.[5]

Putting the risk of sensitisation more accurately into perspective, epidemiological data reporting the frequency of sensitisation should be correlated with the probable topical exposure to these preservatives. The exposure risk for preservatives can be quantified using the sensitisation exposure quotient (SEQ), that is, the ratio of the relative percentage of products containing a biocide (product share) and the corresponding positivity ratio considering all positive biocides (allergy share).[8] Schnuch et al[8] demonstrated that parabens ranked the third lowest of 12 preservative systems, with an SEQ of 0.35, using data of the IVDK for 2006 to 2009. Only phenoxyethanol and benzyl alcohol scored better, with an SEQ value of 0.06 and 0.30, respectively. Other commonly used preservative ingredients, such as urea derivatives, isothiazolinones, iodopropynyl butylcarbamate, sorbates, and benzoates, had SEQ values ranging between 0.92 and 9.0. These findings only reinforce the general epidemiological trend of low and rather stable paraben allergy prevalence rates, as illustrated by the large body of retrospective data above.[8]

Despite their ubiquitous use as preservatives,[8,10] parabens are associated with a low risk of skin sensitisation, especially when compared with other commonly used topical antimicrobials and preservatives. Parabens were even formally declared the American Contact Dermatitis Society (ACDS) non-allergen of the year in 2019, indicating that concerns raised during the past century are no longer of significant relevance.[67]

3 | ENDOCRINE DISRUPTION

Because of their vast utilisation as a preservative system in a variety of topicals (eg, personal care products such as those for wound management, cosmetics, and medical devices), pharmaceuticals, and food products, not only was the potential of paraben esters to cause skin sensitisation questioned but also their potential to elicit systemic effects.

Following cutaneous application, the penetration of paraben esters through the skin is highly dependent on the type of ester applied, the vehicle used, and the integrity of the dermal barrier. However, absorption through normal and intact human skin is rather minimal. The ability to penetrate skin declines even further with increasing length or degree of branching of the ester alkyl side chain.[68,69] In addition, paraben esters, both via oral and dermal uptake, are rapidly metabolised to their primary metabolite, *p*-hydroxybenzoic acid, via non-specific esterases present in the skin and liver.[70] The limited proportion of intact paraben esters and their hydrolysates are rapidly and predominantly excreted in the urine, either as conjugates or in free form.[69-72] The rapid urinary excretion, and thus relatively short biological half-life (ie, less than 24 h), of paraben esters after both cutaneous and oral absorption was illustrated by a study by Dodge et al,[73] which indicated that human urinary excretion of parabens peaked within 7 h of the use of paraben-containing products. Both human and laboratory animal studies have failed to show any acute toxicity stemming from paraben esters, whether administered topically or orally.[69,74]

Paraben esters have been shown to have weak estrogenic activity in both *in vitro* laboratory and *in vivo* animal studies. Claims regarding their endocrine-disrupting properties, however, are less substantiated. In 1998, Routledge et al[12] reported that methyl-, ethyl-, propyl-, and particularly butyl-paraben displayed weak estrogenic properties via *in vitro* receptor-binding capacity assays (rat uterine oestrogen receptor) and oestrogen-related gene expression studies in a recombinant yeast model. Their conclusions were supported by data from other *in vitro* human or rodent receptor-binding capacity assays[75-77] and oestrogen-related gene expression in recombinant yeast models.[78-80] These properties were shown to be related to the molecular weight of the paraben ester, with a progressive estrogenic activity with increasing molecular weight.[78,81] Furthermore, weak binding activity was observed in studies applying human oestrogen-sensitive cell lines, including MCF7, T-47-D, and ZR-75-1 human breast cancer cell lines.[82-87] This binding, however, does not necessarily result in the activation of a receptor, and binding avidity does not automatically correlate with degree of transcriptional activity identified. In 2004, Darbre et al[13] demonstrated for the first time the presence of a series of intact paraben esters in 20 human breast cancer tissue samples, with methylparaben representing the majority of the total amount of paraben esters retrieved. Barr and colleagues[88] in turn demonstrated the quantifiable presence of paraben esters in 158 of 160 human breast cancer samples examined in four serial locations across the breast, including the upper outer quadrant, which was suggested to be the most frequent site for breast cancer incidence.[89] As a result, Charles and Darbre[90] organised a follow-up study in which they showed that 27% of the 160 tissue samples examined compromised one or more paraben esters at a concentration greater than that leading to the lowest observed effect for *in vitro* MCF7 oestrogen-sensitive human breast cancer cell proliferation,[90] further fuelling the suggestion that underarm and body care products, such as antiperspirants and deodorants, could be related to the incidence of oestrogen-mediated human breast cancer.[91]

Darbre and Harvey[92] contended, in their hypothesis, that paraben esters can facilitate cancer development in human breast epithelial cells by meeting the criteria of four of six basic hallmarks: (a) being present in human breast tissue samples and possessing estrogenic activity that could possibly stimulate sustained proliferation of human breast cancer cells at concentrations measurable in the breast; (b) inhibiting suppression of breast cancer cell growth by hydroxy tamoxifen and through binding to the oestrogen-related receptor γ, preventing deactivation by growth inhibitors; (c) providing dose-dependent evasion of apoptosis in high-risk donor breast epithelial cells; and (d) long-term exposure (>20 weeks) to parabens leading to increased migratory and invasive activity in human breast cancer cells, properties that they link to the metastatic process. Reviewing these data, Fransway et al[22] noted that the concentration of oestradiol present in normal human breast tissue suggested a safety margin of 10 to 1000 times that of paraben esters to approximate normal oestradiol activity. They further noted that, although parabens mimic the activity demonstrated by the naturally occurring hormone oestrogen, the magnitude of activity (ie, their potency) was substantially lower for parabens, and the potential to result in an adverse effect mediated via an oestrogen mode of action has still not been established in humans. In addition, Golden et al[93] asserted that it is biologically implausible that parabens could increase the risk of any oestrogen-mediated endpoint, including effects on the male reproductive tract or breast cancer, a conclusion they based on worst-case scenario assumptions pertaining to total daily exposures to parabens and dose/potency comparisons with both human and animal no-observed-effect levels and lowest-observed-effect levels for oestrogen or diethylstilbestrol.[93]

To further assess the *in vivo* impact of reported weak estrogenic effects, the impact of paraben esters on oestrogen-controlled uterine growth has been investigated in immature or ovariectomised female rodents (uterotrophic assays). In their initial study, Routledge et al[12] indicated the lack of uterotrophic effects in immature rats upon oral administration of methyl-, ethyl-, propyl-, and butyl-paraben. In case of subcutaneous

exposure at high doses (ie, 400 mg/kg bodyweight), however, an increased uterine weight was noted for butyl-paraben. Based on their study, several other *in vivo* uterotrophic assays in rodents were conducted and often reported mixed results. Hossaini et al[94] indicated a weak estrogenic response for butyl-paraben upon subcutaneous administration at 600 mg/kg bodyweight to immature rats, whereas oral and subcutaneous administration of methyl-, ethyl-, propyl-, and butyl-paraben and their primary metabolite *p*-hydroxybenzoic acid to immature mice did not result in any uterotrophic effect (tested up to 100 mg/kg bodyweight). Also in ovariectomised adult mice, subcutaneous exposure of propyl- and butyl-paraben at dose levels up to 950 mg/kg bodyweight were reported to demonstrate no uterotrophic effects.[95] In contrast, Lemini et al[75,96] reported an effect on the uterine growth in both immature and adult ovariectomised mice upon subcutaneous administration of methyl-, ethyl-, propyl-, and butyl-paraben and confirmed that the positive correlation between estrogenic potency and the length or degree of branching of the alkyl side chain of the paraben ester tested was also present in *in vivo* uterotrophic assays. The impact of paraben esters on early gestation has also been evaluated to assess *in vivo* estrogenic activity. Shaw and DeCatanzaro[95] indicated that subcutaneous administration of butyl-paraben at high doses (ie, up to approximately 950 mg/kg bodyweight) to inseminated mice did not affect pregnancy continuation, litter size or postnatal survival, and weight of the pups. Because of the suggestion of weak estrogenic activities, the effect of paraben esters on the male reproductive system and function has also been investigated, with variable results being reported. Oishi[97,98] indicated that propyl- and particularly butyl-paraben, upon oral administration in rats (doses of approximately 10, 100, and 1000 mg/kg bodyweight), resulted in a decreased sperm count in both the epididymis and testis. Serum testosterone level decreased at 100 mg/kg bodyweight and above.[97,98] For butyl-paraben, a decrease in epididymis weight was observed at 100 mg/kg bodyweight and above.[97] In contrast, Hoberman et al[99] indicated that oral administration of butyl-paraben to rats at doses of approximately 1000 mg/kg bodyweight did not affect any male reproductive organs, functions, or hormones. In the case of methyl- and ethyl-paraben, anti-spermatogenic effects and changes in serum testosterone level were not observed (tested via oral administration up to 1000 mg/kg bodyweight).[99-101]

Although weak estrogenic activities are illustrated in a series of *in vitro* laboratory and *in vivo* animal studies, there is a lack of consistency. Reasons for these discrepancies may largely result from differences in methodology.[95] Notwithstanding, the relevancy of the studies should be properly addressed, and those reporting endocrine-disrupting effects should be put into perspective. First, paraben esters have been demonstrated to possess only a very small fraction of the estrogenic potency of natural oestradiol. Routledge et al[12] indicated that the most potent paraben ester implicated in their *in vitro* study (ie, butyl-paraben) was demonstrated to be at least 10 000-fold less potent than 17β-oestradiol. Similarly, Miller et al[78] illustrated that, when compared with 17β-oestradiol, methyl-, ethyl-, propyl-, and butyl-paraben showed only a relative *in vitro* potency of 1/3 000 000, 1/200 000, 1/30 000, and 1/8000, respectively. With regard to the *in vivo* observed uterotrophic effects, the relative estrogenic potency of the four most commonly used paraben esters and their main metabolite *p*-hydroxybenzoic acid was shown to be several orders of magnitude lower than that of 17β-oestradiol.[75] In particular, the weak estrogenic effect of butyl-paraben on uterine growth was illustrated to be at least 100 000-fold less potent.[12] In addition, for early gestation studies, it was clearly stated that the administration of 17β-oestradiol, even at much lower doses (ie, 13 μg/kg bodyweight), consistently resulted in detrimental effects (eg, pregnancy termination or reduction in implantation sites), whereas the impact of the paraben esters was neglectable (tested up to 950 mg/kg bodyweight).[95] In addition, it has been indicated that the oestrogen-related gene expression in human mammary gland cell lines, such as MCF7, for paraben esters was different from that induced by 17β-oestradiol, and consequences to the human mammary gland cell lines are therefore not identical.[102] Furthermore, the strength of the animal studies reported has been questioned as paraben esters were often tested in extremely high doses (up to 1000 mg/kg bodyweight).[103] As the maximum total concentration of paraben esters allowed in topical products can only constitute 0.8% (w/w) (for methyl- and/or ethyl-paraben) and 0.19% (w/w) (for propyl- and/or butyl-paraben) of the total product,[18,23] and the acceptable daily intake for oral exposure is set at a maximum of 10 mg/kg bodyweight (methyl- and ethyl-paraben),[18,104] these animal experiments may not reflect the actual biological impact of paraben esters at regular doses of use.[103] Finally, studies on the actual biological outcome, if any, of these purported weak estrogenic effects in human subjects are still lacking.

The European Scientific Committee on Consumer Safety (SCCS) repeatedly concluded in its paraben safety reports that there is no demonstrable risk for the development of breast cancer caused by the use of paraben ester-containing underarm care products and found that the submitted information had too many shortcomings to be considered scientifically valid.[23,105-108] In its most recent report, it is stated that the use of methyl- and ethyl-paraben as preservatives in cosmetics and personal care

products is considered safe for human health. The maximum total concentration of paraben mixtures has been set at 0.8% (w/w), with no single paraben having an individual concentration higher than 0.4% (w/w). For propyl- and butyl-paraben, it is stated that safety assessments are not finalised yet.[23] However, both are considered safe to consumers if their maximum concentration, when used individually or in a mixture with other paraben esters, does not exceed 0.14% (w/w). If both propyl- and butyl-paraben are used in the same formulation, the maximum permitted total concentration of this specific paraben mixture has also been set at 0.14% (w/w) instead of 0.8% (w/w).[23,109] In case of leave-on cosmetic products designed for the nappy area of young children younger than 3 years of age, the use of propyl- and butyl-paraben is not allowed as skin irritation and occlusion may allow increased penetration.[23,109] As indicated in the European Chemicals Agency (ECHA) database, the most frequently used paraben esters are all under continuous evaluation regarding their safety to consumers.[110-113] Regulatory and supervisory entities from the United States, such as the FDA and CIR, also strongly confirm that they will continuously review all published studies on the safety of paraben esters and indicate that, based on current scientific knowledge, paraben esters have not been shown to be harmful when used in cosmetics, in which they are present only in very small amounts.[114,115] The CIR has recommended the same threshold limitation for the total sum of paraben esters in any personal care product as that set in European law, that is, 0.8% (w/w).[18]

For other frequently used topical antimicrobial and preservative ingredients, certain regulatory requirements are in place as well to ensure that the finished topical product does not elicit any complications to human health.[9,116] Most antimicrobial and preservative ingredients have, as such, some biological effect against both microbial and mammalian cells.[116,117] Besides stimulating allergic contact dermatitis, these ingredients can, similar to the parabens, be associated with potential systemic effects at certain levels of concentration.[116,117] Formaldehyde and formaldehyde releasers, such as the urea derivatives and Quaternium 15, have provoked public health concerns because of their potential carcinogenic and mutagenic properties.[9,117] In addition, both formaldehyde and the urea derivatives have been associated with a cytotoxicity potential on various cell types.[117] Similarly, the isothiazolinones are also associated with high cytotoxic effects.[117] For phenoxyethanol, adverse systemic effects were observed in laboratory animals only at levels of exposure higher than those allowed in topical products.[118] In case of organic acids, such as sodium benzoate, genotoxicity is reported, but not consistently.[119] Nevertheless, at those levels of exposure consumers would be exposed to when using topical antimicrobial or preservative ingredient-containing end products and based on the currently available scientific knowledge, these agents are, as are the parabens, generally not considered harmful.[117-120]

4 | CONCLUSION

In order to manage both minor and major wounds, various topical wound care products are available on the market and can comprise of antimicrobial agents or preservatives. The latter are not only essential for prolonging the shelf life of the multi-use wound care product, but they also safeguard the consumer of unwanted infections. Furthermore, it is crucial to ensure that topical antimicrobials and preservatives guarantee both product and consumer safety. However, in the past years, the safety of these ingredients has been challenged, and public concerns have been raised about their potential to induce skin sensitisation and adverse systemic effects. The safety of parabens, one of the most widely used preservative types in the manufacturing of topical formulations, has especially been questioned.

Despite their extensive utilisation worldwide, the capacity of paraben esters to act as skin sensitisers and cause allergic contact dermatitis has remained remarkably uncommon, especially when compared with other frequently used topical antimicrobial agents and preservative ingredients. Reported prevalence rates are low, ranging between 0.6% and 1.7% in North America and 0.5% and 1.3% in Europe, especially when compared with other commonly used preservatives. With an average prevalence rate of approximately 1.0%, paraben mix is considered an infrequent allergen. This assessment of safety was further substantiated by the ACDS highlighting parabens as non-allergens of the year in their safety report of 2018.[67] There is no scientific data available to suspect that this interpretation will change in the future.

In addition, claims related to the assumed oestrogen-like activity of paraben esters should be put into perspective. Paraben esters have been repeatedly shown to possess only weak estrogenic effects in both laboratory and *in vivo* animal studies, especially when compared with the effects of natural 17β-oestradiol. It was further evidenced that *in vitro* and *in vivo* activity was augmented with an increasing length or branching of the alkyl side chain, indicating that methyl- and propyl-paraben, which are most often used in topical wound care products, are less estrogenic than butyl-paraben. When evaluating the potential of adverse health effects, one should consider that not all members of this effective family of preservatives cause an effect in the same order of magnitude. Furthermore, it has to be noted that *in vivo* animal studies reported to date are inconsistent and lack reflection of

the actual biological impact at regular doses of use. Claims of carcinogenic activity of parabens are less supported by the literature, and no human studies have confirmed significant or even suggestive biological effects regarding hormone disruption, breast cancer, or skin cancer *in vivo*. However, it is important to note that generally accepted standards are in place to ensure that these ingredients are used in such levels they do not pose a risk to the recipients.[116] As such, despite the ongoing concern for paraben preservatives, current scientific knowledge as well as regulatory agencies indicate that, with standard safety regulations regarding their use in place, this effective and well-documented group of safe preservatives should not warrant drastic measures to replace them.

CONFLICT OF INTEREST

The authors report the following conflict(s) of interest: Both Dr. E. Torfs and Dr. G. Brackman are employed by Flen Health NV.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as all data used for the review stems from data derived from resources available in the public domain as indicated in the reference list.

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