Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

Exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acrylate; isobornyl acrylate

EC Number: **227-561-6**

CAS Number: **5888-33-5**

Index Number: **-**

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1 HEALTH HAZARDS

1.1 Skin sensitisation

1.1.1 Animal data

1.1.1.1 Local Lymph Node Assay in mice

Study reference: RCC (2012): Local lymph node assay (LLNA) in mice with isobornyl acrylate. Report no. Harlan CCR 1482701, study no. UNTER 12-024. RCC Cytotest Cell Research GmbH. Evonik Industries AG, unpublished

Detailed study summary and results[1]:

Test type: Local lymph node assay LLNA: OECD 429/GLP. According to the registrant, the study was performed according to OECD Guideline 429, Skin Sensitisation: Local Lymph Node Assay, adopted at 24 April 2002. GLP compliance is claimed, nevertheless, the DS did not have access to the full study report. The study is deficient in that at the time of study (study period: 2012-05-30 to 2012-07-03) the expiration date of the test substance batch (cf. below) had been exceeded by more than five years. It is not known whether the integrity of the batch has been checked at the time the study was performed and, given a limited stability of isobornyl acrylate (IBOA) in contact with air (REACH Registration Dossier, as of 2018-04-18) as well as the fact that the substance was stored at room temperature it is unclear to what extent the test substance still consisted of IBOA or its degradation products. Therefore the study has to be rated "not reliable" (Klimisch code 3).

Test substance: Isobornyl acrylate (IBOA), lot/batch No.: 1210180017, expiration date: 2007-02-23

Test animals: Female CBA/CaOlaHsd mice were used (provided from Harlan Netherlands, B.V. Postbus 6174, NL - 5960 AD Horst/The Netherlands). Age at study initiation: 8 -9 weeks (first pre-test) and 10 - 11 weeks (2nd and 3rd pre-test and main study). Animals were single-housed and received ad libitum pelleted standard diet (Harlan Lab., Horst, The Netherlands) as well as tap water (Gemeindewerke, D-64380 Rossdorf). Animals were allowed an acclimation period of at least five days. Only animals without any visible signs of illness were used for the study. The environmental conditions were maintained with a temperature of 22 ± 2 °C with a relative humidity of 45-65 % while the photoperiod (hrs dark/hrs light) was provided with artificial light: 6.00 a.m. - 6.00 p.m.

Administration/exposure: For the pre-tests the concentrations (non-GLP) were 5, 10, 25, 50, and 100% while for the main study the test concentrations were 0 (vehicle group), 5, 10, and 25 %. For the pre-tests (non-GLP) 3 x 2 females and for the main study 20 females (nulliparous and non-pregnant) were used, separated as three dose groups and 1 vehicle group of 5 animals, respectively. Positive control substance: hexyl cinnamic aldehyde (CAS No 101-86-0). Each test group was treated by topical (epidermal) application to the dorsal surface of each ear with different test item concentrations of 5, 10, and 25% (w/w) in acetone:olive oil (4+1 v/v). The application volume, 25 µL/ear/d, was spread over the entire dorsal surface of each ear once daily for three consecutive days. A further group of mice was treated with an equivalent volume of the vehicle alone (control animals). 3H-methyl thymidine (^{3}HTdR) was purchased from Hartmann Analytic, 38124 Braunschweig, Germany (specific activity, 2 Ci/mmol; concentration, 1 mCi/mL). Five days after the first topical application (day 6) 250 µL of phosphate-buffered saline (PBS) containing 20.2 µCi of ^{3}HTdR (equivalent to ^{3}HTdR 80.6 µCi/mL) were injected into each test and control mouse via the tail vein. Approximately five hours after treatment with 3HTdR all mice were euthanised by intraperitoneal injection

[1] Based on the registrant's summary in the technical dossier (IUCLID), with amendments by the DS.

of pentobarbital-sodium (Release, WDT, 30827 Garbsen, Germany). The draining lymph nodes were rapidly excised and pooled per animal (2 nodes per animal). Single cell suspensions (in phosphate buffered saline) of pooled lymph node cells were prepared by gentle mechanical disaggregation through stainless steel gauze (200 µm mesh size). After washing two times with phosphate buffered saline (approx. 10 mL) the lymph node cells were re-suspended in 5% trichloroacetic acid (approx. 3 mL) and incubated at approximately +4 °C for at least 18 h for precipitation of macromolecules. The precipitates were then re-suspended in 5 % trichloroacetic acid (1 mL) and transferred to plastic scintillation vials with 10 mL of 'Ultima Gold' scintillation liquid (Perkin Elmer (LAS) GmbH, 63110 Rodgau, Germany) and thoroughly mixed. The level of 3HTdR incorporation was then measured on a scintillation counter (Tricarb 2900 TR, Perkin Elmer (LAS) GmbH, 63110 Rodgau, Germany). Similarly, background 3HTdR levels were also measured in two 1 mL aliquots of 5% trichloroacetic acid. The scintillation counter expresses ^{3}HTdR incorporation as the number of radioactive disintegrations per minute (DPM). The proliferative response of the lymph node cells was expressed as the number of radioactive disintegrations per minute per lymph nodes of each animal (DPM/animal) and as the ratio of ^{3}HTdR incorporated into lymph node cells of test animals relative to that recorded for control animals (Stimulation Index; S.I.). Before DPM/animal values were determined, mean scintillation-background DPM was subtracted from test and control raw data.

Results and discussion: A test item is regarded as a sensitiser in the LLNA if the following criteria are fulfilled:

- Exposure to at least one concentration of the test item resulted in an incorporation of ^{3}HTdR ≥ 3-fold that recorded in control mice, as indicated by the Stimulation Index.

- Data were compatible with a conventional dose response, nevertheless taking into account (especially at high topical concentrations) local toxicity and/or immunological suppression.

In addition to the sensitising reactions the following observations and data were recorded during the test and observation period:

- Mortality/viability: At least once daily from experimental start to necropsy;

- Body weights: In the pre-test: prior to the first application and prior to sacrifice. In the main experiment: prior to the first application and prior to treatment with 3HTdR;

- Ear thickness: In the pre-test prior to the first application of the test item (day 1), on day 3 and before sacrifice (day 6);

- Ear weights: In the pre-test after sacrifice; biopsy punches were taken from each ear;

- Clinical signs (local/systemic): Clinical signs (systemic toxicity or local skin irritation) were recorded at least once daily. Especially the treatment sites were observed carefully.

Statistics: The mean values and standard deviations were calculated in the body weight tables and for the DPM values (group mean DPM ± standard deviation). The Dean-Dixon-Test was used for identification of possible outliers (performed with Microsoft Excel 2003). Both biological and statistical significance were considered together.

Positive control results: The sensitivity and reliability of the experimental technique employed was assessed by use of a substance known to have skin sensitisation properties in CBA/CaOlaHsd mice. The periodic positive control experiment was performed with α-hexyl cinnamaldehyde in acetone:olive oil (4+1 v/v) using CBA/CaOlaHsd mice in April 2012.

The results are summarised in
Table 1 and Table 2 below.

Table 1: Calculation and Results of Individual Data (BG = Background (1 mL 5% trichloroacetic acid) in duplicate; 1 = Control Group; 2-4 = Test Groups; S.I. = Stimulation Index; a) = values corrected for mean background value (BGI and BGII); b) = Stimulation Indices relative to the mean of the control group (Group 1)).

Test item concentration			DPM values measured	DPM-BG per animal (2 lymph nodes)[a)]	S.I.[b)]
% (w/w)	Group no.	Animal no.			
---	---	BG I	21	---	---
---	---	BG II	23	---	---
0	1	1	442	420	---
0	1	2	1174	1152	---
0	1	3	369	347	---
0	1	4	1073	1051	---
0	1	5	794	772	---
5	2	6	2308	2286	3.1
5	2	7	3784	3762	5.0
5	2	8	3546	3524	4.7
5	2	9	2909	2887	3.9
5	2	10	2779	2757	3.7
10	3	11	6640	6618	8.8
10	3	12	10884	10862	14.5
10	3	13	7731	7709	10.3
10	3	14	12319	12297	16.4
10	3	15	15193	15171	20.3
25	4	16	16576	16554	22.1
25	4	17	22879	22857	30.5
25	4	18	16657	16635	22.2
25	4	19	15713	15691	21.0
25	4	20	13734	13712	18.3

Table 2: Calculation of Stimulation Indices per dose group (where (a) Mean DPM/animal were determined by dividing the sum of the measured values from lymph nodes of all animals within a group by the number of animals in that group (5 animals); (b) Standard Deviation.

Test item concentration	Group Calculation		
	Mean DPM per animal (2 lymph nodes)[a)]	SD[b)]	S.I.
Vehicle Control Group (acetone:olive oil (4+1 v/v))	748.4	361.9	1.00
5% Isobornyl acrylate	3043.2	597.4	4.07
10% Isobornyl acrylate	10531.4	3465.3	14.07
25% Isobornyl acrylate	17089.8	3432.2	22.84

Conclusion by the DS: Under the test conditions of this study, IBOA was found to be a skin sensitiser Category 1 based on GHS criteria. An EC3 value was not calculated by the study authors. From the mean group S.I. values given in Table 2 it is also not possible to determine the S.I. at a hypothetical concentration of 3% with sufficient certainty. Therefore, a sub-categorisation is not possible based on these results.

1.1.2 Human data (sorted by first author)

1.1.2.1 Observation of allergic reactions in patients testing a glucose monitoring system

Study references:

Aerts O., Herman A., Bruze M., Goossens A., and Mowitz M. (2017): FreeStyle Libre: Contact irritation versus contact allergy. The Lancet 390 (10103). DOI: 10.1016/s0140-6736(17)31455-1;

Bolinder J., Antuna R., Geelhoed-Duijvestijn P., Kröger J., and Weitgasser R. (2016): Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: A multicentre, non-masked, randomised controlled trial. The Lancet 388 (10057), 2254-2263. DOI: 10.1016/s0140-6736(16)31535-5

Bolinder J., Antuna R., Geelhoed-Duijvestijn P., Kröger J., and Weitgasser R. (2017): Cutaneous adverse events related to FreeStyle Libre device – Authors' reply. The Lancet 389 (10077), 1396-1397. DOI: 10.1016/s0140-6736(17)30893-0

Detailed study summary and results by the DS:

The aim of the study was to investigate whether a factory-calibrated, sensor-based, flash glucose-monitoring system[2] could reduce hypoglycaemia in patients with type 1 diabetes as compared to self-monitored glucose testing. Here, only the part relevant to allergic reactions is reported.

In this multi-centre, prospective, non-masked, randomised controlled trial, adult patients with well controlled type 1 diabetes were enrolled from 23 European diabetes centres. After two weeks of all participants wearing the sensor, one group (those with readings for at least 50% of the period) was randomly assigned (1:1) to flash sensor-based glucose monitoring (intervention group) while the other switched to self-monitoring of blood glucose with capillary strips (control group).

All participants wore a FreeStyle Libre™ device for the 14 day baseline period. IBOA has been shown by chemical analysis to be present in the adhesive used to affix the FreeStyle Libre™ device to the skin.

[2] In contrast to continuous glucose monitoring systems (CGM), in „flash“ glucose monitoring systems, glucose levels are monitored discontinuously, e.g. by occasionally scanning the sensor measurement with a reading device.

Adverse events and sensor insertion-site symptoms were monitored throughout the study, as seen in Table 3 below.

Table 3: Overview of adverse events observed during the study (reproduced from (Bolinder et al., 2016))

	Intervention group (n=120)	Control group (n=121)
Participants with adverse or serious adverse events	63 (53%)	61 (50%)
Number of adverse or serious adverse events	138	138
Participants with serious adverse events	5 (4%)	4 (3%)
Number of serious adverse events	5	5
Participants with hypoglycaemic serious adverse events*	2 (2%)	3 (2%)
Number of hypoglycaemic serious adverse events*	2	4
Participants with hypoglycaemic adverse events	0	2 (2%)
Number of hypoglycaemic adverse events	0	3
Participants with device-related adverse events†	10 (8%)	0
Number of device-related adverse events	13	0
Participants who discontinued due to adverse events	6 (5%)	1 (<1%)‡

Table includes the full analysis set and two participants that became pregnant. *A hypoglycaemic serious adverse event was reported during the baseline phase. †Device-related adverse events were all related to wearing the sensor: four participants with allergy (one severe, three moderate); one with itching (mild); one with rash (mild); four with insertion-site symptom (severe); two with erythema (one severe, one mild); and one with oedema (moderate); all resolved. ‡Due to severe hypoglycaemia.

In the intervention group, 13 adverse events were reported by ten participants (8 %) related to the sensor, separated by the study authors into four "allergy" events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-site symptom (severe); two erythema (one severe, one mild); and one oedema (moderate). The basis for this distinction (e.g. why only four of these events are termed "allergy" events) is not clear from the original publication. According to the study protocol, individuals with known sensitivity to medical-grade adhesives had been excluded from participation. However, a few participants might have been unaware of their sensitivity until they had exposure to the product for longer than a few days.

The onset of the dermatitis (≥ 2 weeks after the first use of the device) indicated primary sensitisation by isobornyl acrylate, instead of a preexisting allergy to acrylates.

Conclusion by the DS: In the study group exposed to the sensor for ≥ 14 d, ≤ 10 cases (≤ 8 %) of dermatitis with assumed allergic background have been noted. These cases are attributed to an allergic reaction to the adhesive with which the sensor was glued directly to the skin. While IBOA was confirmed as one of the constituents of the adhesive, the possibility that some or even all of the dermatitis cases were caused by other constituents of the adhesive cannot be completely ruled out (Aerts et al., 2017; Bolinder et al., 2016; Bolinder et al., 2017).

1.1.2.2 Case reports of diabetes patients using insulin pumps

Study reference: Busschots A.M., Meuleman V., Poesen N., and Dooms-Goossens A. (1995): Contact allergy to components of glue in insulin pump infusion sets. Contact Dermatitis 33 (3), 205-206. DOI: 10.1111/j.1600-0536.1995.tb00554.x

Detailed study summary and results (with excerpts from the original publication):

"Case no. 1: A 27-year-old woman had had insulin-dependent DM since the age of 8 years. 3 months before she consulted us, she went over to an insulin pump, using a Cliniset® infusion set (Pharmaplast, Denmark). After I month, eczema appeared on the abdomen mainly under the 'butterfly'. A Disetronic® infusion set (Disetronic Medical Systems, Switzerland) gave the same response. Patch tests with the European standard series, components of the antiseptics used, the adhesives, and allergens present in adhesives, i.e., ditertiary pentylhydroquinone, diphenylthiourea, hydroquinone monobenzylether, and carba mix, were positive only to fragrance mix, though negative to its individual components. However, patch testing with scrapings of the plastic of the infusion sets was also positive. The ingredients of the glue used (mainly acrylates) were obtained from the manufacturer and tested. The results of further patch tests are shown in Table 4.

Table 4: Patch test results (reproduced from (Busschots et al., 1995))

		Patient no. 1		Patient no. 2	
		D2	D4	D2	D4
Acrylates					
phenoxypoly(ethyleneoxy)ethylacrylate	0.1%	++	++	+++	+++
	0.01%	NT		+	++
	0.001%	NT		−	?+
isobornyl acrylate	0.1%	++	++	+++	+++
	0.01%	NT		+	++
	0.001%	NT		−	+
beta-carboxyethyl acrylate	0.1%	++	++	−	+
1-benzoylcyclohexanol	1%	++	++	−	++
ethylene glycol dimethacrylate		−	−	−	−
hydroxyethyl methacrylate		−	−	−	−
bis-GMA		−	−	NT	
epoxy acrylate		−	−	NT	
methyl methacrylate		NT		−	−
n,n-dimethylaminoethyl methacrylate		NT		−	−
urethane dimethacrylate		NT		−	−
butanediol dimethacrylate		NT		−	−
Cliniset® infusion set					
plastic around the needle (A)		+	+	++	++
'butterfly' (B)		−	+	?+	+
catheter (C)		NT		−	−
Disetronic® infusion set					
plastic around the needle		+		NT	
Clini Soft® infusion set					
plastic around the needle		NT		?+	−
catheter		NT		−	−
Pureline® Basic infusion set					
plastic around the needle		NT		−	−
'butterfly'		NT		−	−
catheter		NT		−	−

Case no. 2: A 26-year-old woman had had insulin-dependent DM for 4 years. She had discontinued using an insulin pump after 14 months, because of eczema and abscesses at and around the injection site, first apparent after 4 to 5 months. The same had occurred with 2 different sets: Cliniset® and Clini Soft® (Pharmaplast, Denmark). Patch tests with the European standard series, the plastic of the infusion sets, the adhesives used, and the adhesive allergens cited above, were positive [+ +(+)] only to nickel sulfate and to the plastic scrapings. The results of additional tests are shown in Table 4.

Patch tests with the components (0.1% pet. for acrylates and 1% pet for 1-benzoylcyclohexanol) in 10 control subjects were negative.

Discussion: […] The patients described here reacted to phenoxypoly(ethyleneoxy)ethylacrylate, isobornyl acrylate, and betacarboxyethylacrylate, and 1 of them also to 1-benzoylcyclohexanol; these are all components of the UV-cured glue (Loctite 302®, Loctite International, Ireland) used to fix the needle into the plastic of the set. We have no information about the purity of the compounds that we tested […]."

Conclusion by the DS: In both cases, sensitisation to IBOA was established.

1.1.2.3 Case report of skin allergy likely caused by IBOA present in a continuous glucose monitoring system

Study reference: Corazza, M., V. Scuderi, D. Musmeci, C. Foti, P. Romita and A. Borghi (2018). Allergic contact dermatitis caused by isobornyl acrylate in a young diabetic patient using a continous glucose monitoring system (Freestyle Libre). Contact Dermatitis 2018; 1-2. DOI: 10.1111/cod.13075.

Detailed study summary and results (with excerpts from the original publication):
The study was initiated due to observed allergic reactions in diabetic patients that use continuous glucose monitoring systems (here "Freestyle Libre"). The original publication is herein cited as it is (Corazza et al., 2018):

" A 27-year-old male, who had been suffering from diabetes mellitus type I for 6 years, developed chronic eczema on the upper part of the arm where Freestyle Libre was applied. […] The medical device has to be replaced every 14 days. The patient was patch tested with the Italian Society of Allergological Occupational and Environmental Dermatology (SIDAPA) baselineseries (Lofarma, Milano, Italy), including 2-hydroxyethyl methacrylate (HEMA) 2% pet., the internal and external sides of the adhesive "asis", methylmethacrylate 5% pet., bisphenol A dimethacrylate 2% pet., ethyl acrylate 1% pet., and Compositae mix II 5% pet. Subsequently, patch tests were performed with acrylic acid 0.1% in saline solution and IBOA 0.1% pet. Patch test chambers (Van der Bend, Brielle, The Netherlands) were applied under occlusion on the patient's back for 2 days. Readings were performed on day (D) 2, D3 and D4 according to ESCD guidelines. Positive reactions were seen to both the external and internal sides of the adhesive (−/?+/+), acrylic acid (+/++/++), and IBOA (++/+++/+++). There was cross-reactivity between acrylic acid and IBOA, but not to other acrylates tested, including HEMA."

Conclusion by the DS: In this case report, the allergic contact dermatitis developed by the diabetes patient appeared upon the continuous dermal contact with the glucose monitoring device that contained IBOA. The results observed in the patch test indicate strong skin reactions upon exposure to 0.1% IBOA in petrolatum. Nevertheless, the patch test outcome might have been influenced by other unknown components (Corazza et al., 2018).

1.1.2.4 Case report of occupational skin allergy likely caused by IBOA

Study reference: Christoffers W.A., Coenraads P.J., and Schuttelaar M.L. (2013): Two decades of occupational (meth)acrylate patch test results and focus on isobornyl acrylate. Contact dermatitis 69 (2), 86-92. DOI: 10.1111/cod.12023
Detailed study summary and results (with excerpts from the original publication):
The study was triggered by a case of occupational dermatitis which is reproduced here in the words of the original publication:

"A 47-year-old atopic man was referred to our centre because of therapy-resistant hand eczema. He had been working as a process operator in a factory producing glass fibres for over 20 years. His work involved

painting glass fibres with UV-cured paint, printing the glass fibres, covering them with an acrylate coating, and cleaning the machines. His skin problems cleared during holidays, and relapsed when he returned to work. The patient was patch tested with the European baseline series and 12 department-specific additions, the cosmetic series, and our (meth)acrylate series containing 29 commercially available (meth)acrylates (Chemotechnique Diagnostics, Vellinge, Sweden). The patch tests were applied on the upper back for 48 hr under occlusion with van der Bend® square chambers (Van der Bend BV, Brielle, The Netherlands) and Fixomull® Stretch (BSN Medical, Hamburg, Germany). The tests were read on D3 and D7 according to the guidelines of the International Contact Dermatitis Research Group (ICDRG). There were no positive reactions to the extended European baseline series and the cosmetic series. The patient showed 1+ and 2+ positive patch test reactions to 11 different (meth)acrylates. However, all of the acrylates turned out to be currently clinically irrelevant, because they were not present in the substances that the patient worked with at that moment. Nonetheless, an acrylate was suspected to be the causative allergen, given the nature of his present occupation. A workplace visit showed that isobornyl acrylate was a component of the glass fibre coatings [Desolite™ (DSM Desotech, Heerlen, The Netherlands) and Bufferlite™ DU-2002 (DSM Desotech)] and UV-cured ink (Herkula-Ultracoat™ OF 813; Krefeld, Germany) with which he came into contact during the production process. Thus, isobornyl acrylate was suspected as a relevant allergen. A patch test with isobornyl acrylate 0.1% pet. (SigmaAldrich, Zwijndrecht, The Netherlands; in-house preparation) under 48 h of occlusion resulted in a 2+ positive reaction on D3 and D7. […] In this occupational case, the sensitizerswere uncured UV ink and acrylate coating. With avoidance of these products, the skin problems of the industrial process operator resolved. To date, one year later, he is working at another department in the same factory without any complaints."

"Since the in-house (meth)acrylate test series did not include IBOA, this case triggered an investigation into historical cases of (meth)acrylate allergy observed at the University Medical Centre of Groningen, The Netherlands, in order to clarify the need to include IBOA in the test series for future patch-testing. A total of 14 patients patch-tested positive to acrylates in the period between 1993 and 2012 was patch-tested with a IBOA dilution series of 0.3, 0.1, 0.03, and 0.01% IBOA in petrolatum. The sensitisation status with respect to the (meth)acrylate series apparently was not re-established. While at the highest concentration irritant reactions were observed in 3 of the 14 subjects, no allergic reaction was noted. Five healthy control subjects were also patch-tested, but did not show any irritant or allergic reactions."

Conclusion by the DS: in the reported case, there is a high likelihood that the allergic contact dermatitis can be attributed to IBOA. Nevertheless, even if historical cases were investigated they did not provide meaningful results relevant to this CLH report. The reason might be the small number of tested subjects as well as their unknown previous exposure to IBOA (Christoffers et al. (2013)).

1.1.2.5 **Investigations in patients showing allergic reactions to a glucose sensor**

Study reference: Herman A., Aerts O., Baeck M., Bruze M., De Block C., Goossens A., Hamnerius N., Huygens S., Maiter D., Tennstedt D., Vandeleene B., and Mowitz M. (2017): Allergic contact dermatitis caused by isobornyl acrylate in Freestyle(R) Libre, a newly introduced glucose sensor. Contact dermatitis 77 (6), 367-373. DOI: 10.1111/cod.12866

Detailed study summary and results (excerpt from the original publication):

"FreeStyle® Libre (Abbott Diabetes Care, Witney, Oxfordshire, UK) is a popular 'flash' continuous glucose monitoring system recently developed for diabetes patients. […] Following its introduction, several patients, both adults and children, have presented with eczematous skin eruptions, provoked by the adhesive part of the sensor, and suggestive of allergic contact dermatitis.

We here report 15 subjects suffering from severe allergic contact dermatitis caused by FreeStyle® Libre, and we highlight isobornyl acrylate (IBOA) […] as a relevant and causative contact allergen in the majority of them.

Patients and Methods:

Patients:

The demographic data, period of onset of the dermatitis, test series and allergens tested, and patch test results for all 15 patients are shown in Table 5 (on page 12). All patients suffered from diabetes mellitus type I, and had used FreeStyle® Libre on the upper arm. […]. Patient 14 had specifically noted the occurrence of the rash just beneath the adhesive part of the device, whereas the central needle opening remained unaffected. Some patients (e.g. patients 5, 14, and 15) had tried multiple protective barrier dressings, such as Opsite® (Smith & Nephew, London, UK) and Tegaderm® (3M™, Minneapolis, MN, USA), between the affected skin and the device, without improvement, or even with aggravation of the dermatitis. Patient 14 had additionally tried using corticosteroid nebulizers and barrier sprays under the adhesive, but again without any relief. A few patients had experienced similar skin reactions to other medical devices used for diabetes; for example, patient 4 had previously also reacted to an insulin pump (Minimed®; Medtronic, Los Angeles, CA, USA), whereas patient 6 had developed vesicular dermatitis a few days following the use of FreeStyle® Navigator (Abbott) on her abdomen.

Patch tests:

Patients 1–3 were evaluated at the Department of Dermatology of University Hospital Antwerp, patients 4–9 were evaluated at the Department of Dermatology of the Cliniques Universitaires Saint-Luc in Brussels, patients 10–13 were evaluated at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, and at its branch clinic in Karlshamn, and patients 14 and 15 were evaluated at the Department of Dermatology in Leuven.

Patch tests were performed with a baseline series (except in patient 15), and sometimes with additional series, such as plastics and glues, (meth)acrylates, epoxy resins, and/or isocyanates. All commercial allergens were supplied by Chemotechnique (Vellinge, Sweden) in Antwerp, Brussels, Leuven, and Malmö, and/or by Trolab® (Hermal, Reinbek, Germany) in Brussels and Leuven.

In Antwerp, Brussels, and Leuven, all patients except for patient 15 were initially patch tested with (pieces of) the adhesive part of the glucose sensor FreeStyle® Libre. In Malmö, 2 patients were patch tested with acetone extracts made from the adhesive part of the sensor, and one patient was tested with an acetone extract made from the whole sensor. When these extracts were prepared, the adhesive patches and the sensor were extracted in ~20mL of acetone in an ultrasonic bath for 5 min. The extracts were then concentrated to a volume of 1mL with a rotary evaporator. Moreover, on the basis of literature research regarding potential contact allergens in diabetes medical devices, the Antwerp department, after obtaining IBOA raw material from Kowa Europe (Düsseldorf, Germany), prepared additional in-house patch test preparations of IBOA in three different concentrations, that is, 0.1%, 0.05%, and 0.01% pet. These were patch tested in patient 1, and subsequently in all patients from the Antwerp, Brussels and Leuven departments, except for patient 8.

The Malmö patients were patch tested with IBOA purchased from Sigma-Aldrich (Steinheim, Germany). Preparations with IBOA in pet. and acetone were made at the Malmö department. Patient 11 was tested with pet. preparations containing 0.1% and 0.01% w/w IBOA. Patients 12 and 13 were tested with a dilution series of IBOA in acetone, in the following concentrations: 0.10%, 0.032%, 0.010%, 0.0032%, 0.0010%, 0.00032 %, 0.00010 %, 0.000032 %, 0.000010 %, and 0.0000032 % (wt/vol). Patch testing with IBOA has not […] been performed in patient 10, as he moved to another city.

Patch tests were applied on the upper back with IQ Ultra™ test chambers® from Chemotechnique in Brussels and Leuven, with Allergeaze® patch test chambers (SmartPractice, Calgary, Canada) in Antwerp, and with 8-mm Finn Chambers® (Smart Practice, Phoenix, AZ, USA) in Malmö, and IQ Ultra™ test chambers at its branch clinic in Karlshamn, and when patch testing was performed with acetone solutions of IBOA. For fixation, Fixomull® stretch (BSN Medical, Hamburg, Germany) was used in Antwerp and Brussels, Scanpor® tape (Norgesplaster, Vennesla, Norway) in Malmö, and Mefix® (Mölnlycke, Göteborg, Sweden)

in Leuven. In Antwerp, Brussels, and Leuven, following occlusion for 2 days, all patch test reactions were read, according to ESCD guidelines, on day (D) 2 and on D3 or D4, and sometimes also later. In Malmö, following occlusion for 2 days, the tests were read on D3 or D4 and on D7. In Malmö, 20 dermatitis patients were patch tested with the ultrasonic bath extract of the device as controls.

Chemical investigations:

Acetone extracts made from different parts of FreeStyle® Libre sensors were analysed by means of gas chromatography–mass spectrometry (GC-MS) at the Malmö department. Initially, extracts made from the adhesive patches from three different sensors (including those tested in patients 11 and 12), and also the extract of the whole sensor tested in patient 10, were analysed after being filtered and concentrated to a volume of 0.2 mL. Another sensor was disassembled, and separate acetone extracts were made from the adhesive patch, the transparent plastic on the top of the sensor (immediately under the adhesive patch), the circuit board, and the white plastic from the back of the sensor. Furthermore, the white plastic from the back of a different sensor was divided in two fractions, and separate extracts were made from these fractions. One fraction contained areas where the white plastic material was joined to the transparent plasticmaterial from the top, whereas the other contained material taken from areas not fixed to the top material. The different materials were cut into small pieces and placed in test tubes. Two millilitres of acetone was added to the test tube containing the circuit board, and 1 mL of acetone was added to the rest of the test tubes. The test tubes were then placed in a shaker for 1 h. After the solid materials had been removed, the extracts were filtered and analysed.

The gas chromatography system consisted of an Agilent 6890N gas chromatograph (Agilent Technologies, Santa Clara, CA, USA) equipped with an HP-MSI capillary column (Agilent Technologies) with a length of 30 m, an internal diameter of 0.25 mm, and a film thickness of 0.25 μm. The carrier gas was helium of Alphagaz 2 quality (Air Liquide, Malmö, Sweden) with a flow rate of 1.0 mL/min. The injection was splitless, and the inlet was heated to 250 °C. The injection volume was 1 μl. The temperature program was as follows: isothermal at 70 °C for 3 min, raised by 8 °C/min to a final temperature of 300 °C, and isothermal at this temperature for 10 min. Electron-ionization mass spectra were recorded with a Jeol GCmate II mass spectrometer (Jeol Datum, Tokyo, Japan) in scan mode recording ions with m/z from 50 to 600 u, with a scan duration of 0.3 seconds and an interscan delay of 0.2 seconds. The temperature of the ion source was 250 °C, and the GC-MS interface temperature was 250 °C. The electron energy was 70 eV. IBOA dilutions in acetone were used as reference standards.

Results: Patient characteristics and patch tests results are shown in Table 5. The patients reacted positively to (pieces of) the adhesive part of FreeStyle® Libre, or to extracts made from the whole sensor, or from the adhesive part of the sensor. All patients patch tested with IBOA (n=13) reacted positively to it, except for patient 3. Sometimes, positive reactions down to 0.01% pet. were observed . In Malmö, no reactivity to IBOA < 0.01% was observed with the dilution series of the allergen in acetone. Positive patch test reactions could sometimes also be observed to allergens from additionally patch tested series. For example, patient 4 had a positive reaction (+) to cycloaliphatic epoxy resin, and patient 8 had positive reactions to abitol (++) and to hydroquinone (++), as well as to hexamethylene diisocyanate (++). Positive patch test reactions were often, in 7 out of 15 patients, also observed to sesquiterpene lactone mix present in the baseline series. However, the relevance of all of these additional positive reactions could not be established.

Whenever an acrylate series was patch tested, there were no positive reactions observed to acrylates other than IBOA, except in patients 1 and 15, who also reacted to hydroxypropyl acrylate (HPA) (+) and to ethyl acrylate (EA) (+), respectively. None of the controls reacted positively to the ultrasonic bath extract of FreeStyle® Libre. Moreover, patch testing in 14 Belgian control patients with IBOA 0.1% pet. did not result in any positive reactions, whereas 10 out of 11 diabetes patients with exposure to the glucose sensor reacted positively.

Table 5: Demographic data, period of onset of the dermatitis, test series and allergens tested, and patch test results for 15 patients with diabetes mellitus showing contact dermatitis caused by FreeStyle® Libre (reproduced from (Herman et al., 2017)).

Patient	Centre	Age (years)	Sex	Onset of the dermatitis following the use of FreeStyle® Libre	Baseline series D2/D4*	Additional patch tests D2/D4*	(Pieces of) adhesive of FreeStyle® D2/D4*	IBOA 0.1% D2/D4*	IBOA 0.05% D2/D4*	IBOA 0.01% D2/D4*
1	UZA	9	M	U	Negative	MA series: HPA +/+ P&G series: NT ISO series: NT ER series: NT	+/+	++/++	++/++	+/+
2	UZA	14	M	U	Negative	NT	+/+	++/++	++/++	+/+
3	UZA	7	M	U	Negative	NT	+/+	–/–	–/–	–/–
4	UCL	12	F	2 months	MP –/+ SQTL ++/++ TP +/+ FM I +/+ PG +/+ BIT +/?+	MA series: negative P&G series: negative ISO series: NT ER series: epoxy resin(cycloaliphatic) +/+	++/++	++/++	++/++	++/++
5	UCL	40	F	1 month	Nickel ++/++	MA series: negative P&G series: negative ISO series: negative ER series: negative	++/+	++/++	++/++	–/–
6	UCL	44	F	1 month	Negative	MA series: negative P&G series: negative ISO series: negative ER series: negative	?+/+	++/++	++/++	++/++
7	UCL	52	F	U	SQTL +/++ Nickel ++/++	MA series: negative P&G series: negative ISO series: negative ER series: negative	++/++	++/++	++/++	++/++
8	UCL	8	M	U	Negative	MA series: negative P&G series: abitol ++ (D3), hydroquinone ++ (D3) ISO series: HMDI ++ (D3) ER series: negative	+ (D3)	NT	NT	NT
9	UCL	41	F	U	FM I +/+ SQTL +/++	MA series: negative P&G series: negative ISO series: negative ER series: negative	–/–	++/++	++/++	–/–
10	MAL	41	M	Several months	SQTL +/?+	NT	+/–†	NT	NT	NT
11	MAL	43	F	U	SQTL +++/+++ TDM ?+/+	MA series: negative P&G series: NT ISO series: NT ER series: NT	+/+†	+++/+++	NT	++/++
12	MAL	38	F	7 months	SQTL ?+/?+ MP ?+/?+ MI ?+/?+	NT	++/+†	+++/++‡	+++/+‡(0.032%)	?+/?+‡
13	MAL	29	F	18 months	Negative	MA series: negative P&G series: negative ISO series: NT ER series: NT	+/–	++/+‡	?+/–‡(0.032%)	?+/–‡
14	LEU	58	F	6 months	SQTL +/+ MP +/+ Nickel +/+ Palladium +/+ FM I +/+	MA series: negative	+/+	++/++	+/++	?+
15	LEU	8	M	2 weeks	NT	MA series: ethyl acrylate +/+	NT	NT	+/+	+/+

BIT, benzisothiazolinone; ER series, epoxy resin series; F, female; FM, fragrance mix; HMDI, hexamethylene diisocyanate; HPA, hydroxypropyl acrylate; IBOA, isobornyl acrylate; ISO series, isocyanate series; LEU, Dermatology, University Hospitals KU Leuven; M, male; MA series, (meth)acrylate series; MAL, Dermatology, University Hospital Malmö; MI, methylisothiazolinone; MP, *Myroxylon pereirae*; NT, not tested; P&G series, plastic & glues series; PG, propylene glycol; SQTL, sesquiterpene lactone mix; TDM, textile dye mix; TP, tixocortol pivalate; U, unknown; UCL, Dermatology, Cliniques Universitaires Saint-Luc; UZA, Dermatology, University Hospital Antwerp. –, negative; ?+, doubtful, + to +++, positive patch test reaction.

* In Malmö, the readings were performed on day (D) 3 or D4, and on D7.

† Adhesive patch tested as an acetone extract.

‡ Dilutions made in acetone.

IBOA was found in all of the extracts analysed by GC-MS. The extracts made from the adhesive patches contained IBOA in concentrations corresponding to 2–50 μg/patch, which in turn correspond to a surface dose of 0.2–5 μg/cm2. The IBOA concentrations in the different parts of the disassembled sensor were approximately 0.006 % (wt/wt) in the adhesive patch, 0.004% in the top plastic, 0.003% in the circuit board, and 0.3 % in the white plastic from the back of the sensor. The parts of the white plastic that were joined to the transparent plastic contained ~0.4% (wt/wt) IBOA, whereas the parts not fixed to the transparent plastic contained only 0.005 % (wt/wt) IBOA. Furthermore, IBOA was also found in the Freestyle Navigator II sensor, used by patient 6, who had also shown skin reactions to this specific device […]."

Conclusion by the DS: FreeStyle® Libre glucose sensor caused several cases of severe allergic contact dermatitis after it was introduced on the market. The observed allergic contact dermatitis could be attributed to IBOA (acrylate allergen). In the diagnostic patch test, a concentration of IBOA 0.1% pet. seems to be justified, and little to no cross-reactivity with other acrylates is to be expected. However, other unknown contact allergens might play a role as well (Herman et al. (2017)).

1.1.2.6 Investigation into cases of occupational allergic contact dermatitis from an acrylic glue

Study Reference: Kiec-Swierczynska M., Krecisz B., Swierczynska-Machura D., and Zaremba J. (2005): An epidemic of occupational contact dermatitis from an acrylic glue. Contact dermatitis 52 (3), 121-125. DOI: 10.1111/j.0105-1873.2005.00527.x

Detailed study summary and results (excerpts from the original study report):

"Dermatological examinations were performed in 81 workers involved in the manufacture of electric coils for television displays, who had worked for 4 years in contact with a glue containing isobornyl acrylate, acrylic acid, N,N dimethyleneacrylamide, phosphine oxide, bis(2,6-dimethoxybenzoyl) (2,4,4-trimethylpentyl)- and beta-carboxyethyl acrylate. The glue was cured by 350–500 nm ultraviolet and visible radiations. From these subjects, acrylate-specific dermal lesions were detected in 21 (25.9%) people. Occupational irritant contact dermatitis was diagnosed in 12 (15%) of the workers and occupational allergic contact dermatitis in 9 (11.2%). 12 people reacted to acrylates. Cross-reactions with methacrylates were not observed. The highest number of positive tests was obtained with triethyleneglycol diacrylate (10 people) and diethyleneglycol diacrylate (9), followed by 1,6-hexanediol diacrylate (5), 1,4-butanediol diacrylate (4), beta-carboxyethyl acrylate (3), tripropyleneglycol diacrylate (2) and pentaerythritol triacrylate (2). No cases of allergy to isobornyl acrylate, N,N-methylenebisacrylamide or phosphine oxide were noted.

Patients and methods:

Dermatologic tests were run in a plant manufacturing video display units (VDUs) for TV receivers. All workers employed in 3-shift system in the production of electric coils for TV VDU and exposed, among other things, to Delo-photobond1 VE 50606 (DELO Industrieklebstoffe GmbH & Co. KG, Landsberg, Germany) acrylic glue, which had been used in the plant for 4 years, were tested. The glue containing (meth)acrylates had not been used in this factory previously.

The study group comprised 81 people (59 women and 22 men). As specified in the material safety data sheet (MSDS), the glue contained isobornyl acrylate (25–50%), acrylic acid (10–25%), N,N dimethyleneacrylamide (10–25%), phosphine oxide, bis(2,6-dimethoxybenzoyl) (2,4,4-trimethylpentyl) (2.5%) and beta-carboxyethyl acrylate (2.5%). The glue was cured in curing chambers by 350–500-nm ultraviolet (UV) and visible lights. The process of glue application and curing were automatic. Thereafter, the workers examined the coils for defects and manually disassembled the defective ones. They also fastened small magnets using adhesive tape. To ensure better operative precision, they used vinyl protective gloves with severed fingertips. Some workers who developed painful fissures of the skin, wrapped the distal parts of their fingers with sticking plaster to be able to continue their job.

Patch tests with a 30-allergen series were performed in all subjects (except for 1 worker with extensive psoriasis vulgaris lesions), according to the criteria developed by the International Contact Dermatitis Research Group (3). The series of 30 allergens contained derivatives of acrylic and methacrylic acids (16 and 5 chemical compounds, respectively), and also other contact allergens found most frequently in the environment. 26 were commercial allergens from Chemotechnique Diagnostics (Malmö, Sweden). Instead of N,N-dimethyleneacrylamide, which was in glue, we used a similar compound – N,N-methylenebisacrylamide for testing. 4 compounds were prepared at the Nofer Institute of Occupational Medicine in Lodz, Poland: phosphine oxide at 2 concentrations, isobornyl acrylate and beta-carboxyethyl acrylate (Sigma-Aldrich Inc., St. Louis, MO, USA). Patches were removed and read after 2 days, with a second and final reading at day 4. 20 voluntary controls tested with 1% phosphine oxide were negative at D2 and D4.

Results:

Dermatological examination:

Work-related dermal complaints were reported by 40 workers (34 women and 6 men), usually in the form of hyperkeratosis, fissuring and scaling of the fingers and fingertips, and also pruritic papulovesicular areas of the dorsal hands and distal phalanges. The lesions occurred after several weeks to several months since starting work in contact with the glue. The lesions occurred predominantly in workers performing the coil disassembling operations. Before they were disassembled, the coils had been heated. Additionally, 9 people (8 women and 1 man) reported conjunctivitis, rhinitis and cough.

Dermatologic examinations showed current dermal lesions in 40 people (28 women and 12 men). In 21 (25.9%) of those patients, the clinical picture suggested an occupational aetiology. In 17 women and 3 men, the dermal lesions were located on the palmar and flexor finger areas and took the form of hyperkeratosis, fissures and scaling, while 1 patient developed contact eczema (erythema and papules/vesicles) on the dorsa of his hands. The remaining 19 cases were classified as dermal diseases with an aetiology generally recognized as non-occupational. These included 3 cases of psoriasis vulgaris, 5 of keratosis pilaris, 4 of acne vulgaris, 4 of hyperhidrosis manuum, 1 of pityriasis versicolor, 1 of tinea cutis glabrae and 1 of neck dermatitis at the site of contact with metal objects.

Contact allergy, i.e. at least 1 positive patch test result, was found in 35 (43.7%) people (30 women and 5 men). Table 6 shows the positive patch test results. 28.7% workers showed a positive patch test to nickel. 12 (15%) workers (9 women and 3 men) reacted to acrylates, which gave 35 positive test results. They had never been exposed to acrylates before. Non-occupational allergy to methacrylic acid derivatives was noted in 1 woman. Her allergy was due to methacrylates found in artificial fingernails. After 3 weeks, she had had to remove them because of hand dermatitis. She reacted to methyl methacrylate (D4 +), 2-hydroxyethyl methacrylate (D4 ++), ethyleneglycol dimethacrylate (D4 ++) and nickel sulfate (D4+++).

Patch test results:

Table 6: Positive patch test results with series tested (reproduced from (Kiec-Swierczynska et al., 2005))

		Positive patch tests					
		Female = 59		Male = 21		Total = 80	
Number	Allergens - Concentration, vehiculum	n	%	n	%	n	%
	Common allergens (Chemotechnique Diagnostics, Malmö, Sweden)						
1	Nickel sulfate – 5% pet.	22	37.3	1	4.8	23	28.7
2	Potassium dichromate – 0.5% pet.	3	5.1	2	9.5	5	6.2
3	Fragrance mix – 8% pet.	3	5.1			3	3.7
4	Euxyl K 400–1.5% pet.	1	1.7	1	4.8	2	2.5
5	4-Phenylenediamine base – 1% pet.	1	1.7			1	1.2
6	Formaldehyde – 1% aq.	1	1.7			1	1.2
7	Thiuram mix – 1% pet.						
	Acrylates (Chemotechnique Diagnostics)						
8	Triethyleneglycol diacrylate (TREGDA) – 0.1% pet.	9	15.2	1	4.8	10	12.5
9	Diethyleneglycol diacrylate (DEGDA) – 0.1% pet.	6	10.2	3	14.3	9	11.2
10	1,6-Hexanediol diacrylate (HDDA) – 0.1% pet.	3	5.1	2	9.5	5	6.2
11	1,4-Butanediol diacrylate (BUDA) – 0.1% pet.	2	3.4	2	9.5	4	5.0
12	Tripropyleneglycol diacrylate (TPGDA) – 0.1% pet.	1	1.7	1	4.8	2	2.5
13	Pentaerythritol triacrylate (PETA) – 0.1% pet.	2	3.4			2	2.5
14	Ethyl acrylate (EA) – 0.1% pet.						
15	2-Ethylhexyl acrylate (2-EHA) – 0.1% pet.						
16	Trimethylolpropane triacrylate (TMPTA) – 0.1% pet.						
17	Oligotriacrylate 480 (OTA 480)−0.1% – pet.						
18	Epoxy acrylate – 0.5% pet.						
19	Urethane diacrylate (aliphatic) – 0.1% pet.						
20	Urethane diacrylate (aromatic) – 0.05% pet.						
21	N,N-methylenebisacrylamide – 1% pet.						
	Methacrylates (Chemotechnique Diagnostics)						
22	Methyl methacrylate (MMA) – 2% pet.	1	1.7			1	1.2
23	2-Hydroxyethyl methacrylate (2-HEMA) – 2% pet.	1	1.7			1	1.2
24	Ethyleneglycol dimethacrylate (EGDMA) – 2% pet.	1	1.7			1	1.2
25	Triethyleneglycol dimethacrylate – 2% pet.						
26	BIS-GMA – 2% pet.						
	Own test substances (Sigma-Aldrich Inc., St. Louis, MO, USA)						
27	Beta-Carboxyethyl acrylate – 0.1% pet.	2	3.4	1	4.8	3	3.7
28	Isobornyl acrylate – 0.1% pet.						
29	Phosphine oxide, bis(2,6-dimethoxybenzoyl) (2,4,4-trimethylpentyl) – 0.1% pet.						
30	Phosphine oxide, bis(2,6-dimethoxybenzoyl) (2,4,4-trimethylpentyl) – 1% pet.						

aq., water (aqua); pet., petrolatum.

Table 7 presents the results of patch tests and the clinical picture for the patients sensitive to acrylates. Most frequently, the patients reacted to triethyleneglycol diacrylate (TREGDA) and diethyleneglycol diacrylate (DEGDA), then to 1,6-hexanediol diacrylate (HDDA), 1,4-butanediol diacrylate (BUDA), beta-carboxyethyl acrylate, tripropyleneglycol diacrylate (TPGDA) and pentaerythritol triacrylate (PETA). None reacted to isobornyl acrylate, N,N-methylenebisacrylamide and phosphine oxide. Among the 12 workers with positive tests to acrylic acid derivatives, active lesions characteristic of allergy to acrylates were recorded in 9 people (11.2%), including 6 women and 3 men. In the remaining group of 3 people, in spite of positive tests, no lesions were noted at the time of the testing: in the past, they had complained of dermal lesions, and for that reason, they had already been transferred to packing finished products. Dermal lesions from the irritant activity of the work environment, including that of acrylic acid and its derivatives, were diagnosed in 12 (15%) people. These included people with dermal lesions whose allergy test results had been negative. “

Conclusion by the DS: In this study, out of 81 workers exposed to a glue containing, inter alia, isobornyl and other acrylates, of which 21 showed dermatological lesions with a suspected occupational aetiology none reacted positive in a patch test with 0.1 % IBOA in pet. (Kiec-Swierczynska et al. (2005)).

Table 7: Positive patch test results and clinical features in 12 cases with allergy to acrylates (reproduced from (Kiec-Swierczynska et al., 2005))

Patients	Age	Sex	Acrylates positive patch test reaction	Other allergens identified	Clinical diagnosis
1	49	Female	BUDA (++) HDDA (++) DEGDA (+++) PETA (+) TREGDA (+++) beta-Carboxyethyl acrylate (++)		Eczema hyperkeratoticum manuum
2	34	Male	DEGDA (++)		Eczema hyperkeratoticum manuum
3	40	Female	TREGDA (+++)		No skin lesion
4	39	Female	DEGDA (++) PETA (+) TREGDA (++) beta-Carboxyethyl acrylate (++)	Cr (++)	No skin lesion
5	49	Female	HDDA (+) TREGDA (++) TPGDA (++)		Eczema hyperkeratoticum manuum
6	48	Female	TREGDA (+)		No skin lesion
7	24	Male	BUDA (+) HDDA (+) DEGDA (++)		Eczema manuum
8	45	Female	BUDA (++) HDDA (+) DEGDA (++) TREGDA (+)	Ni (+++)	Eczema hyperkeratoticum manuum
9	43	Male	BUDA (++) HDDA (++) DEGDA (+++) TPGDA (++) beta-Carboxyethyl acrylate (+++) TREGDA (++)	Euxyl K 400 (+)	Eczema hyperkeratoticum manuum
10	44	Female	DEGDA (+++) TREGDA (++)		Eczema hyperkeratoticum manuum
11	40	Female	DEGDA (++) TREGDA (++)		Eczema hyperkeratoticum manuum
12	53	Female	DEGDA (++) TREGDA (++)	Ni (+)	Eczema hyperkeratoticum manuum

BUDA = 1,4-butanediol diacrylate; DEGDA = diethyleneglycol diacrylate; HDDA = 1,6-hexanediol diacrylate; PETA = pentaerythritol triacrylate; TREGDA = triethyleneglycol diacrylate; TPGDA = tripropyleneglycol diacrylate.

1.1.2.7 Case Report: severe allergic contact dermatitis caused by IBOA contained in an insulin patch pump

Study Reference: Oppel, E., C. Högg, B. Summer, F. Ruëff, F. X. Reichl and S. Kamann (2018). Isobornyl acrylate contained in the insulin patch pump OmniPod as the cause of severe allergic contact dermatitis. Contact Dermatitis, 1-3. DOI: 10.1111/cod.13017

Detailed study summary and results (excerpts from the original study report):

The study reports a case of severe allergic contact dermatitis caused by the use of insulin patch pump OmniPod that contained IBOA (Oppel et al., 2018). The original publication is herein cited:

"A 10-year-old boy who had suffered from type 1 diabetes from the age of 6 years started treatment with the glucose monitoring system Freestyle Libre in May 2016. Usually, the sensor was attached to the upper arm, and was left there for 14 days; no other external preparations had been used.

In July 2016, before formally requesting […] insulin patch pump OmniPod from his health insurance, the patient tested this device for 3 days without any problems. In November 2016, […] the boy complained about an itch underneath his Freestyle Libre sensor; the itching progressively worsened, and an erythematous and vesicular rash developed, forcing the patient to remove the sensor after 2 days. Following treatment with topical corticosteroids, the skin symptoms subsided after a few days. A new sensor was then attached to the

other upper arm. Within 24 hours, severe itching and ACD recurred. Meanwhile, however, the use of the OmniPod system had been formally approved by the boy's health insurance. One day after the start of OmniPod use, the patient developed similar skin lesions underneath the insulin patch pump.

Patch tests were performed with allergens from the baseline series and from a plastics and glues series, according to the recommendations of the German Contact Allergy Group. The latter test series included several acrylates. The test substances were applied on the patient's back by the use of Finn Chambers (Smart Practice, Phoenix, Arizona) on Scanpor tape (BARD/Angiomed, Karlsruhe, Germany), and were fixed with Fixomull stretch (BSN, Hamburg, Germany). The cutaneous reactions were evaluated upon removal (after 2 days of application) and on day (D) 3. Reactions were classified according to German Contact Dermatitis Research Group criteria. All tests gave negative results.

The manufacturers (Abbott, Chicago, Illinois and Ypsomed, Burgdorf, Switzerland respectively) […] provided information on potential contact allergens in the Freestyle Libre and OmniPod devices [...] and it became clear that, owing to structural differences, it was unlikely that the patch test substances already applied would show contact sensitization to the acrylates contained in medical devices.

According to the manufacturer of the OmniPod device, there should be no additional layer between the adhesive and the patch pump, as the plastic box is fixed to the adhesive by a heating process. In the case of the Freestyle Libre device, 2 adhesives, that is, (1) the adhesive that attaches the sensor to the skin, and (2) the layer of glue that fixes the sensor to the adhesive layer, were kindly provided by the adhesive manufacturer supplying Abbott. […] Patch testing with these 2 adhesives used for the Freestyle Libre device and the 1 adhesive used for the OmniPod device gave negative results.

Subsequently, IBOA 0.1% pet. […] was used and elicited a strong (++) reaction on D3; […] the allergen was not part of the adhesive, but was possibly contained in another part of the OmniPod device, supported by the observation that ACD was most prominent in the centre, where the needle is fixed.

Consequently, after removal of the patch (Fixomull stretch), samples from only the bottom side of the insulin pump (OmniPod) in contact with the skin were immersed in 6 mL of water [liquidchromatography (LC)-mass spectrometry (MS) Grade, ROTISOLV;Roth, Karlsruhe, Germany] or in 6 mL of methanol [gas chromatography(GC) Ultra Grade, RATISOLV ≥ 99.9%; Roth]. After 3 days of incubation in the dark at room temperature, the samples were analysed by GC-MS. Only the water eluate has to be extracted once with ethylacetate (1:1 vol/vol) (LC-MS grade, ROTISOLVE >99.9%; Roth) beforethe GC-MS analysis […]. Identification of IBOA was achieved by comparing the mass spectra and retention time with those of the reference standard IBOA (Merck, Darmstadt, Germany). The quantity of IBOA was calculated by correlating its characteristic mass peak area with the corresponding precompiled calibration curve. In the water eluates of the insulin pump (skin contact side), and in the water and methanol eluates of the Fixomull patches, no IBOA could be detected. In the methanol eluate of the insulin pump (skin contact side), however, we found 10 μg/mL IBOA. This corresponds to a dose/area of ~0.53 μg/cm^2 (immersed surface area) […] "(Oppel et al., 2018).

Conclusion by the DS: It has been hypothesied that IBOA present in the glue used to fix medical devices such as continuous glucose monitoring systems, flash glucose monitoring systems and advanced insulin pumps might be the reason of causing allergic contact dermatitis in diabetes patients. In this report it is shown that severe allergic contact dermatitis was caused by IBOA contained in the insulin patch pump OmniPod. High amounts of IBOA could be detected on the bottom side of the insulin pump that is in contact with the skin and therefore it is very likely that IBOA is the reason of (10 μg/mL corresponds to a dose/area of ~0.53 μg/cm^2) severe allergic contact dermatitis observed in this specific case.

1.1.2.8 Case Reports: Allergic contact dermatitis caused by isobornyl acrylate in tubeless insulin pump

Study Reference: Raison-Peyron, N., M. Mowitz, N. Bonardel, O. Aerts and M. Bruze (2018). Allergic contact dermatitis caused by isobornyl acrylate in OmniPod, an innovative tubeless insulin pump. Contact Dermatitis 79(2): 76-80.

Detailed study summary and results (excerpts from the original study report):

The study reports four cases of allergic contact dermatitis caused by OmniPod insulin pump (Insulet Corporation, Billerica, Massachusetts). The cases are reproduced as described in the paper (Raison-Peyron et al., 2018). All four cases reacted positively in patch tests with different concentrations of IBOA as shown in Table 8 below.

Table 8: Patch test results in all 4 cases of allergic contact dermatitis caused by the OmniPod insulin pump.

	Case 1	Case 2	Case 3	Case 4
IBOA 0.1%	+	++ (Figure 2)	+	++
IBOA 0.05%	+	++	+	+ (0.032% Ac.)
IBOA 0.01%	-	?	-	?
Other positive tests (D3 or D4 unless otherwise stated)	*Myroxylon pereirae* +	*Myroxylon pereirae* + 2-HEA 0.1% pet. ++ EA 0.1% pet. + (D7) 2-HEMA 2% pet. ++ (D7)		Nickel sulfate 5% pet. + Ac. extract of the OmniPod patch +
Patch test with a small piece of the OmniPod adhesive	-	-	- (FreeStyle Libre adhesive also negative)	- (FreeStyle Libre adhesive also negative)

Ac, acetone; D, day; EA, ethyl acrylate; 2-HEA, 2-hydroxyethylacrylate; 2-HEMA, 2-hydroxyethylmethacrylate; IBOA, isobornyl acrylate; pet., petrolatum.

"**Case 1:** a 67-year-old woman with diabetes mellitus type 1 diagnosed 12 years previously presented with itchy, red and vesicular plaques and secondary desquamation at the application sites of an OmniPod insulin pump, 4 months after she had started using it. She continued using the device for another 10 months while trying to alleviate the symptoms by putting a hydrocolloid dressing between the adhesive part of the pod and her skin. However, the skin eruption persisted and had to be regularly treated with topical corticosteroids.

Case 2: 48-year-old woman with type 1 diabetes mellitus diagnosed 10 years previously was referred for localized, pruritic dermatitis at the application sites of an OmniPod insulin pump that she had used for 2 years; skin problems started after she had used the pump for 1 year. In spite of the use of a hydrocolloid dressing between the adhesive of the pod and the skin, eczema persisted, requiring the intermittent application of topical corticosteroids. Interestingly, this patient later also showed eczematous skin reactions to the FreeStyle Libre glucose sensor, which she had previously tolerated, having used this device only on an irregular basis. The patient later reported that, a few years previously, she had applied long lasting nail polish without observing any reaction. Positive patch test reactions to isobornyl acrylate 0.05% and 0.1% pet. on day 3 (case 2).

Case 3: A 16-year-old girl, with type 1 diabetes mellitus diagnosed 1 year previously, consulted with localized, pruritic and erythematous dermatitis at the application sites of an OmniPod insulin pump that she had used for 2 months. This dermatitis occurred after the first use of this system. The patient's history showed that […]this patient had experienced contact dermatitis caused by the FreeStyle Libre glucose sensor, after using it for 6 months, leading to discontinuation of its use.

These patients were patch tested on the back with allergens from the European baseline series and a plastics and glues series (Chemotechnique, Vellinge, Sweden), with IQ Ultra Chambers (Chemotechnique). Patch testing was also performed with an inhouse (meth)acrylate series, consisting of 13 (meth)acrylates supplemented with IBOA, […] patch tested at 0.01%, 0.05% and 0.1% pet.; additionally, a small piece of the adhesive from the OmniPod device was patch tested "as is". All patch tests were occluded for 2 days with Oper tape (Iberhospitex, Innovative Health Technologies,Barcelona, Spain) and read on day (D) 2 and D3. The patient was instructed to observe the patch tested area until D7, and to contact the department if any new reactions appeared.

Case 4: 34-year-old woman was referred with an itchy rash at the application site of her OmniPod pump. She was diagnosed with diabetes mellitus 11 years previously, but had no previous history of dermatitis. She had started to use the FreeStyle Libre glucose sensor in April 2015, and the OmniPod pump in August 2015. In October 2015, she developed an itchy rash at the site of the FreeStyle Libre sensor, and she switched to a Dexcom G4 Platinum glucose sensor (Dexcom, San Diego, CA, USA), which she tolerated. However, in spring 2016 she developed an itchy rash at the site of the OmniPod application site. She tried to alleviate the dermatitis with topical corticosteroids and the use of adhesive tape under the device. On examination, dermatitis corresponding to the application areas of the insulin pump was documented.

Patch tests were applied on the back with 8-mm Finn Chambers (Smart Practice, Phoenix, Arizona), and fixation with Scanpor tape (Norgesplaster, Vennesla, Norway). Patch test preparations were supplied by Chemotechnique. Patch tests, applied for 2 days and read on D3 and D7, were performed with the Swedish baseline series, the department's extended baseline series, and an acrylate series. Additionally, the patient was tested with the adhesive patch from the OmniPod pump "as is", and with an ultrasonic bath extract of the patch in acetone. Later, this patient was additionally tested with the adhesive patch from FreeStyle Libre "as is", with an ultrasonic bath extract of the latter in acetone, and with a dilution series of IBOA in acetone ranging from 0.1% (wt/vol) to 0.00000032% (wt/vol). Because of the severity of the dermatitis, the OmniPod insulin pump eventually had to be replaced with another brand (Animas Vibe pump; Animas Corporation, West Chester, Pennsylvania), after which the dermatitis resolved.

In the analyses of two OmniPod devices (1 used and 1 unused) from case 3, possible traces of IBOA were seen in the patch from the unused OmniPod, but not in the patch from the used one. However, higher amounts of IBOA were found in both OmniPod units (with the patches removed). The concentrations of IBOA in these extracts correspond to total amounts of approximately **5 µg** in the used unit and **40 µg** in the unused unit. In the extract of the adhesive patch from case 4, small amounts of IBOA, **corresponding to a total of ~5 µg in the patch**, were observed. The concentration of IBOA in the extract from the OmniPod unit (from which the patch was removed) corresponded to a total amount of **190 µg in the unit**. The analysis of the dismantled OmniPod showed the presence of IBOA only in parts from the inside of the unit, containing electronics, the delivery pump, and the connection between the pump and the cannula. Manufacturers of OmniPod and FreeStyle Libre refused to give any information about the exact composition of the adhesives or other materials contained in these medical devices […]".

Conclusion by the DS: In this study, the authors describe four cases of allergic contact dermatitis that were highly likely to be caused upon using IBOA containing insulin pumps. All patients reacted positively to patch tests with different concentrations of IBOA. High amounts of IBOA have been detected in parts of the medical device and could be the culprit sensitizer in medical devices used by diabetic patients.

1.1.3 **Other data**

Kanerva and co-workers report the case of a woman working in the production of car rearview mirrors and exposed to different glues, one containing the known skin allergens IPDI and MDI and another containing inter alia 61.9% IBOA, but also other (meth)acrylates. After six years on the job, she developed a dry and fissured dermatitis on fingers III and IV of both hands. The dermatitis later spread to fingers I and II, and she also developed slight dermatitis on her palms. She started to use protective gloves regularly only after the dermatitis had started. The dermatitis also spread to the lower arms, chest, neck and face, and she developed rhinitis and tenderness of the mucous membranes of the nose. She also had paresthesia of the fingertips and gastrointestinal complaints. On sick leaves her dermatitis cured but relapsed immediately at work, i.e., after the 1st working day. When patch-tested, the patient gave a strong reaction to the (meth)acrylate glue, however, she did not react to a dilution series of 0.1, 0.032, and 0.01% IBOA. Therefore this study cannot be used for the classification of IBOA as a skin sensitiser (Kanerva et al., 1988).

Some other studies in which acrylate-containing glues used to affix glucose sensors to the skin were tested showed that these glues can cause skin sensitisation (Table 9). Nevertheless, since it was unknown whether these glues contained IBOA (and, if so, how much) these reports cannot be used for classification. Thus, the DS did not further consider these studies in the overall assessment.

Table 9: Summary table of other studies that include acrylate glues of the medical devices or occupational exposure

Test substance,	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
Sensor adhesive tape containing acrylates	Continuous glucose monitoring (CGM) by young children with type 1 diabetes (T1D) 169 children with T1D between the ages of 1 and 9 years who wore a CGM device daily. Problems related to skin irritation	Skin rashes were reported related to the CGM adhesive	(Englert et al., 2014)
Adhesive containing acrylates	Medical devices for diabetes treatment such as the continuous glucose monitoring systems (CGM) in practice: rashes, itching, site reactions	Skin reactions were reported related to the CGM adhesive	(Heinemann and Kamann, 2016)

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