

skin sensitizers and have become a major cause of allergic contact dermatitis in the construction industry in recent years.¹

In this issue of the *BJD*, Christiansen *et al.*² present the results of a cross-sectional study in 180 highly epoxy-exposed workers from two wind turbine factories in Denmark and 41 nonexposed office workers. Patch testing with a panel of test substances including epoxy-containing products from the two factories revealed that almost 9% of production workers compared with none of the office workers were sensitized to an epoxy component. Resins based on the diglycidyl ethers of bisphenol A (DGEBA-R) and bisphenol F (DGEBA-F) were the most frequent sensitizers. Notably, sensitizations in one-quarter of the workers were not detected by the TRUE Test panel, which contains only DGEBA-R. Dermatitis affected about 40% of the sensitized workers based on clinical examination or self-reporting.

Usually, information on the prevalence of sensitization to epoxy components derives from patch test studies in individuals with dermatitis.^{1,3} In contrast, Christiansen *et al.* performed patch tests regardless of the presence or absence of dermatitis, providing a clearer picture of the prevalence of sensitization to epoxy components in the wind turbine industry. Apart from prevalence studies, there is no need for routine patch testing, but in epoxy-exposed workers with suspected occupational dermatitis, tailored patch testing is required. Christiansen *et al.* showed that some epoxy-sensitized individuals are missed when only the TRUE Test panel is tested, stressing the need for patch testing a broader spectrum of epoxy resin components commercially available as test preparations.³ If the test remains negative and contact allergy is still suspected, patch testing of the patients' own products should be considered; however, this requires extensive experience and diligence. Patch testing patients' own products might still be the only way to discover contact allergies that are not otherwise detected.⁴

The high rate of workers sensitized to epoxy components in the wind turbine industry is alarming as such sensitizations frequently result in job discontinuation.⁵ Christiansen *et al.* found that the prevalence of sensitization to epoxy components was highest in the first year of exposed employment and decreased with increasing duration of exposed work, indicating its well-known short latency period and a healthy worker effect.^{1,6} This suggests that the true prevalence of epoxy sensitization in this industry might be underestimated. Despite protection measures, the skin of workers handling epoxy resin systems is frequently contaminated.⁷ Hence, there is clearly a need for intensified prevention efforts including raising awareness among exposed workers and intensive training in correct use of personal protective equipment, as well as development and usage of epoxy resin systems with a lower sensitization potential.⁸ Prevention of sensitizations to epoxy components, and thus preserving the occupational health of the workforce in the wind turbine industry, is of particular importance considering the pursuit of renewable energies in light of climate change and the current European energy crisis.

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Richard Brans ^{1,2}

¹Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrück, Osnabrück, Germany and ²Institute for Interdisciplinary Dermatologic Prevention and Rehabilitation, University of Osnabrück, Osnabrück, Germany
Email: rbrans@uos.de

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References

- Geier J, Krautheim A, Uter W *et al.* Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. *Int Arch Occup Environ Health* 2011; **84**:403–11.
- Christiansen A, Carstensen O, Sommerlund M *et al.* Prevalence of skin sensitization and dermatitis among epoxy-exposed workers in the wind turbine industry. *Br J Dermatol* 2022; **187**:988–96.
- Ponten A, Carstensen O, Rasmussen K *et al.* Epoxy-based production of wind turbine rotor blades: occupational contact allergies. *Dermatitis* 2004; **15**:33–40.
- Houle MC, Holness DL, Dekoven J, Skotnicki S. Additive value of patch testing custom epoxy materials from the workplace at the occupational disease specialty clinic in Toronto. *Dermatitis* 2012; **23**:214–19.
- Caroe TK, Ebbehøj NE, Bonde JP, Agner T. Occupational hand eczema and/or contact urticaria: factors associated with change of profession or not remaining in the workforce. *Contact Dermatitis* 2018; **78**:55–63.
- Bangsgaard N, Thyssen JP, Menne T *et al.* Contact allergy to epoxy resin: risk occupations and consequences. *Contact Dermatitis* 2012; **67**:73–7.
- Suuronen K, Back B, Aalto-Korte K *et al.* Skin exposure to epoxy chemicals in construction coating, assessed by observation, interviews, and measurements. *Contact Dermatitis* 2019; **80**:18–25.
- Ponting DJ, Ortega MA, Niklasson IB *et al.* Development of new epoxy resin monomers – a delicate balance between skin allergy and polymerization properties. *Chem Res Toxicol* 2019; **32**:57–66.

Atypical clinical manifestation and protracted latency are observed in the emerging variant of checkpoint inhibitor-associated bullous pemphigoid

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The last two decades have witnessed a substantial increase in the incidence of bullous pemphigoid (BP) worldwide.¹ One

of the most compelling interpretations accounting for this epidemiological observation is the growing exposure to novel drug classes that might be implicated in eliciting the disease.¹ Multiple lines of evidence have recently accumulated to suggest that exposure to dipeptidyl peptidase 4 (DPP4) inhibitors and checkpoint inhibitors (CPIs) is associated with an elevated risk of BP.^{2,3} As these drugs were introduced only in the past two decades, their rising utilization underlies, at least in part, the growing incidence of BP.¹

In their novel multicentre cohort study in the current issue of the *BJD*, Kawsar *et al.* evaluated 7391 patients managed by CPIs throughout an extended period of 13 years.⁴ Twenty-two patients (0.3%) developed bullous immune-related adverse events (irAEs), of whom 16 (73%) fulfilled the immunopathological diagnostic criteria of BP. Applying a longitudinal follow-up on a large study population, the current study provides novel insights into the epidemiology of CPI-associated BP. The prevalence rate of BP in patients treated with CPIs was estimated at 202 per 100 000 individuals, considerably outreaching its prevalence in the general British population, which was recently evaluated at 48 per 100 000 individuals.⁵

The vast majority (19 of 22, 86%) of CPI-associated bullous irAEs evolved in patients with melanoma.⁴ Attention should be paid to the finding that melanoma conferred an independent risk of developing subsequent BP, regardless of exposure to CPIs.⁶ In a recent population-based study, we found that a history of melanoma imposed a 50% increase in the odds of subsequent BP, even after adjusting for programmed death (PD)-1/PD ligand 1 antagonists (adjusted odds ratio 1.53, 95% confidence interval 1.14–2.06).⁶ It cannot be thoroughly refuted that CPI-associated BP in patients with melanoma represents, at least in part, a manifestation of the underlying association between melanoma and BP. Longitudinal studies comparing the incidence of BP among patients with melanoma treated with CPIs vs. other treatment modalities will help to delineate the independent contribution of CPIs to the development of BP, irrespective of the inherent comorbidity between melanoma and BP.

In accordance with DPP4 inhibitor-associated BP,⁷ CPI-associated bullous irAEs might arise over extended times following drug initiation, with two patients manifesting with BP even after drug cessation.⁴ This knowledge is of critical importance as clinicians should suspect the presence of CPIs as a predisposing factor for BP. Of note, a combination of two CPIs led to faster onset of bullous irAEs.⁴ Further research is required to elucidate the pathomechanism underlying this observation.

Regarding the clinical manifestations, CPI-associated BP in the current study features atypical clinical characteristics of BP, with a notable presence of mucosal involvement and nonbullous lesions.⁴ This accords with the previous literature^{8,9} and necessitates consideration of prodromal or nonbullous variants

of BP in patients under CPIs presenting with protracted pruritus and refractory eruptions. An early immunohistological evaluation (preferably by direct immunofluorescence microscopy) may lead to improved patient outcomes by facilitating timely initiation of treatment and preventing disruptions in antineoplastic therapy.

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Khalaf Kridin ^{1,2,3} and Christoph M. Hammers ^{1,4}

¹Lübeck Institute of Experimental Dermatology (LIED), University of Lübeck, Lübeck, Germany; ²Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel; ³Unit of Dermatology and Skin Research Laboratory, Barch Padeh Medical Center, Poriya, Israel; and ⁴Department of Dermatology, Christian-Albrechts-University of Kiel, Kiel, Germany
Email: christoph.hammers@uksh.de

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References

- 1 Kridin K, Ludwig RJ. The growing incidence of bullous pemphigoid: overview and potential explanations. *Front Med (Lausanne)* 2018; **5**:220.
- 2 Kridin K, Cohen AD. Dipeptidyl-peptidase IV inhibitor-associated bullous pemphigoid: a systematic review and meta-analysis. *J Am Acad Dermatol* 2021; **85**:501–3.
- 3 Asdourian MS, Shah N, Jacoby T *et al.* Association of bullous pemphigoid with immune checkpoint inhibitor therapy in patients with cancer: a systematic review. *JAMA Dermatol* 2022; **158**:933–41.
- 4 Kawsar A, Edwards C, Patel P *et al.* Checkpoint inhibitor-associated bullous cutaneous immune-related adverse events: a multicentre observational study. *Br J Dermatol* 2022; **187**:981–7.
- 5 Persson MSM, Harman KE, Vinogradova Y *et al.* Incidence, prevalence and mortality of bullous pemphigoid in England 1998–2017: a population-based cohort study. *Br J Dermatol* 2021; **184**:68–77.
- 6 Kridin K, Hundt JE, Ludwig RJ *et al.* Melanoma is associated with an increased risk of bullous pemphigoid: a large population-based longitudinal study. *Arch Dermatol Res* 2022; **314**:77–83.
- 7 Kridin K, Avni O, Damiani G *et al.* Dipeptidyl-peptidase IV inhibitor (DPP4i) confers increased odds of bullous pemphigoid even years after drug initiation. *Arch Dermatol Res* 2022; in press; doi: <https://doi.org/10.1007/s00403-021-02317-9>.
- 8 Lopez AT, Khanna T, Antonov N *et al.* A review of bullous pemphigoid associated with PD-1 and PD-L1 inhibitors. *Int J Dermatol* 2018; **57**:664–9.
- 9 Sadik CD, Langan EA, Gutzmer R *et al.* Retrospective analysis of checkpoint inhibitor therapy-associated cases of bullous pemphigoid from six German dermatology centers. *Front Immunol* 2021; **11**:588582.