

# Further Evidence of Allergic Contact Dermatitis Caused by 2,2'-Methylenebis(6-*tert*-Butyl-4-Methylphenol) Monoacrylate, a New Sensitizer in the Dexcom G6 Glucose Sensor

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**Background:** Since the spring of 2020, we have seen several patients experiencing severe allergic contact dermatitis (ACD) from the Dexcom G6 glucose sensor after the composition of the sensor's adhesive patch had been changed. We have previously reported the finding of a new sensitizer, 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate, in the Dexcom G6 adhesive patch. Three patients with ACD from Dexcom G6 tested positive to this sensitizer. They were also allergic to isobornyl acrylate, a sensitizer present both in Dexcom G6 and in other medical devices previously used by these patients.

**Objective:** The aim of the study was to report the first 4 cases sensitized to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate without a simultaneous allergy to isobornyl acrylate.

**Methods:** The cases were patch tested their own materials, a medical device series, and 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate in several concentrations.

**Results:** All 4 cases tested positive to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate at either 1.0% or 1.5% in petrolatum, whereas 20 controls tested negative to both concentrations.

**Conclusions:** The cases reported here provide further evidence of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate as a relevant culprit sensitizer in patients with ACD from Dexcom G6. However, the initially used patch test concentration (0.3%) did not suffice to elicit positive reactions in these cases, which is why patch testing at 1.5% is recommended.

Individuals with type 1 diabetes (T1D) will need some kind of life-long monitoring system. During the last decades, flash glucose monitoring (FGM) and continuous glucose monitoring (CGM) systems and insulin pumps have revolutionized the daily care for many patients with diabetes and have enabled normal life. Unfortunately, skin reactions are common and are perhaps the major cause of termination of use of this sort of medical devices, and allergic contact dermatitis (ACD) from the medical device is most likely underdiagnosed in the group.<sup>1-3</sup>

In the last years, several contact allergens have been identified in these medical devices.<sup>4-9</sup> The culprit contact allergens have mainly been used in glues in attachment areas, that is, where different materials must adhere to each other, but not necessarily primarily in the adhesive patch in direct contact with the skin. However, the contact allergens migrate from the original attachment areas to the adhesive patch. Many patients have been diagnosed with isobornyl acrylate (IBOA) contact allergy. Isobornyl acrylate was initially found sensitizing in the FGM system FreeStyle Libre (Abbott Diabetes Care, Witney, United Kingdom)<sup>4</sup> but has thereafter also been identified in several CGM systems and insulin pumps, including the Dexcom G6 CGM system (Dexcom, Inc, San Diego, CA).<sup>7,10-13</sup>

Since the spring of 2020, there have been an increasing number of referrals to our department, the Department of Occupational and Environmental Dermatology in Malmö, Sweden, concerning patients having a similar history and a suspected ACD from Dexcom G6. We have recently reported 3 of these patients.<sup>8</sup> A common feature for these patients<sup>8</sup> was that they had previously been able to use their devices for many months, sometimes years, without any problems, and then suddenly experienced an oozing dermatitis. Another common feature was that they all had a suspected or

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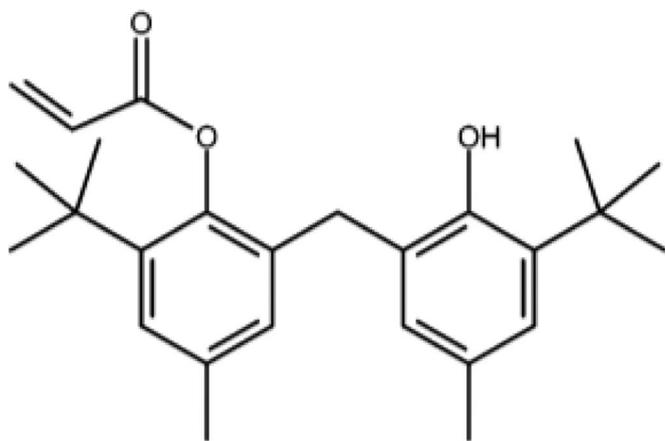
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**Figure 1.** Molecular structure of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate.

diagnosed ACD from a medical device being used before Dexcom G6. They were all found allergic to IBOA. Chemical analyses of Dexcom G6 in these patients' investigations not only showed the presence of IBOA but also strongly indicated a change of the adhesive, which was confirmed by the manufacturer. The patients were patch tested and found allergic not only to IBOA but also to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (CAS No. 61167-58-6; Fig. 1), an antioxidant in the sensor's adhesive patch identified at our department.<sup>8</sup> Here, we present the 4 first cases with a contact allergy to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate, without a concomitant contact allergy to IBOA.

## MATERIALS AND METHODS

### Ethical Approval

The patients (and parents of the girls) gave written consent to the use of patch test results, report of their history, and the use of photographs. Patient data were registered and used with the approval by the ethical review board, Stockholm, Sweden (diary no 2020-02190).

## Patients

### Case 1

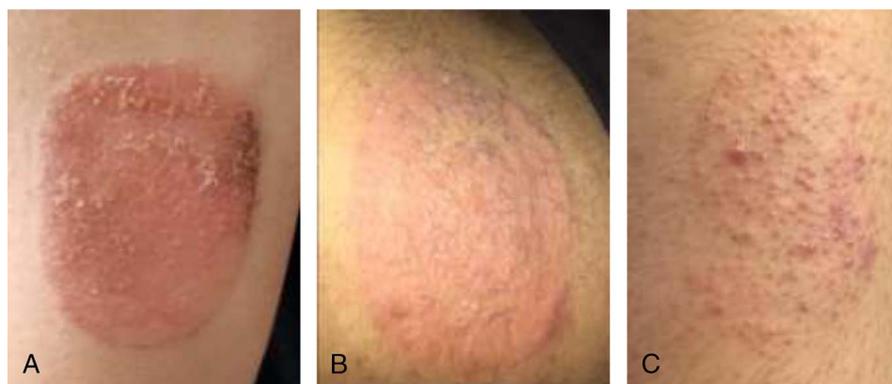
A girl, 11 years old, had no atopic dermatitis but dry skin and rhinoconjunctivitis. She had T1D since the age of 2 years. An insulin pump from Medtronic (Medtronic MiniMed, Northridge, CA) had been used since 2011 without any skin problems. In 2016, she started to use FreeStyle Libre and never experienced any dermatitis with this system. In 2018, she started to use Dexcom G6, at first without associated skin problems. In January 2020, she had an itching, oozing dermatitis at the application site of the CGM system (Fig. 2A). Because of the dermatitis, she had to change the sensor every third or fourth day as compared with the recommended 10 days. She was recommended, both by her caregivers and at Internet forums for diabetic patients, to use a local corticosteroid solution (hydrocortisone butyrate), a corticosteroid nasal spray (mometasone furoate), and Cavilon barrier film (3M Health Care, St Paul, MN) before attaching the device. Using these products, she still developed dermatitis but could stand using the device for the recommended number of days.

### Case 2

A man, 34 years old, had no atopic diseases. He had T1D since the age of 7 years. He never had any insulin pump because he preferred insulin pen injections. He previously monitored his blood sugar levels with FreeStyle Libre, but after 2 months of usage without any skin reactions, he changed to Dexcom G6 to have a CGM system. In April 2020, after using Dexcom G6 for 18 months, he developed dermatitis at the site of application of the sensor. He treated the skin eruptions with different moisturizers without relief.

### Case 3

An adolescent girl, 14 years old, had no atopic dermatitis and no rhinoconjunctivitis, but had experienced childhood asthma. She had T1D since the age of 8 years. Initially, she used an insulin pump from Animas (Animas Corp, West Chester, PA), and since 2018, she used the Omnipod (Insulet, Billerica, MA) patch pump. Both insulin pumps were used without associated skin reactions. Shortly after she was diagnosed with T1D, she started to use a CGM system from Dexcom (likely model G4 or G5), by that time with application



**Figure 2.** Allergic contact dermatitis caused by Dexcom G6 in case 1 (A), case 3 (B), and case 4 (C).

intervals of 5 days. She experienced minor skin discomfort but was able to continue using it until 2018 when the device was changed to FreeStyle Libre. She used FreeStyle Libre, without any skin problems, until the summer of 2020 when she switched to Dexcom G6. When the first applied sensor was removed after 10 days, a severe, oozing dermatitis was present at the application site. She continued using the device with shorter application intervals of 3 to 7 days and with the pretreatment of Cavilon and hydrocolloid dressings, with minor effect on the skin problems (Fig. 2B). Hence, the device was changed again in November 2020, and she has been since then using the FreeStyle Libre 2 sensor without any skin discomfort.

#### Case 4

An adolescent girl, 14 years old, twin sister of case 3, had no atopic dermatitis and no rhinoconjunctivitis, but had experienced childhood asthma. She had T1D since the age of 10 years. She initially used an insulin pump from Animas until 2018 when that device was changed to Omnipod, without any skin problems caused by either. In 2016, she started using the same model of Dexcom sensor as her sister. In 2018, she changed to the FreeStyle Libre sensor. She did not experience skin reactions when using any of these sensors. However, in the summer of 2020, she changed to the Dexcom G6 sensor. When the first applied sensor was removed after 10 days, an itchy dermatitis was present at the application site (Fig. 2C). Her skin reactions were less severe than her sister's. Thereafter, she could continue wearing the Dexcom G6 for 5 to 6 days without any pretreatment, which she never tried. However, in November 2020, she changed to FreeStyle Libre 2, which she is still using, without any skin problems.

#### Patch Testing and Reading

The patients were patch tested according to our routine, for children with the in-house child baseline series and for adults with the Swedish baseline series and the extended Malmö baseline series. All of them were also patch tested with the in-house medical device series used in 2020.<sup>14</sup> Patch test substances were also added according to the patient history and the results of updated chemical analyses in recent investigations of medical device patients.

For patch testing, IQ Ultimate chambers (Chemotechnique Diagnostics, Vellinge, Sweden) were used. Applied on the chambers were 25 mg of the petrolatum (pet) test preparations and 20  $\mu$ L of the liquid preparations.<sup>15</sup> For case 2, IQ Ultimate chambers (Chemotechnique Diagnostics) were used for patch testing the extracts, and 8-mm Finn Chambers Aqua (SmartPractice, Phoenix, AZ) were used for the rest of the patch-tested substances. Chemotechnique Diagnostics provided the patch test preparations, unless otherwise stated.

All cases were tested with 0.3%, 0.5%, and 1.0% (wt/wt) pet preparations of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (Chemtronica, Sollentuna, Sweden; Fig. 1) made at the Department of Occupational and Environmental Dermatology in Malmö. Cases 3 and 4 were additionally tested with 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate at 1.5% in pet. All cases were also tested with benzisothiazolinone at 0.1% and/or 0.15% (wt/wt) in pet.

In case 1, the patch test was supplemented with pet preparations of mometasone furoate, hydrocortisone-17-butyrate, and also with the Cavilon barrier film solution tested "as is" and at 10% in acetone. Ultrasonic bath extracts<sup>16</sup> of materials from a Dexcom G6 sensor were also patch tested in all cases. Cases 2 to 4 were all patch tested with the same ethanol extracts; one extract of the Dexcom G6 adhesive patch and one extract of the sensor housing (without adhesive patch) were prepared as formerly described<sup>8</sup> but more concentrated with an end volume of approximately 0.2 mL. Case 1 was tested with corresponding extracts prepared from a sensor from another batch. These extracts were concentrated to a volume of 0.5 mL.

The tests were occluded on the back for 48 hours. Cases 2 to 4 were also patch tested with the Dexcom G6 adhesive patch tested "as is" with a prolonged occlusion time of 96 hours (4 days).

Reading of the tests was performed on day (D)3/4 and D7. The tests were read and scored according to the International Contact Dermatitis Research Group and European Society of Contact Dermatitis classification.<sup>15,17</sup>

#### Controls

Twenty controls were patch tested with 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate at 1.0% and 1.5% (wt/wt) in pet. All controls were dermatitis patients referred to our department for patch testing giving their permission for additional patch testing with the substance. Exclusion criteria for being a control were known pregnancy and diabetes mellitus as well as age of younger than 18 years.

#### RESULTS

The patch test results are summarized in Table 1. All cases were negative to IBOA patch tested at 0.01%, 0.1%, and 0.3% in pet at 2 test readings on D3/4 and D7. For the adhesives patch tested "as is" with ordinary occlusion time of 48 hours, case 2 reacted with a doubtful reaction. With a prolonged occlusion time of 96 hours, both cases 2 and 3 reacted with ++ reactions on the second test reading on D7 for adhesives patch tested "as is." All cases were positive to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate.

All 20 controls patch tested negatively and with no irritant reactions to 1.0% and 1.5% 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate in pet (2/4 vs 0/20 [1.0%] and 2/2 vs 0/20 [1.5%],  $P = 0.022$  and  $0.004$ , respectively; Fisher's exact test, 2-sided). There were no reports on late-appearing reactions from the controls.

#### DISCUSSION

Isobornyl acrylate has been the main allergen involved in ACD from medical devices for diabetic patients, and it has been identified in several different devices from different manufacturers.<sup>4,7,10-14,18</sup> Dexcom sensors have previously been reported to be free from IBOA and has thus been recommended as an alternative in IBOA-allergic individuals.<sup>19,20</sup> However, during patient investigations, we have found low concentrations of IBOA in Dexcom G6 sensors in analyses carried out at our laboratory.<sup>12</sup> In a case series

**TABLE 1. Summary of Patch Test Reactions to IBOA and of Positive Reactions Found in the Patients**

Patch Test Preparations	Case 1 D3/4/D7	Case 2 D3/4/D7	Case 3 D3/4/D7	Case 4 D3/4/D7
IBOA 0.1% pet	–	–	–	–
IBOA 0.3% pet	–	–	–	–
2,2'-Methylenebis(6- <i>tert</i> -butyl-4-methylphenol) monoacrylate 0.3% pet	(+)/–	–/–	NT	NT
2,2'-Methylenebis(6- <i>tert</i> -butyl-4-methylphenol) monoacrylate 0.5% pet	(+)/–	–/–	–/–	–/–
2,2'-Methylenebis(6- <i>tert</i> -butyl-4-methylphenol) monoacrylate 1.0% pet	+ /NR	++ /NR	–/–	–/–
2,2'-Methylenebis(6- <i>tert</i> -butyl-4-methylphenol) monoacrylate 1.5% pet	NT	NT	++ /NR	+ /NR
Ethyl cyanoacrylate 5% pet	–	–	++ /+	–
Ethyl acrylate 0.1% pet	–	–	++ /+	–
Colophonium 20% pet	–	–	–	–
Colophonium 60% pet	–	–	++ /+	–
Fragrance mix I 8% pet	–	–	– /+	–
Carba mix 3% pet	NT	+ /–	NT	NT
1,3-Diphenylguanidine 1% pet	NT	+ /–	NT	NT
Benzisothiazolinone 0.15% pet	NT	+ /–	++ /+	– /–
Benzisothiazolinone 0.1% pet	–	+ /–	NT	NT
Adhesive patch, Dexcom G6 “as is”	NT	(+) /–	–	–
Adhesive patch, Dexcom G6 “as is,” prolonged occlusion time 96 h	NT	(+) /++	(+) /++	– /(+)
Adhesive patch, Dexcom G6 ethanol extract	(+) /NR	(+) /–	+ /NR	(+) /NR

(+), doubtful reaction; D, day; IBOA, isobornyl acrylate; NR, not read; NT, not tested; pet, petrolatum.

of 11 patients with a suspected ACD from Dexcom G6 referred between January 2019 and March 2020, IBOA contact allergy was diagnosed in 6 patients. All 6 IBOA-allergic patients had previously used other IBOA-containing medical devices, such as FreeStyle Libre, and had likely been sensitized to IBOA when using these devices. However, it is possible that the low IBOA concentrations in Dexcom G6 may have elicited ACD in sensitized individuals, especially in those individuals with a strong IBOA allergy.<sup>12</sup>

We have since the spring of 2020 seen an increasing number of patients with more severe skin reactions to the Dexcom G6 sensor. The reactions occurred after a change in the adhesive composition had been made by the manufacturer in late 2019.<sup>21</sup> A new sensitizer, 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate, was identified by gas chromatography/mass spectrometry analyses in the sensors with revised adhesive composition. We have recently reported 3 patients sensitized to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate from the use of Dexcom G6 sensors.<sup>8</sup> This substance, to the best of our knowledge, had not previously been described as an allergen or as an irritant in men or in animals. All 3 patients were also diagnosed with contact allergy to IBOA, which we had found in low concentrations also in our analyses of sensors with the revised adhesive composition. All 3 patients were likely sensitized to IBOA when using the FreeStyle Libre sensor, which they all had reacted to previously. Whether the IBOA allergy may have predisposed the sensitization to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate cannot be determined in retrospect.

In this report, however, we present the first cases with contact allergy to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate without a simultaneous IBOA allergy. Initially, all 4 patients were tested with a negative result to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate at both 0.3% and 0.5% in pet. The 0.3% concentration

sufficed to elicit positive reactions in the cases reported recently, whereas no reactions were observed in 20 controls tested with the same preparation.<sup>8</sup> Were the reactions in the cases presented here false negative as the history strongly suggested a diagnosis of ACD from Dexcom G6 in all cases? How do we know that the concentration of 0.3% in pet, corresponding to a dose of 120  $\mu\text{g}/\text{cm}^2$ , is optimal as there understandably have been no systematic investigations on the optimal patch test concentration for 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate? The highest possible concentration should be used with as few adverse reactions as possible, particularly active sensitization, as it is contact allergy rather than ACD that shall be diagnosed.<sup>22</sup> 2,2'-Methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate is an acrylate, and many acrylates are potent sensitizers. Acrylates, including ethyl acrylate, have been reported to actively sensitize at patch testing when a concentration at 1% was used.<sup>23</sup> To avoid active sensitization, a concentration at 0.1% has been recommended for acrylates. However, the molar concentration of 0.3% 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate is actually approximately 20% lower than that of 0.1% ethyl acrylate. Furthermore, the content of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate in the Dexcom G6 adhesive patch was calculated to 40  $\mu\text{g}/\text{cm}^2$ . For many sensitizers, including preservatives, the required patch test concentration is approximately 20 times higher than in leave-on products, which at patch testing “as is” may give false-negative reactions.<sup>24</sup> Applying a factor of 20 on the concentration of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate in the Dexcom G6 adhesive results in a patch test dose of 800  $\mu\text{g}/\text{cm}^2$ , corresponding to a concentration of 2% in pet. Thus, the concentration used to get positive patch test reactions in the 4 cases was 75% (1.5%) of the maximum possible concentration used for patch testing of some preservatives.<sup>24,25</sup> Still,

it is necessary to test controls to substantially diminish the possibility of false-positive reactions. Twenty controls tested negative when the same pet preparations of 1.0% and 1.5% 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate were used as for the cases.

Investigating patients with suspected ACD to CGM/FGM systems and insulin pumps has been proven to be complicated.<sup>26</sup> Patch testing with materials from the patients' devices may result in false-negative reactions because the concentration of allergens in the material may actually be too low to elicit a positive reaction at ordinary patch testing, even if an extract of the product is made.

As the Dexcom G6 sensors are worn for up to 10 days, 3 of the patients were patch tested with the adhesive patch "as is" with a prolonged occlusion time (96 hours) in an effort to better simulate the actual use. This increases the possibility of allergens and irritants in low concentrations to actually penetrate the skin and elicit a reaction. However, similar to a repeated open application test, this testing does not discriminate between an irritant or a contact allergic reaction.

None of the 3 patients who were tested with the adhesive patch "as is" were positive using the ordinary 48-hour occlusion time, whereas 2 of the patients showed ++ reactions to pieces of the adhesive patches, which were adhered to the back for 96 hours. Expectedly, the testing with a longer occlusion time demonstrates that the adhesive patch causes a contact dermatitis as the history indicates that the Dexcom G6 sensor has to be worn more than 2 days for dermatitis to develop. However, to conclude that the contact dermatitis is due to contact allergy, testing in controls resulting in negative reactions has to be performed.

Unlike other patients whom we have examined because of a suspected ACD from Dexcom G6, cases 3 and 4 reported development of skin reactions already when wearing the first applied sensor for 10 days. This may indicate that they were already sensitized to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate when starting to use this device. However, in our chemical investigations, we have so far not observed this substance in any other medical device than the current versions of Dexcom D6. Furthermore, according to the patients' histories, they had not experienced any skin reactions to other adhesives or medical devices than the Dexcom sensors. Therefore, although it cannot be completely excluded, a previous sensitization to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate seems less likely. At least theoretically, it is possible that the first 10-day exposure to Dexcom G6 was sufficient for both sensitization and elicitation of ACD. The patients were able to wear the sensors for the full 10-day period at the first application. Subsequently, applied sensors in both cases could be used only for 3 to 7 days because of the skin reactions, although case 3 treated her skin with a barrier film and hydrocolloid dressings. It is also possible that the quickly developed skin reactions were caused by other (unknown) sensitizers or by irritation due to the occlusive effect.

Case 3 experienced minor skin discomfort when using a previous Dexcom sensor model (likely G4 or G5) and may have been sensitized to ethyl cyanoacrylate from the use of these sensors.<sup>6,27</sup> Ethyl cyanoacrylate was previously used to fix the adhesive patch to the sensor housing but is no longer used in the production of Dexcom

sensors.<sup>28</sup> Case 3 was positive to colophony but not to the test preparation at 20% in the baseline series but to the test preparation at 60%,<sup>29</sup> which is in accordance with some other diabetic patients reacting to their devices.<sup>12</sup> She may have been exposed to colophony when using the Omnipod insulin pump.<sup>30</sup> Furthermore, our analyses have indicated a possible presence of colophony-related substances also in adhesive patches from Dexcom G6 sensors.<sup>12</sup>

After developing reactions to Dexcom G6, cases 2 to 4 are now instead using FreeStyle Libre 2 without any skin problems. However, case 1 is still using the Dexcom G6 system with minor skin discomfort. Before applying the device, she treats her skin with a corticosteroid solution (hydrocortisone butyrate), as recommended by her referring dermatologist.

Patients are often recommended to use barrier films or topical creams to prevent or ameliorate the skin problems. This advice comes from caregivers and dermatologists and is also flourishing on social media. In addition, manufacturers of the medical devices give advice on how to avoid skin reactions to the devices.<sup>31</sup> When investigating patients with suspected ACD, products used to prevent or ameliorate the dermatitis should be investigated, because also these products may cause contact allergy.<sup>32</sup> The use of protective barriers may help to some extent,<sup>33,34</sup> and it might be a mistake to neglect or unconditionally criticize their use.

With regard to case 1, it is difficult to tell whether she should be advised to stop using Dexcom G6. An ACD may facilitate the penetration of hazardous substances, including other allergens. It is impossible to foresee the effect of the corticosteroid that she treats her skin with before application of the sensor. Theoretically, the use of "the correct" steroid, that is, mometasone furoate, which is claimed to have a low sensitization potential, might lower the risk of a sensitization and elicitation of contact allergy to other substances in the device, for example, IBOA or 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate.<sup>35,36</sup>

The possibility to perform chemical investigations of medical devices causing suspected ACD is crucial to identify culprit sensitizers. One should also keep in mind that changes of the medical device may be done by the producers without this being communicated to the users or health care professionals. Therefore, repeated analyses of sensors from batches that actually cause the skin reactions may be necessary. Once a suspected sensitizer has been identified, a suitable and safe patch test concentration reflecting an actual dose in milligrams per square centimeter must be chosen, which may be difficult especially concerning substances where limited toxicological data are available. If patch tests using the initial chosen concentration give negative reactions, although there is a strong suspicion of contact allergy, the concentration may have to be reevaluated. We have previously observed that an increase of the patch test concentration of IBOA from 0.1% to 0.3% (wt/wt) in pet resulted in additional positive cases, which would otherwise have been missed. Controls tested negative to IBOA at 0.3%.<sup>14</sup> Similarly, the initially used patch test concentrations of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate failed to elicit positive reactions in the cases presented here, and an increase in concentration was necessary to diagnose contact allergy.

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