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Changes in adhesive ingredients in continuous glucose monitoring (CGM) systems may induce new contact allergy pattern?

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Abstract

Medical devices (MD) in close skin-contact for prolonged time such as glucose monitoring(CGM) systems are a risk factor for contact allergy. There is an increase in patients using these. Correct diagnosis demands aimed correct testing.

We report a new allergen in a continuous CGM system where the adhesive was changed. The allergy pattern of the patients diagnosed is reported due to the finding of polysensitization.

Methods

The three patients reported were patch tested with an MD series, own material and possible allergens found through analysis with gas chromatography-mass spectrometry comparing analysis from the CGM system prior and after change.

Results

The patients were previously sensitized to isobornyl acrylate (IBOA), found in previously used devices and the present CGM. Apart from IBOA, the culprit allergen was found to be 2,2'-methylenebis(6-tert-butyl-4-methylphenol) monoacrylate.

Conclusion

Allergic contact dermatitis due to CGM systems and insulin pumps are difficult to investigate and require chemical analysis. Due to lack of information on substances used in the production and when changes with MDs are initiated, it is difficult to give advice to the patients, especially since they risk sensitization to several allergens. The use of MDs increase and thus the need for collaboration between producers, clinicians and patient organizations.

Introduction

Investigating patients with suspected allergic contact dermatitis to medical devices such as continuous glucose monitoring(CGM) systems, intermittently scanned glucose monitoring (isCGM) /flash glucose monitoring systems and insulin pumps is complicated (1). The diagnosis has to be suspected and the patient must be patch tested with the right substances. The investigation should also include patch testing with the patient's own material. This testing may however result in false negative reactions since 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 (2). Producing an extract can in itself be complicated due to lack of material especially if extraction solvents with different physico-chemical properties are desired (1). The culprit contact allergens found have mainly been used in attachment areas ie where different material must adhere to each other, but not necessarily primarily in the adhesive patch in direct contact with the skin. Therefore, identification and finding the optimal patch test substance and dose have been intricate as the final dose on skin exposure is not necessarily the same as where the substance is originally used. The need for collaboration with the companies producing the devices has been emphasized (2,3) especially as the number of patients being sensitized to several allergens found in different medical devices increases. As product ingredients may be changed without change of brand name or declaring this to the clinicians or the users, helping the user find a reliable product is made further difficult.
We here report three cases reacting to the Dexcom G6®, CGM system (Dexcom, Inc., San Diego, California, USA), who suddenly experienced symptoms after the composition of the adhesive was changed and where a new allergen was found. The identification of the allergen was simplified by the fact that there at our laboratory in Malmö existed previous analyses of Dexcom G6® for comparison (2).

Material and methods

The three patients below were all referred due to sudden onset of problems related to made efforts by the manufacturing company to improve the adhesive in Dexcom G6®.

Case 1: Female 40 years old, office worker, with diabetes mellitus since the age of 8, rhinoconjunctivitis but never atopic dermatitis nor asthma and no other skin diseases. She started to use insulin pump in 2008 and had at first referral used 3 different brands without any dermatitis problems (Medtronic®, Animas Vibe® and Tandem t:slim®) but also due to dermatitis problems stopped using certain brands; Freestyle Libre and Dexcom G6.In 2015, she started to use the FreeStyle Libre® glucose sensor. After 1 month she experienced an oozing dermatitis at the contact site for the sensor and therefore changed to Dexcom G4® then G5® without experiencing any problems. In October 2019 she started to use Dexcom G6®. In March the following year the patient started getting an itchy dermatitis that gradually deteriorated at the contact site of the sensor. At that time she had received a new batch of sensors with an adhesive that was more difficult to remove from the skin. At referral she could only use the sensor for 2-3 days (normal wear :10 days) before getting a severe dermatitis. She had therefore started to use Tegaderm ® Transparent film style 9534 HP (St Paul, Minnesota, USA) under the sensor adhesive, but even then she could not use the sensor for more than 5-7 days before the dermatitis forced removal of the device. The patient was thus referred for patch testing.

Case 2: Female 35 years old, office worker, with diabetes mellitus since the age of three, no history of skin disease or atopy. She started to use Freestyle Libre® in 2015 but developed dermatitis at the contact site for the sensor after a couple of months. In 2016 the patient started to use the insulin pump Omnipod®. In March 2017 a dermatitis developed. As CGM the patient during this period used Dexcom G5® and G6 ® without complications. The patient started in October 2017 on the Medtrum A6® CGM and insulin patch pump system and immediately experienced problems. Due to a contact dermatitis she was investigated and found to have an allergic contact dermatitis (4). Due to multiple contact allergies found (Table 1) in the earlier investigation and the fact that the patient now had started having symptoms from Dexcom G6® she was once more referred for patch testing.

Case 3: Male 44 years old, office worker, with diabetes mellitus since the age of 29, no history of skin disease or atopy. He started to use Freestyle Libre® in 2017 but developed dermatitis at the contact site after 9 months. He had previously used Medtronic® insulin pump without dermatitis problems and was in 2018 recommended CGM system Dexcom G5® and then Dexcom G6®. At referral the patient used Dexcom G6 with Dexcom overpatch. Initially he had no dermatitis problems but in summer of 2020 developed an

oozing dermatitis. At referral for patch testing he could only use his device for 2-3 days due to the dermatitis (Fig. 1). He developed dermatitis both with and without the overpatch.

Ethical approval

The patients gave written consent to the use of patch test results, report of their case history and use of photo. Patient data are registered and used with approval by the Ethical Review Board, Stockholm, Sweden Dnr 2020-02190.

Patch testing and reading

The patients were patch tested with the Swedish baseline patch test series, the extended Malmö baseline series, the in house medical device patch test series used in 2020 (5), and relevant patch test substances according to the updated chemical analysis see below. Chemotechnique Diagnostics (Vellinge, Sweden) provided the patch test preparations unless otherwise stated (Table 1). All other test preparations were prepared at the Department of Occupational and Environmental Dermatology in Malmö, Sweden. Case 1 and 3 were patch tested with the Dexcom G6® adhesive patch *as is* and with separate ethanol extracts of the adhesive patches and the sensor housings. For case 1 materials from two sensors (LOT no 5268614) were used. The adhesive patches and the sensor housings were extracted in ~20 ml ethanol for 5 minutes in an ultrasonic bath. Thereafter the extracts were concentrated to a volume of 0.5 ml. For case 3, extracts of the adhesive patch and sensor housing from one sensor (LOT no 7273137) were prepared in the same way. Case 3 was also tested with the Dexcom Overpatch both *as is* and as an ethanol extract.

All three patients were patch tested with two antioxidants detected in the chemical investigations. 2,2'-Methylenebis(6-*tert*-butyl-4-methylphenol) (Vulkanox BKF, CAS no 119-47-1, obtained as a gift from Trelleborg AB (Trelleborg, Sweden) tested at 1.0% (w/w) in petrolatum. 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (>98%, CAS no 61167-58-6, Chemtronica, Sollentuna, Sweden) was tested at 0.3% and 0.1%, in case 1 in acetone (w/v) and in case 2 and 3 in petrolatum (w/w). Case 3 was also tested with a 0.5% preparation in petrolatum (w/w).

The Finn chamber aqua® test chambers (SmartPractice, Phoenix, Arizona, USA) were used. 20 mg of the petrolatum test preparations were applied on the chambers and 15 µl of liquid preparations. The extracts tested in case 3 were applied in IQ Ultimate chambers (applied

volume 20 µl). The tests were occluded on the back for 2 days. Reading of the tests was performed on day (D) 3 and D7. The tests were read and scored according to the ICDRG and ESCD criteria (6,7). In order to discriminate differences in strength in between reactions the patch test readings regarding the medical device series the scoring system was further refined (8).

Controls

20 controls were patch tested with 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate in petrolatum at 0.3% w/w. The controls were dermatitis patients referred for patch testing to the Department of Occupational and Environmental Dermatology in Malmö who gave permission for additional patch testing with the substance. The testing excluded children, those with known diabetes mellitus, and women with known pregnancy.

Chemical investigation

The extracts of the adhesive patches and sensor housings tested in case 1 and 3 were diluted 10-2000 times and thereafter analysed by gas chromatography-mass spectrometry (GC-MS) (5). Furthermore, ethanol extracts of the adhesive patch and sensor housing from another sensor (LOT no 5266562) as well as an acetone extract of the adhesive patch from yet another sensor (LOT no 5267489) were analysed. Previous analysis using the GC-MS (2) existed making comparison with the extracts of the changed adhesive possible, the comparison yielded several possible substances to further investigate but it was clear that a major change in the adhesive had been made and thus this substance was the first to be identified (Fig 3).

Results

The chemical investigations showed the presence of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (fig. 2) in all extracts. For all samples, the concentrations found correspond to a total amount of approximately 1 mg per adhesive patch and 0.03-0.08 mg per sensor housing. Figure 3 shows chromatograms and mass spectra of an adhesive patch extract and a 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate reference sample. All extracts also contained isobornyl acrylate (IBOA) at estimated concentrations in the same order of magnitude as those found in previously analysed sensors from older batches (2), corresponding to a total IBOA content of ≤ 1 µg/patch and ≤ 1 µg/ sensor housing.

Furthermore, all sensors also found to contain 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol).

Table 1 summarizes the positive reactions found in the three patients.
All three cases were found positive to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate, 0.3% with a + reaction. Case 1 was patch tested in acetone due to the fact that acetone had been used in the initial analysis. When found positive in acetone the allergen was prepared in petrolatum and the following patients and controls where thus patch tested in petrolatum as vehicle.

Case 1 was found positive for IBOA at 0.1% w/w in pet with a + reaction, to IBOA 0.3% with a +(+) reaction, i.e. a weak to moderate reactivity. Case 2 was positive to IBOA only at 0.3% with a + reaction and only on D7 i.e. a weak reactivity. Case 3 had a +++ reaction to IBOA 0.3% and a positive reaction in dilution series of the same allergen down to 0.01%. The first 2 patients both reacted to colophony, case 1 with a doubtful reaction at 60 % petrolatum (9) and case 2 with a + reaction to colophony in 20%. Case 2 was furthermore positive to hydroabeityl alcohol. Furthermore, case 1 reacted with a ++ reaction to the adhesive as such and with a doubtful reaction to the adhesive in the alcohol extract, case 3 with a ++ positive reaction to the adhesive as is, + to the alcohol extract and to the extract of the sensor.

Controls: All 20 controls were patch tested negative and with no irritant reactions to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate, 0.3% petrolatum, no reported late reactions (2/2 versus 0/20; p=0.0043; Fisher's exact test, two-sided).

Discussion

For the clinician it is interesting to notice the fact that the three patients were all what is usually called polysensitized (10). The term is complicated and here we, in the definition, include other allergens than those found in the baseline series. They had as a mean 9 contact allergies. Multiple allergies has been discussed previously with regard to patients using the

medical device Freestyle Libre ® (11) but that using a medical device ie glucose sensor or insulin pump should be a risk factor for polysensitization can of course not be argued from case reports. The patients had been patch tested in an aimed manner with substances that also might be found in the same products. The finding does however point to the fact that the group due to exposure may possibly be prone to polysensitization.

Case 3 was positive to 2- hydroxyethyl methacrylate (HEMA) without any known exposure, furthermore a doubtful reaction to ethyl acrylate, to which an association has been indicated in Freestyle Libre®- sensitized patients (12). All three patients were when patch tested found sensitized to allergens from different groups; related to medical devices; acrylates, colophony but also to corticosteroids, preservatives, metals and fragrance substances. The possible association with regard to preservatives, metals and fragrance allergens and the medical device exposure could not be determined. Neither did the patients have any other clear relevance, present or past, for these found contact allergies. With regard to corticosteroids it could not be determined whether the sensitization was related to treatment of medical device-related dermatitis. Among patients with contact allergy to IBOA, sensitized due to the use of medical devices (Freestyle Libre ®), contact allergy to sesquiterpene lactones has also been found to be overrepresented (12, 13). In these cases this was not found, however, 1 patient had a doubtful reaction to alantolactone.

We have previously reported on the finding of IBOA in Dexcom G6® (2). Not only IBOA was found a possible culprit allergen but also possible derivatives of colophony (2). As Dexcom Inc and their Swedish distributors contacted us due to the fact that users reported dermatitis during the spring of 2020 we knew that some alteration had been made in the adhesive. The three cases reported here had previously been able to use Dexcom products, but now showed a reaction pattern with contact allergy to IBOA, in case 2 contact allergy to colophony and hydroabietyl alcohol and in case 1 a doubtful reaction to colophony, and all showed positive reactions to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate 0.3% while there were no reactions in 20 controls ($p=0.0043$). The latter substance has to the best of our knowledge not previously been described as an irritant or as an allergen, neither in man nor in animal.

2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate, also known under the trade names Sumilizer GM, BNX 3052, and Irganox 3052, is a heat and light stabilizer and an antioxidant used in a wide range of adhesive, plastic, and elastomer materials. Unlike

traditional phenolic stabilizers/antioxidants, this substance is an effective alkyl radical scavenger (14,15). This property is especially useful in processes at high temperatures and in low oxygen environments such as during the initial mixing of adhesives (14,16). The stabilizing mechanism involves trapping of polymer alkyl radicals at the double bond of the acrylate group, and subsequent hydrogen transfer from the intramolecular hydrogen-bonded phenolic hydroxyl group, which results in a stable phenoxyl radical (17). 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate may also be grafted using the acrylate moeity (16).

2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate has no harmonized classification according to the CLP (Classification, Labelling and Packaging) regulation. In the vast majority of CLP notifications provided by companies to the European Chemicals Agency (ECHA) no hazards (including skin sensitization) have been classified (18). According to data in ECHA's dossier on the substance, no irritancy was described in animal testing with the Draize test method and it has been classified as a non-allergen in a local lymph node assay (19). The highest tested concentration in LLNA was 25% although neither local irritation nor systemic toxicity were reported at this concentration.

The sensors were also found to contain 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol), a structurally related antioxidant, which however lacks the acrylate group present in 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate (fig 2). The content of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) in the adhesive patches was approximately 20 times lower than the content of methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate. Due to the structural similarities, simultaneous reactions based on cross-reactivity could be expected, and at least theoretically, an enzymatic hydrolysis of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate in the skin generating 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) and acrylic acid could occur (20). Interestingly, none of the patients reacted to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) tested at 1.0%, although this corresponds to a molar concentration which is 3 times higher than that of 0.3% 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate. This may indicate that the presence of an acrylate group is crucial for the sensitizing potential of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate.

From the patients' histories it is quite clear that the initial sensitization was to IBOA and that previous use of Freestyle Libre ® (2) was the medical device that sensitized. Case 2 was

further exposed to IBOA through the use of Omnipod® (21) and was most likely thereby sensitized to colophony and hydroabietyl alcohol giving allergic contact dermatitis almost instantly when using the Medtrum devices (4). The three cases are particularly interesting since they could actually at first use the device without experiencing any skin problems, in case 2 and 3 even for a prolonged time, and then experienced dermatitis. The fact that we know from previous investigations and the investigations reported here is that in Dexcom G6® (2) both IBOA and possibly colophony-related substances are present but presumably here the concentration did not initially initiate an elicitation. It was most probably the change in adhesive components that actually caused dermatitis which at least partially could be explained by contact allergy to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate. This substance has not been observed in our previous analyses of older Dexcom G6 sensors®, but was now found in sensors from newer production batches in relatively high concentrations while the IBOA content was approximately the same as in sensors from previous batches (2). If the patients would have been sensitized to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate had they not had contact allergy for substances already found in the products can of course not be clarified in retrospect. The cases underline two possibly contradictory general principles when using substances which are biologically active and may give rise to contact allergy (i.e. sensitization) and allergic contact reactions- i.e. elicitation. 1) By keeping the concentration of substances low and possibly using different substances concomitantly thus achieving the wanted effect, the risk of sensitization decreases- as can be done with cosmetic consumer products. However 2) in an individual already sensitized to allergens in a mixture; the more possible contact allergens there are at the same skin surface area, the higher the risk of elicitation of contact allergy (22). In Dexcom G6® IBOA has been found in low concentration and the patients could previously use the devices. In the devices used by these patients alterations in the adhesive patch had been made and after this they experienced an oozing dermatitis leaving hyperpigmentation for a prolonged time. However, all patch test reactions, apart from that of IBOA in case 3, were at the most found with a moderate reactivity, and with regard to colophony in case 1 nothing but a doubtful reaction to colophony at 60% (22) could be verified. With regard to colophony and case 1, it can not be clarified in retrospect if colophony-related allergens in Dexcom caused the allergy or if the patient had been exposed to the allergens elsewhere. The patient had been recommended to use 3M Tegaderm ® Transparent film dressing frame style 9534 HP (St Paul USA) under the adhesive and next to the skin. Tegaderm products have been found to contain abietic acid—colophony (23), however, as far as we know not in the product recommended. How can the

very strong reaction to the adhesive when using the device be explained when there were no strong (+++) reactions to 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate in anyone of the patients? 1) The most obvious explanation is of course the application time. 2) Another possible explanation is that the substance 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate, found in a quite high concentration in the product, was patch tested at a too low concentration. In the adhesive the concentration was calculated to 40 µg/cm2, this can be compared to the epicutaneous patch test concentrations where a 0.3% acetone preparation gives a dose of 90 µg/cm^2, and a 0.3% petrolatum preparation gives a dose of 120 µg/cm^2.

The patch test concentration was thus only 3-4 times higher than the concentration in the product. For many sensitizers, including preservatives,the required patch test concentration is around 20 times higher than in leave-on products - which at patch testing may give false negative reactions (1). Whether an optimal patch test concentration for 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate would be around 1.5% needs to be carefully investigated in order to avoid active sensitization (24). 3) A third possible explanation is that a low grade inflammatory reaction to IBOA and in 2 cases colophony and colophony-related substances caused enhanced penetration of allergens thus inducing a greater total reaction. 4) Another possible explanation is that the reaction pattern can be defined as an example of the cocktail effect (25); i.e. that additional low reactivity allergens in a mix will enhance the reactivity by immunological mechanisms and hereby produce a reaction greater than the reactivity of the different components in themselves.

5) The last explanation is of course that the major culprit allergen has not so far been identified.

With regard to patch test results for testing with own material and extracts (26) the patients did not always react, or react with stronger reactions to the extracts , as compared to the material as such which is in agreement with previous results with regard to medical devices.

The reaction pattern of the patients with regard to extract versus material as is indicates that also in these cases the extracts used were not concentrated enough (1). In these cases the analysis of the material and the knowledge that the substance found was an acrylate made us out of precaution limit the amount of adhesive used for extracts.

Conclusion

In the reported cases a new allergen in the CGM system Dexcom G6® is presented: 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate. The three cases showed multiple allergies at the investigation, some with low reactivity. This emphasizes the need for re-testing and re-analysing the devices chemically (2) if a patient suddenly appears to have problems to material that has previously been negative at testing. Besides sensitization to an already known sensitizer in the device, the possibility of increased reactivity due to exposure and sensitization at same area to a presently unknown allergen in the device should be considered. The reactivity pattern, with weak and moderate reactivity to the allergens emphasizes the need for optimal test concentrations (1,2,20) and the need for two patch test readings (1,2). From the three cases, where two were actually patch tested with the allergen in petrolatum and one in acetone, we cannot exclude that we are not patch testing at the optimal concentration. The cases furthermore put focus on the actual importance of occlusion time when using CGMs (2,5,27,28).

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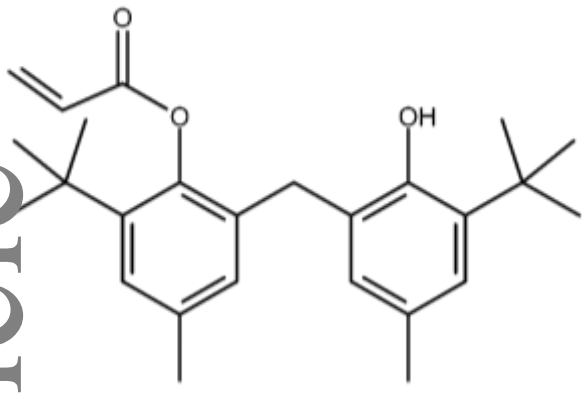
a



b

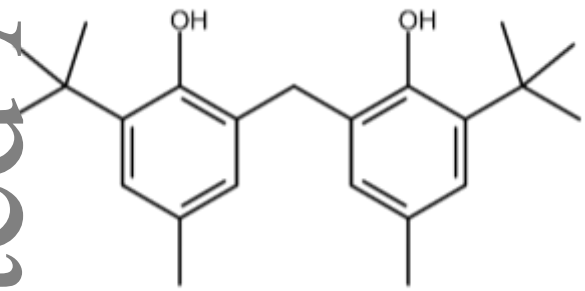


Figure 2. Molecular structure of a) 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate and b) 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol).

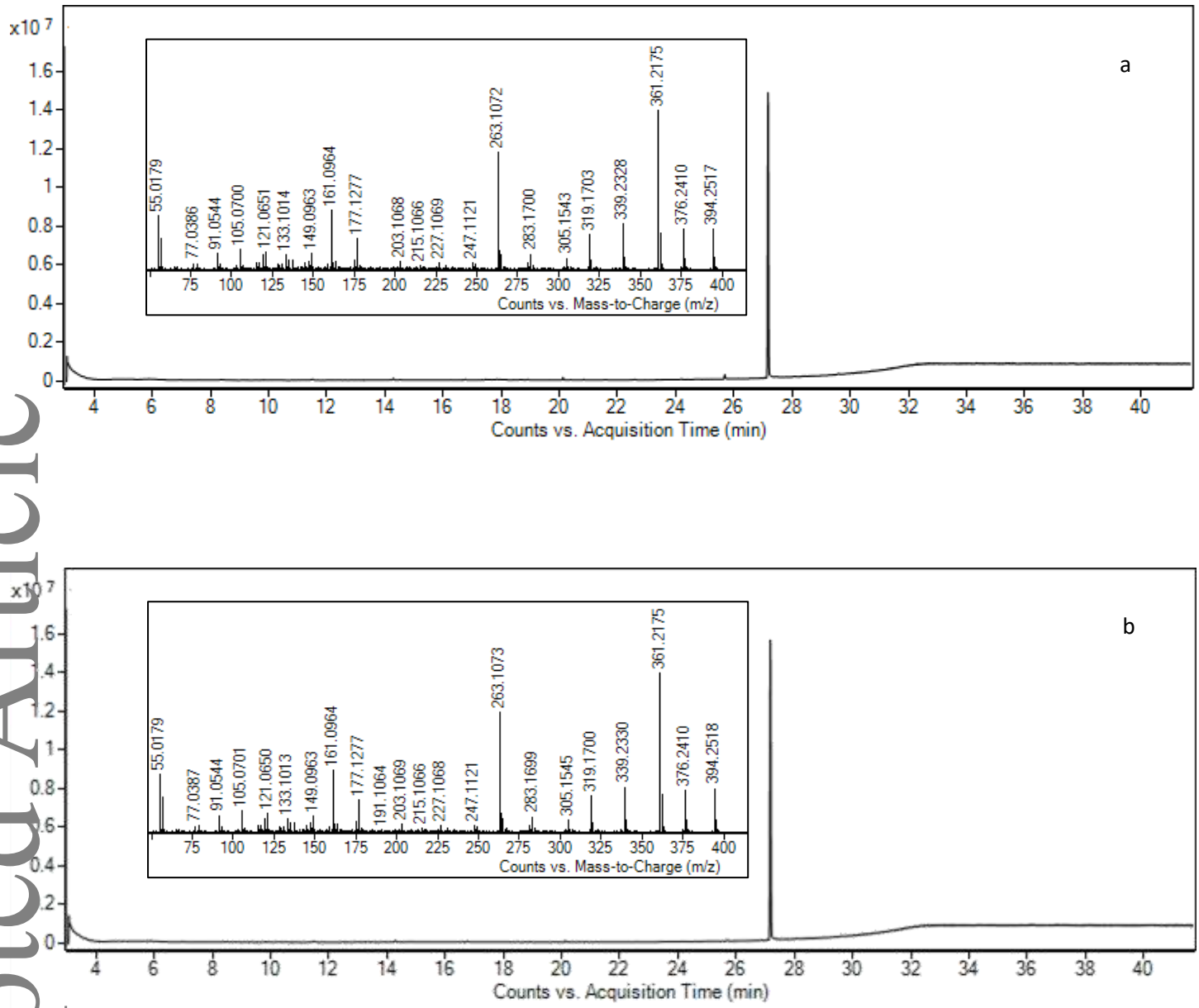


Figure 3. Total ion chromatogram of a) an ethanol extract of an adhesive patch from a Dexcom G6 sensor (0.5 ml diluted 1000 times) and b) a 3 ppm reference sample of 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate. The mass spectra of the 2,2'-methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate peaks at 27.2 min are shown in each chromatogram.

Table 1. Patch test results of the three cases.

Case 2 had been previously investigated and the reactions highlighted in grey are those found positive at former investigation. Abbreviations: (IBOA; isobornylacrylate,pet; petrolatum, NT; not tested, TCMTB; 2-(thiocyanomethylthio)benzothiazole)(Tolcide)

Patch test reactions at first or second reading	*Case 1 D3/4/D7*	*Case 2* D3/4/D7	*Case 3 D3/4/D7*
In- house medical device series 2020 based on earlier used series (5)			
IBOA 0.3% pet	+(+)/++	-/++	+++/++
IBOA 0.1% pet	+/+	-	++/+
IBOA 0.01% pet	-	-	+(+)/-
Ethyl acrylate	-	-	(+)/-
Colophony 20% pet	-	+	-
Colophony 60% pet	(+)/-	-	-
Hydroabietyl alcohol	-	++/-	-
Alantolactone 0.1% alcohol	-	-	(+)/-
All other tested substances in the series	-	-	-
Sensor materials and substances deducted from clinic and analysis			
Dexcom G6 overpatch	NR	NT	-
Adhesive patch as is (outside)	(+)/-	NT	NT
Adhesive patch as is (inside)	++/-	NT	++/+
Sensor extract, ethanol	-	NT	+/(+)
Adhesive patch extract, ethanol	(+)/-	NT	+(+)/+
2,2'-Methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate 0.1% acetone[1]/ 0.1% pet[2]	(+)/(+)[1]	-/-[2]	+/+[2]
2,2'-Methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate 0.3% acetone[1]/ 0.3% pet[2]	+/+[1]	+ /-[2]	+/+[2]

2,2'-Methylenebis(6-*tert*-butyl-4-methylphenol) monoacrylate 0.5% pet	NT	NT	+/+
2,2´Methylenebis(6-tert-butyl-4-methylphenol) 0.3 and 1% pet	-/-	-/-	-/-
Lauryl acrylate 0.1% pet	-/-	-/-	-/-
Baseline series and extended baseline series			
Plastic related substances			
2- Hhydroxyethyl methacrylate	-	-	+
Preservatives			
Methylisothiazolinone	-/-	-	++/+
TCMTB	-	-	+
Benzisothiazolinone	+/-	-	+/+
Fragrances/fragrance related			
Myroxylon pereirae	-	++	+++
Fragrance mix I	-	-	-
Fragrance mix II	-	++	-
Hexyl cinnamal	-	+	-
Evernia prunastri	-	++/+	(+)
Hydroperoxides of linalool	-	+	(+)
Corticosteroids			
Tixocortolpivalate	-	-	+
Budesonide	+	-	-
Metals			
Potassium dichromate	-	-	+
Cobalt(II)hexahydrate	-	-	+
All other tested substances from the baseline series	-	-	-