

Contact allergy induced by bisphenol A diglycidyl ether leachables from aluminium tubes for pharmaceutical use

K. Breuer¹, C. Lipperheide², U. Lipke², T. Zapf², H. Dickel³, R. Treudler⁴, S. Molin⁵, V. Mahler⁶, C. Pföhler⁷, H. Löffler⁸, H. Schwantes⁹ & A. Schnuch¹⁰

¹Department of Allergology and Occupational Dermatology, Dermatologikum Hamburg, Hamburg; ²Federal Institute for Drugs and Medical Devices (BfArM), Bonn; ³Department of Dermatology, Venereology and Allergology, St. Josef-Hospital, Ruhr-University Bochum, Bochum; ⁴Department of Dermatology, Venereology and Allergology, University of Leipzig, Leipzig; ⁵Department of Dermatology and Allergology, Ludwig Maximilians University, Munich; ⁶Department of Dermatology, University Hospital of Erlangen, Erlangen; ⁷Department of Dermatology, Saarland University Medical School, Homburg/Saar; ⁸Department of Dermatology, SLK-Kliniken, Heilbronn; ⁹Department of Occupational Dermatology, Berufsgenossenschaftliche-Klinik Falkenstein, Falkenstein; ¹⁰Information Network of Departments of Dermatology, University of Göttingen, Göttingen, Germany

To cite this article: Breuer K, Lipperheide C, Lipke U, Zapf T, Dickel H, Treudler R, Molin S, Mahler V, Pföhler C, Löffler H, Schwantes H, Schnuch A. Contact allergy induced by bisphenol A diglycidyl ether leachables from aluminium tubes for pharmaceutical use. *Allergy* 2015; **70**: 220–226.

Keywords

allergic contact dermatitis; aluminium tubes for pharmaceutical use; bisphenol A diglycidyl ether; epoxy resin; repeated open application test.

Correspondence

Kristine Breuer, MD, PhD, Dermatologikum Hamburg, Stephansplatz 5, 20354 Hamburg, Germany.
Tel.: +49-40-351075-0
Fax: +49-40-351075-314
E-mail: breuer@dermatologikum.de

Accepted for publication 23 October 2014

DOI:10.1111/all.12538

Edited by: Pascal Demoly

Abstract

Background: Aluminium tubes for pharmaceutical use are internally lacquered with epoxy resins (ER) based on bisphenol A diglycidyl ether (BADGE). Recently, it was shown that remnants of ER polymerization like BADGE are extractable from epoxy-based coatings of commercially available tubes and may leach into semi-solid drug preparations. We aimed to evaluate the safety of BADGE-contaminated macrogol ointments in individuals sensitized to ER based on BADGE by use tests.

Methods: Repeated open application testing (ROAT) in 11 patients sensitized to ER based on BADGE with BADGE in macrogol ointments (3 mg/kg; 30 mg/kg, equivalent to BADGE concentration determined in macrogol ointment after storage in a commercially available tube; 300 mg/kg).

Results: The 30 mg/kg BADGE ointment elicited reactions in three patients, and another three patients reacted to 300 mg/kg BADGE ointment. No reactions to the vehicle control and 3 mg/kg BADGE were observed.

Conclusions: Elevated BADGE concentrations in ER-coated aluminium tubes pose a risk of developing contact dermatitis to patients sensitized to ER based on BADGE. Quality standards are deemed necessary for the production of ER-coated aluminium tubes intended for pharmaceutical use and should consider the results of the present ROAT study.

Exposure to epoxy resin systems (ERS) is a frequent cause of occupational allergic contact dermatitis. Contact sensitization to ERS can be acquired, among others, by exposure to coatings and adhesives used in the boat and aeroplane building industry and in wind turbine construction (1). The resin of ERS is mostly composed of bisphenol A diglycidyl ether (BADGE) and/or bisphenol F diglycidyl ether (BFDGE). Among ER, oligomers of BADGE with a mean molecular weight ≤ 700 Da are the most frequent cause of contact allergy (2). In the departments of dermatology forming the Information Network of Departments of Dermatology (IVDK) (3), the frequency of positive reactions to ER based

on BADGE patch-tested in the standard series ranged from 0.9% to 1.4% (women: 0.6–1.2%, men: 1.6–2.3%) in 1992–2000 (4). Based on these data, the prevalence of sensitization to ER based on BADGE was estimated at 0.1–0.2% for the German general population, corresponding to 80 000–160 000 individuals (5). Apart from contact dermatitis by direct skin contact, airborne contact dermatitis may be caused by ERS due to the volatility of their constituents (6). According to a data analysis from the IVDK, late reactions to ER based on BADGE suggestive of active sensitization occur in 0.3% of those patch-tested with ER with the German standard series (7).

Aluminium tubes for pharmaceutical use are internally lacquered to avoid direct contact between medicinal products and metal which may lead to corrosion and migration of metals. BADGE-based resins are most often used in the production of coatings for aluminium tubes and, as known from foodstuff packaging (8), contamination of the tube content by BADGE and its derivatives may occur. Recently, it was shown that remnants of the ER polymerization, like bisphenol A (BPA) and BADGE, are indeed extractable from epoxy-based coatings of commercially available aluminium tubes for pharmaceutical use (9) (Fig. 1). Maximum amounts of 57.4 mg BADGE per litre solvent (corresponding to 10.5 mg/6 dm² tube surface) were extractable with acetonitrile from the tubes of one vendor, while 50–50 000 times lower concentrations were extracted from the tubes of 6 other vendors (9). Migration of the remnants into various semi-solid drug products (ointment, cream, gel) during storage was verifiable, and the leaching profiles were influenced by storage time, temperature and the matrix polarity. The highest amount of BADGE was found in macrogol ointment containing polyethylene glycol (PEG) 300 and 1500 in a ratio 1 : 1. When using a tube with a high amount of extractable BADGE (30.9 mg/l solvent), more than 90% of the extractable amount migrated into the macrogol ointment during storage at 40°C for 7 days. This resulted in a concentration of 30 mg BADGE per kg macrogol ointment (10).

Health hazards due to contamination of semi-solid drug preparations with BADGE, specifically the risk of contact allergy, are unknown. In this study, we aimed to evaluate the safety of BADGE-contaminated macrogol ointments in individuals sensitized to ER based on BADGE.

Patients

The study was performed in eight departments of dermatology; all of them were members of the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK, www.IVDK.org). The IVDK is a multicentre project collecting clinical and patch test data from 55 departments of dermatol-

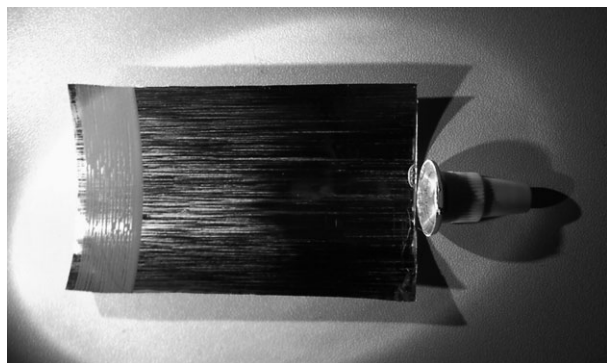


Figure 1 Inner lacquer of an aluminium tube for pharmaceutical use consists of an epoxy resin based on bisphenol A diglycidyl ether (BADGE).

ogy in Germany, Austria and Switzerland. Methods of the IVDK have been described (3, 11). Patients eligible for the ROAT study were those who had been routinely patch-tested with the German standard series from January 2012 to June 2013 and had shown at least a ++ reaction to ER based on BADGE 1% pet. at reading D3. Patch tests were performed and evaluated according to international guidelines (12) further refined by the DKG (13).

Exclusion criteria were age <18 years, systemic or local immunosuppressive treatment, known corticosteroid allergy, immunocompromising disease, current eczema or recent UV light exposure in the skin area concerned, and pregnancy. The study had been approved by the Ethics Committee of the Hamburg Medical Chamber (no PV4327, dated 14 April 2013).

Materials and methods

ER based on BADGE (CAS 25068-38-6) 1% pet. (Almirall Hermal, Reinbek, Germany) was used for routine patch testing.

Macrogol ointment

Macrogol 300 and macrogol 1500 were of Ph. Eur. grade and purchased from Caelo (Hilden, Germany). BADGE was of p.a. grade and supplied by Fluka Analytical (Buchs, Switzerland).

The macrogol ointments contaminated with BADGE were produced in a hospital pharmacy (Zentralapotheke St.-Josef-Hospital, Troisdorf, Germany). Prior to mixing with macrogol 1500, BADGE had been spiked into macrogol 300 (3 g/kg) to prepare macrogol ointments with final concentrations of 3, 30 and 300 mg/kg. A vehicle control (macrogol ointment without addition of BADGE) was also produced. The macrogol ointments were manufactured according to German drug codex (DAC) (14) and stored in glass syringes. The macrogol ointments (spiked and vehicle control) were stored at 2–8°C.

Microbial challenge studies according to Ph. Eur. 5.1.3 reveal that macrogol ointment is self-preserving and does not need any preservation to prevent microbial contamination during use.

The content of BADGE in each macrogol ointment (placebo, 3, 30 and 300 mg/kg) was checked by a certified laboratory using a validated method (9) (HWI Analytik GmbH, Rülzheim, Germany) prior to use in this study and monitored over 16 weeks up to the last day of administration by the patients.

Use test

Repeated open application testing (ROAT) was carried out between October 2013 and January 2014. Three macrogol ointments spiked with different concentrations of BADGE [ointment 1: 3 mg/kg; ointment 2: 30 mg/kg, reflecting the maximum concentration of BADGE determined in macrogol ointment in previous studies (10); ointment 3: 300 mg/kg]

and a vehicle control (macrogol ointment without BADGE) were used. To prevent confusion between ointments, the glass syringes were marked with different colours. The ointments spiked with BADGE were applied to $5 \times 5 \text{ cm}^2$ areas on the volar side of one forearm, beginning with the 3 mg/kg BADGE ointment in each of the 11 participants. The vehicle control was applied on a $5 \times 5 \text{ cm}^2$ area of the contralateral forearm. The test areas were marked using a waterproof pen. At the first visit, the patients were thus given two different ointments (3 mg/kg BADGE ointment and macrogol ointment without BADGE). They were instructed to apply an appropriate dose ($\sim 0.5 \text{ ml}$) of the ointments twice a day (morning and evening) on the same area by gently spreading the material on the areas with a finger and to wash their hands thereafter. The test sites were allowed to dry for 15 min before being covered with clothing. Patients were advised to avoid contact with water for the following 2 h. The application of the same preparations was continued for 2 weeks or until a reaction occurred. After 2 weeks, the test areas were evaluated by the physician. If there was no reaction detectable at this visit, the participants were given the preparation containing the next higher concentration of BADGE (30 mg/kg) to be applied for another 2 weeks. This procedure was repeated for 300 mg/kg BADGE ointment, in case no reaction had occurred at the week 4 visit. The vehicle control was applied to the contralateral forearm during the whole study period. Thus, the theoretical maximum period of application was 6 weeks in patients who did not react to any ointment. The study design is shown in Fig. 2. The ROAT reactions were assessed for erythema, papules/infiltration, vesicles and extent of area involved. The readings were classified according to the recommendations of Johansen et al. (15, 16). The ROAT was assessed as positive if an erythema of at least 25% of the test area along with homogenous infiltration or papules regardless of the number occurred (16, 17). In case a positive reaction was visible at any visit, the patients were scheduled for re-evaluation 1 week later.

Results

BADGE stability in macrogol ointment

The results of the stability tests are summarized in Table 1. They revealed a continuous decrease of BADGE content. Nevertheless, after 16 weeks of storage at $2\text{--}8^\circ\text{C}$, the BADGE content was still within the acceptance criterion of 80–120% of spiked concentration.

Study population characteristics

Ninety six patients meeting the inclusion criteria were identified in the IVDK database. Of these, 11 (five women and six men) were eligible for the study. Their age ranged from 23 to 75 years (mean 53.0 ± 13.3 years, median 50.9 years). According to medical history, two patients suffered from respiratory atopic diseases. Ten patients had been patch-tested due to suspected allergic contact dermatitis or to exclude allergic contact dermatitis; one patient had been patch-tested due to suspected contact stomatitis. Based on the history and the patch test findings, seven patients were finally diagnosed with allergic contact dermatitis, one patient each with allergic contact stomatitis, atopic eczema, drug exanthema and pruritus sine materia. Occupational exposure to ERS was confirmed in four patients and assumed in further two patients. Study population characteristics are shown in Table 2.

ROAT results

The data of all 11 patients were suitable for evaluation. Six of 11 patients (No. 1–6, see Table 2) showed skin reactions to any of the BADGE concentrations in the ROAT. No reactions to the vehicle control were observed. Morphology of test reactions is presented in Table 3. ROAT with 30 mg/kg BADGE ointment elicited reactions in three patients (No. 2, 4, 6), and another three patients reacted to 300 mg/kg

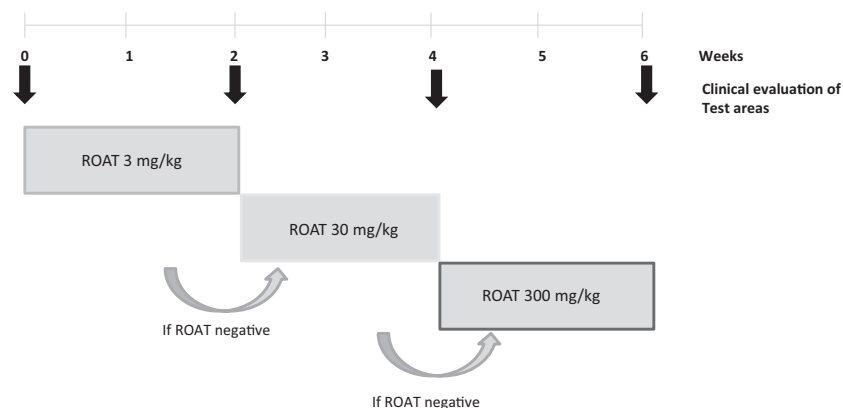


Figure 2 Study design. R1–R3: preparations with bisphenol A diglycidyl ether (BADGE), containing 3, 30 and 300 mg/kg BADGE, were applied consecutively each for 2 weeks at the volar side of one forearm. At the contralateral forearm, the vehicle was applied for the whole application period of BADGE ointments. If a reaction occurred, further application was terminated. ROAT, repeated open application test.

Table 1 Stability results of macrogol ointment spiked with bisphenol A diglycidyl ether (BADGE), stored at 2–8°C

Spiked amount of BADGE in macrogol ointment	Acceptance criterion (%)	Assay after storage for		
		Initial	5 weeks	16 weeks
3 mg/kg	80–120	95% (2.8 mg/kg)	n.t.	89.9% (2.6 mg/kg)
30 mg/kg	80–120	91.3% (27.3 mg/kg)	88.9% (26.6 mg/kg)	87.3% (26.1 mg/kg)
300 mg/kg	80–120	91.9% (275.8 mg/kg)	n.t.	88.2% (264.8 mg/kg)
Placebo	Not detectable	n.d.	n.t.	n.d.

n.t.: not tested; n.d.: not detected.

Table 2 Characteristics of individuals sensitized to epoxy resin based on bisphenol A diglycidyl ether (BADGE) who were exposed to BADGE with repeated open application tests (ROAT)

	Age	Male/female	Diagnosis	Localization of skin lesions	Patch test reactivity to ER	Exposition to ER	Further positive patch test allergens
1	49	M	ACD (ER)	Legs	+++	OE suspected, truck seat (driver)	Yes (nickel sulphate)
2	52	M	ACD (ER)	Arms, face	++	OE suspected, road construction work	Yes (m-xylidine diamine)
3	61	M	ACD (ER)	Hands, forearms	+++	OE, tile glue (production engineer)	Yes (fragrance mix, potassium dichromate, cobalt chloride)
4	57	F	Drug exanthema	Generalized	++	Not stated	Yes (fragrance mix, paraben mix)
5	75	F	Pruritus	Generalized	++	Not stated	No
6	47	F	Contact stomatitis	Oral mucosa	+++	Dental filler (bisphenol A dimethacrylate)	Yes (balsam of Peru, amalgam)
7	56	F	ACD (chromate)	Hands, feet	++	Not stated	Yes (potassium dichromate, propolis)
8	70	M	Atopic dermatitis	Face	++	Not stated	No
9	52	F	ICD, ACD (ER)	Hands	++	OE, varnishes (varnish laboratory technician)	Yes (bisphenol F epoxy resin, mercapto mix, monobenzene, oil of turpentine, fragrance mix)
10	41	M	ACD (ER)	Hands	++	OE, glues and varnishes (model carpenter)	Yes (butyl glycidyl ether, phenyl glycidyl ether, 1,4-butanediol diglycidyl ether, 1,6-hexanediol diglycidyl ether)
11	23	M	ACD (ER)	Hands, feet	++	OE, glues and varnishes (boat builder)	Yes (1,4-butanediol diglycidyl ether, 1,6-hexanediol diglycidyl ether, ammoniated mercury, thiomersal)

ACD, allergic contact dermatitis; ICD, irritant contact dermatitis; ER, epoxy resins; OE, occupational exposure.

BADGE ointment (No. 1, 3, 5). ROAT with 3 mg/kg BADGE ointment elicited no skin reactions at all. Most of the reactions became manifest with spotted erythema and scattered papules spreading beyond the borders of the test area. In patient No. 5, homogenous erythema and infiltration of the test area were observed, and patient No. 1 showed oozing skin lesions. ROAT lesions of patient No. 4 and patient No. 5 are shown in Fig. 3. For organizational reasons, re-evaluation of the ROAT reaction 1 week later could be performed in only three patients. Of these, one patient still

showed mild skin lesions with spotty erythema and sparse papules at the test area, and in the further two patients, the lesions had healed completely (Table 3).

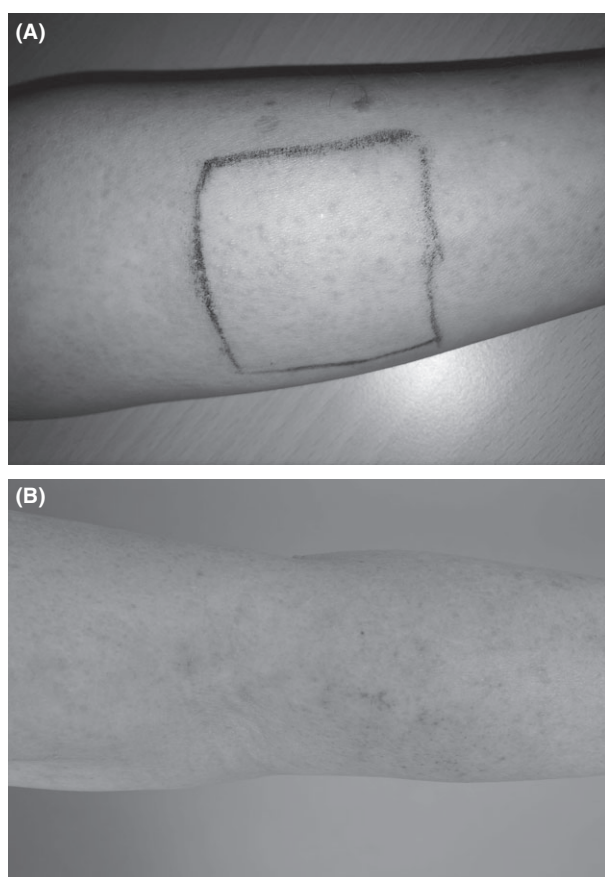
Discussion

The aim of the present study was to evaluate the safety of BADGE-contaminated macrogol ointment in individuals sensitized to BADGE. To identify the maximum tolerable concentration of BADGE, a stepwise ROAT with increasing

Table 3 Morphology of positive repeated open application testing (ROAT) in six epoxy resin based on bisphenol A diglycidyl ether (BADGE)-sensitized patients exposed to BADGE in macrogol ointment

	BADGE concentration of positive ROAT (mg/kg)	ROAT morphology					Re-evaluation after 1 week
		Involved area of application (%)	Erythema	Papules (Number)	Vesicles (Number)	Other	
1	300	<25	Spotty	10–25	None	Oozing, strong pruritus	Spotty erythema, <10 papules
2	30	>25	Spotty	>25	None	–	Negative
3	300	<25	None	10–25	None	–	Negative
4	30	>25	Spotty	>25	None	–	n.d.
5	300	>25	Homogenous	10–25	None	Infiltration, excoriations	n.d.
6	30	>25	None	>25	None	–	n.d.

n.d., not done.

**Figure 3** (A) A positive reaction with follicular papules on the forearm of an epoxy resin-sensitive patient (No. 4) after 14 days of repeated open application test (ROAT) with macrogol ointment containing 30 mg/kg bisphenol A diglycidyl ether (BADGE). (B) A marked positive reaction with homogenous infiltration on the forearm of an epoxy resin-sensitive patient (No. 5) after 14 days of repeated open application testing (ROAT) with macrogol ointment containing 30 mg/kg BADGE.

concentrations of BADGE in macrogol ointment was performed in patients who had shown strong, that is at least ++, reactions to ER based on BADGE upon routine patch

testing. Our results clearly demonstrate that BADGE-contaminated macrogol ointment may induce contact dermatitis in individuals sensitized to ER based on BADGE. Three of 11 patients developed skin reactions upon application of 30 mg/kg BADGE [i.e. the maximum concentration of BADGE leachables in macrogol ointment packaged in aluminium tubes for pharmaceutical use found in previous studies (10)], and further three patients showed a reaction to the 10-fold higher concentration. ROAT morphology showed characteristic features of allergic contact dermatitis with spreading papules and resembled ROAT reactions as described previously (15, 18), confirming the clinical relevance of the patch test reactions to epoxy resin.

Our findings imply that the use of ER-lacquered aluminium tubes with elevated concentrations of nonprocessed BADGE poses a health hazard to individuals sensitized to ER because of the risk to contaminate the medicinal product with BADGE quantities able to induce allergic skin reactions. These findings were not unexpected, as it was shown previously that the allergen concentration needed to elicit a skin reaction under in-use conditions as in the ROAT is substantially lower than that needed for the induction of patch test reactions (19). This may be caused by the accumulation of allergen in the skin or repeated stimulation of immune cells. For nonvolatile compounds, the formula $ED_{xx}(ROAT) = 0.0296ED_{xx}(\text{patch test})$ was calculated, with $ED_{xx}(ROAT)$ as the elicitation dose of the ROAT and $ED_{xx}(\text{patch test})$ as the elicitation dose of the patch test ($\mu\text{g}/\text{cm}^2$) (19). In convergence, the ER concentrations used for the patch tests (i.e. 1.0%) may be used to calculate the BADGE concentration eliciting a positive ROAT. Using the above formula, the BADGE concentration eliciting a ROAT reaction would account to 0.03% (i.e. 300 mg/kg). However, our results show that there is a variable individual susceptibility to the application of BADGE under use conditions in individuals sensitized to ER based on BADGE, as shown for other allergens [e.g. isoeugenol (20), methyl dibromoglutaronitrile (21, 22) and hydroxyisohexyl 3-cyclohexene carboxaldehyde (16, 23)].

Our study has some limitations. We chose an exploratory approach to evaluate whether persons sensitized to ER may or may not react to BADGE-contaminated semi-solid drug preparations. With regard to the 'epidemiological' risk of

contact dermatitis posed upon the general population by the use of ER-coated aluminium tubes for pharmaceutical use, our data should be interpreted with caution. Health problems resulting from the use of ER-lacquered aluminium tubes may be lower than suspected due to our data. For our study, 'worst case conditions' were chosen using macrogol ointment and high BADGE concentrations for the ROAT: in the previous extraction and leaching experiments (9), small 5-g tubes had been used to obtain high surface-to-volume ratios. Seventeen tubes of 6 vendors had been investigated, and the extraction profiles had revealed a great variability in the nature and amount of extractables. BADGE concentrations as high as 57.4 mg per litre solvent had been extracted from the tubes of one vendor, and 50–50 000 times lower concentrations had been found in tubes of the other vendors. Moreover, batch-to-batch variability had been found, pointing to a crucial impact of the coating process to the amount of extractables (9). Almost complete leaching of BADGE into the matrix was observed when the tubes had been filled with macrogol ointment, a commonly used base formulation for a number of medicinal products intended for epicutaneous application (10). Up to 30 mg BADGE/kg was determined when macrogol ointment was stored in the tube with high amounts of extractables. On the other hand, the health risk posed by aluminium tubes coated with ER based on BADGE may be greater than estimated due to our data. First, mechanical stress of aluminium tubes under in-use conditions may increase BADGE concentrations in semi-solid drug preparations as shown in previous extraction and leaching studies (9). While in-use conditions did not have an influence on BADGE concentrations when macrogol ointment was used as matrix (10), BADGE concentrations were shown to be elevated in other matrices like nonionic hydrophilic cream. When compared to cream in the same tubes, but unstressed, the extent of migration was increased 10-fold. Second, there is a certain risk of false-negative ROAT results due to the limited study period of 14 days. Third, ROAT was performed on intact, undamaged skin, but not on inflamed skin or on ophthalmic mucosa. According to the results of stability measurements (see Table 1), it could be excluded that BADGE concentrations in macrogol preparations changed substantially over time and false-negative ROAT results due to degradation of BADGE are improbable. Moreover, to exclude patients with false-positive reactions to ER in routine patch testing, only patients who had shown at least twofold positive reactions were included into the ROAT study.

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In conclusion, elevated BADGE concentrations in ER-coated aluminium tubes of minor quality may pose patients sensitized to ER based on BADGE at risk of developing allergic contact dermatitis. What are the consequences of our findings? ER-coated aluminium tubes with a low level of polymerization remnants in the inner lacquer are a prerequisite of medicinal products to prevent contamination of semi-solid dosage forms with a high-quantity of BADGE. Our results suggest that 3 mg/kg BADGE in semi-solid drug preparations may be a concentration safe for patients with contact sensitization to ER based on BADGE. Quality standards are deemed necessary for the production of ER-coated aluminium tubes for pharmaceutical use and should consider the results of the present study. To ensure quality and safety of semi-solid pharmaceutical preparations, interactions between the coating material and the drug product should be thoroughly evaluated. Extraction testing of coated tubes using suitable media and conditions and taking into account all extractable compounds are considered necessary for the quality assessment of the final container closure system.

Acknowledgment

The authors are grateful to the valuable technical assistance of Ms R. Endler.

Author contributions

K. Breuer, C. Lipperheide, U. Lipke, T. Zapf and A. Schnuch contributed to the study design. K. Breuer, H. Dickel, R. Treudler, S. Molin, V. Mahler, C. Pföhler, H. Löffler and H. Schwantes were involved in the data acquisition. K. Breuer wrote the first draft of the manuscript. All authors critically revised and approved the final submitted version of the manuscript.

Funding

The study was supported by a grant from the Federal Institute for Drugs and Medical Devices (BfArM), Germany (V-15012/54401/2012–2013).

Conflicts of interest

The authors declare that they have no conflicts of interest.

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