the Patch Tester

Contact Dermatitis | Haptens | Patch Testing

Edition #8
September 2021

THE HAND ISSUE

"The Patch Tester" is a quarterly e-magazine from Chemotechnique to the Patch Testers of the world.

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PURPOSE

The Patch Tester is an e-mag developed by Chemotechnique to serve as an information resource for all Patch Testers and other Dermatologists around the world; not just in Sweden, or Europe, or America, but wherever the English language can be read and understood. This eighth issue comprises thirty-eight pages with various different topics and features. Ultimately, we plan for The Patch Tester to become the forum for all of us to communicate and cooperate, in all directions.

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ACKNOWLEDGEMENTS

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Photo-assessment for Day 7 Reading of Patch Test Reactions

The recent COVID-19 pandemic has greatly accelerated the adoption of telemedicine and distance consultations, including in Dermatology. However. Patch Testing is 100% an *in vivo* test that cannot be replaced even temporarily by *in vitro* tests. In contrast, *in vivo* skin prick tests can be replaced by laboratory-based *in vitro* s-IgE tests for the identification of Type I allergens.

Telemedicine is already widely used within dermatology, and diagnoses based on photos as compared to clinical assessments have been shown to be acceptable from a dermatological as well as technical perspective, and the use of self-forwarded photos has already been suggested for other dermatological diseases.

One of the aspects of patch testing that could theoretically be replaced is the evaluation of any late-phase reactions whereby the clinic visit, and the examination, could theoretically be replaced by digital photography by the patient.

A recent study published in the May issue of CONTACT DERMATITIS has evaluated this concept of employing digital photography by the patient to replace a clinical examination at or after D7.

Value of photo assessment in late patch test readings – A multicenter study from six European patch test clinics
by Yasemin T. Yüksel, et al.
in CONTACT DERMATITIS, Volume 84, Issue 5, pp 283-289
Also published as https://doi.org/10.1111/cod.13736.

It is generally recommended that patch test readings include a day (D)7 reading.
Substitution of the D7 reading with a photo may be a valid option.
The purposes of the study were:

1. To compare the sensitivity of digital photos at D7 to clinical readings,
2. To assess the number of positive reactions appearing at D7 only (late reactions),
3. To assess the number of positive reactions appearing after D7 only (delayed reactions).

In this study, patients patch tested in six European clinics were instructed to forward photos of the patch test reactions to the respective clinics at D7 (before attending the clinic) and at D21.
Only haptens in the (European) Baseline Series or TRUE Test were included in the data analysis.
The key findings of the study were:

1. Two hundred ninety-three of 629 patients had a total of 599 positive reactions, with 6.3% occurring at D7 only.
2. When substituting the D7 reading with a photo (90% submitted), 26.3% of late reactions were missed and nine false-positive reactions were found.
3. Delayed reactions were detected in four patients at D21 (65.3% submitted).

Patch testing is a necessary diagnostic tool for identification of contact allergies. Attempts to substitute the test procedure by para-clinical methods have not been successful, and patch testing remains the absolute gold standard for the diagnosis of allergic contact dermatitis. According to

recent guidelines for diagnostic patch testing by the European Society of Contact Dermatitis, readings should ideally be performed three times: day (D)2, D3 or D4, and around D7, thus requiring the attendance by the patient at four different visits.

Several studies have previously confirmed the importance of the D7 reading to detect late reactions, which would otherwise be missed, in particular for diagnosing contact allergy to allergens such as neomycin and topical corticosteroids, but reactions to other haptens may also be discovered at D7 only. However, absence from work due to patch testing may be inconvenient or stressful for the patient.

Smartphones taking digital photos are available for most patients today and forwarding photos of the test areas on the patient's back to the patch test clinic by the patient could be a valid option to substitute the D7 reading at the clinic. However, validation of substitution of a clinical reading by a digital photo is lacking.

Reactions appearing after D7 and typically 2–3 weeks after application of patch tests, often referred to as "delayed reactions", may indicate active sensitisation by the test procedure, although that is probably not always the case. Delayed reactions are assumed to be very rare; however, studies exploring this area and systematically investigating numbers of delayed reactions after patch testing are few.

The replacement of the D7 reading by a photo comprises advantages for both the patient and the patch test clinic. Because the patients traditionally are required to attend the patch test clinic up to four times during a patch testing procedure, one appointment less with required attendance would be timesaving and prevent the patients from further work absence, and may also be particularly valuable for patients with long travel time to the clinic. Affected quality of life (QoL) and stress are well-known issues among patients with dermatitis. It is anticipated that fewer appointments at the patch test clinic may prevent further distress for patients. Moreover, the reduction of visits at the patch test clinic may give more time for the personnel to care for other patients and diminish costs.
In this study, the authors aimed to evaluate the sensitivity of assessing patch test reactions by digital photos taken on D7 compared to clinical readings. In addition, they assessed the number of positive patch test reactions discovered at D7 only, and the frequency of delayed positive reactions appearing after D7 only, the latter verified by digital photos taken by the patient and forwarded to the patch test clinic on D21.

The study was a prospective multicentre study comprising six European patch test clinics performed within the European Environmental and Contact Dermatitis Research Group (EECDRG).
The following chambers were used in the clinics:

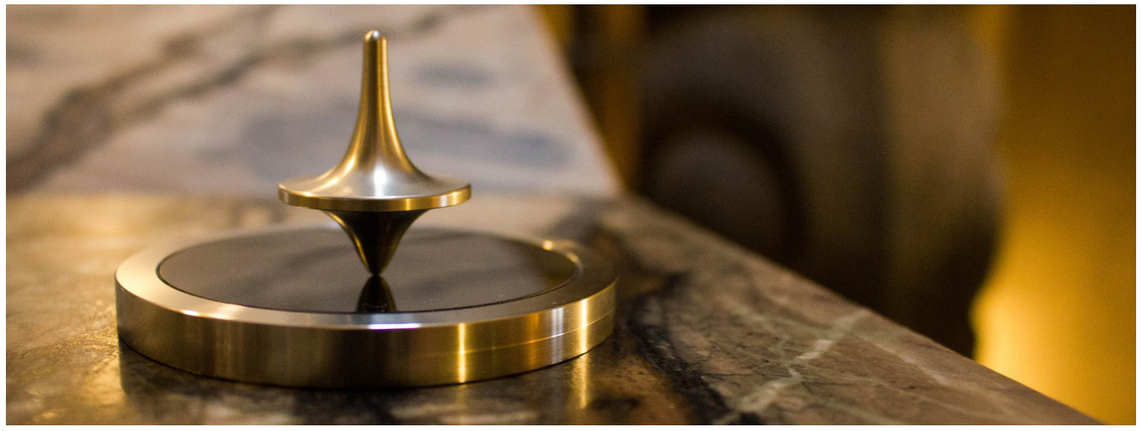
1. IQ Ultimate (Chemotechnique MB Diagnostics AB, Vellinge, Sweden),
2. Finn Chambers 8 mm (Epitest, Tuusula, Finland) on Scanpor tape (Norgeplaster, Oslo, Norway)
3. allergEAZE clear (Smartpractice Europe, Greven, Germany),
4. Al test (Euromedical, Calolziocorte, Italy).

Patch testing was performed according to the standard procedure in the respective patch test clinics with a clinical D7 reading being mandatory.

The reaction was considered a "late reaction" if it was positive at D7 only, not being doubtful or positive before D7, whereas a positive reaction appearing only after D7 was classified as a "delayed reaction" and evaluated by photo on D21.
A total of 629 patients from six patch test clinics in Europe were included in the study.
Two hundred ninety-three patients (46.6%) had a total of 599 positive patch test reactions to the European Baseline Series with minor national modifications, or TRUE Test.

There were a number of interesting findings and observations:

- Fifty-three per cent of these patients were positive to two or more allergens.
  Thirty-five patients (5.6%) had a reaction at D7 only, comprising 38 positive reactions (6.3% of all positive reactions).
- Digital photos were received at D7 from 566 patients (90.0%).
- This is the first study to compare digital photos of patch test reactions taken at D7 with clinical readings.
- A total of 6.3% late reactions on D7 only were found, underscoring the importance of maintaining a D7 reading.
- The data show that by replacing the clinical examination on D7 with a digital photo, 26.3% of late reactions corresponding to only 1.7% of all positive reactions were missed.
- Delayed reactions after D7 were identified in 4 of 411 photos received at D21, indicating that delayed reactions to European Baseline Series or TRUE Test are rare.
- A D7 photo reading would pick up 73.7% of all late reactions and could be considered for patients who may be prevented from attending the patch test clinic on D7.
- However, 26.3% of late reactions were missed by photo assessment.
- If a positive reaction at D7 is identified by photo, a visit to the patch test clinic should follow to verify the reaction and identify the causative allergen. In our study, the reactions not seen on photos but detected at the clinical reading were primarily weak (+) reactions, indicating that these reactions may be difficult to identify by photo, when camera quality and/or lighting is suboptimal, and likewise false-positive late reactions may occur, although infrequently.
- In a study by Grey et al exploring the utility of tele-dermatology in relation to patch testing, the majority of the failed photographic assessments were false-positive reactions. The false-negative and false-positive photographic assessments underscore the necessity of the patients' attendance in the patch test clinics.
- A high submission rate for the D7 photo is essential. In the present study, 90% submitted a photo (with 11.3% receiving help from the health care personnel), and with anticipation that the photo reading at D7 is used preferably by patients who wish to avoid an in-person appointment at the clinic on D7, the submission rate could be even higher.
- In this study, 6.3% of all positive reactions were found on D7 only, comprising nickel, formaldehyde, cobalt, gold, and budesonide as the most frequent causative allergens, which is in accordance with previous findings.
- Other studies have also found similar results: Van Amerongen et al found 13.6% new positive reactions on D7 in patients tested with allergens from the European Baseline Series, TRUE Test, and additional unspecified allergens chosen by the investigator through a 10-year period.
- Cantwell et al found approximately 30% new positive reactions on D7 in 411 patients tested with multiple series. Madsen et al reported 4.4% new positive reactions on D7 in patients with hand eczema who were tested with TRUE Test only.
- In this study, delayed reactions (>D7), delayed reactions were identified in 1% only.
  The number of delayed reactions is anticipated to be associated with some uncertainty, since photos were submitted from only 65.3% of the patients, and a clinical examination was not performed to confirm the reactions. Therefore, it cannot be precluded that some reactions may have been missed. The magnitude of the problem regarding delayed reactions seems to be rare. Also, it is not correlated to one or more specific allergens.
- If the D7 reading is not performed, 6.3% of positive reactions from the baseline series would be missed.
- If substituting the D7 reading by digital photo, 26.3% late reactions would be missed.
- Therefore, forwarding a digital photo at D7 may be an opportunity for patients having difficulties with attending the clinical D7 reading.



SPIN Factor for haptens in various International and National Series, and compared to TRUE Test®

The Significance-Prevalence Index Number (SPIN) of the recent NACDG paper gives a very clear illustration of which haptens are important to be included in any screening series. The SPIN not only indicates the prevalence/frequency of the hapten but also the strength/potency of the sensitisation that the particular hapten can invoke.

At the one extreme is of course MI and MI/MCI (SPIN Factors 763 and 565 respectively) which are not only frequently encountered but also are extremely strong sensitisers, thereby resulting in an extremely high SPIN factor. Towards the other end of the scale (in the NACDG Patch Test Results for 2017/8) is Black Rubber Mix, which attained a SPIN Factor score of just 21. It can be inferred that MI + MCI/MI is approx. 30 times more important as a hapten than Black Rubber Mix.

It is therefore revealing to see in a table the SPIN Factor values of the named 70 haptens, compared to the constituents of some important screening series. This 10-variate table is shown below.

The various Series 2 – 9 are based upon data from the Chemotechnique website (2021):

SPIN Factor (70 tests)
International Comprehensive Baseline Series (80 tests)
North American Comprehensive Series (80 tests)
American Core 2021 Series (90 tests)
North American Series (50 tests)
International Standard Series (30 tests)
European Comprehensive Baseline Series (43 tests)
British Standard Series (50 tests)
Swedish Baseline Series (29 tests)
TRUE Test® (35 tests).

The table shown on the next pages can be **<u>downloaded as an Excel file here.</u>**

Various inferences, indications and conclusions can be drawn from this comparison.

- The SPIN panel of 70 haptens is by no means an exhaustive list of clinically interesting haptens, as there are many that feature in numerous international and national series that are not present in the SPIN Top 70; for example: Textile Dye Mix, Disperse Yellow 3, Mercapto Mix, and many others.

- The North American Comprehensive Series (NAC-80) of 80 haptens appears identical to the International Comprehensive Baseline Series (ICB-1000) according to the data from the Chemotechnique website.

- There are several haptens represented in different concentrations. These are most usually identified by the suffix A, or B or C etc in the Chemotechnique hapten code.
  For example: Mercapto Mix is present as Mx-05A in 2% and Mx-05B in 1% or Mx-05C in 3.5% concentration. Also, Formaldehyde is SPIN Rank 7 with SPIN Factor 220 at 2.0% concentration and is also at SPIN Rank 12 with SPIN Factor 166 at 1% concentration.

- The very new American Core Series from early 2021 includes 28 new haptens, of which only a very few are present in any other screening series. This American Core Series could be considered to be the latest state-of-the-art of patch test screening panels.

- Of the 150 haptens and mixes described as constituents of any of these 10 Series, 146 out of 151 are currently available in the Chemotechnique hapten range, out of approx. 550 different haptens and mixes available in total from Chemotechniques.

- There is a great convergence between the European Baseline Series and the British Standard Series, though many of their haptens are not in the SPIN Top 70 and so may be of reduced clinical interest.

- TRUE Test hapten concentrations on their chamber strips cannot be equated to the percentage concentrations for the petrolatum-based or liquid-based haptens of the operator-loaded patch test systems such as Chemotechnique.

- The Swedish Baseline Series comprises just 29 haptens, which would seem to be distinctly inadequate when measured against the various other screening series in number of haptens, and also lacking some high-ranking haptens including the top 4, and 13 of the top 20.

- The TRUE Test screening system is also low in number of haptens at 35 and also lacking 10 of the top 20 ranked haptens. It also has 8 of its 35 haptens which are not even ranked in the SPIN Top 70, and so will be of little clinical interest, thus further reducing the clinical value of the test system.

- The TRUE Test was originally, approx. 35 years ago, based on the European Series of that time. Although changes have been made and the test system has been developed over the years, there is now a great divergence from the current European Baseline Series, with just 17 of the TRUE Test 35 haptens in common with the European Baseline Series. Regulatory restrictions and cost considerations will continue to greatly inhi bit any further development of the range of haptens in TRUE Test.

- Further information on each of the Series can be found in the Chemotechnique website by clicking on the Chemotechnique code underlined in blue text. From information on each Series, further information can be found on each constituent hapten including Safety Data Sheets and Patient Information Sheets for each hapten.

Comparison table of SPIN factor with constituents of various Screening Series

Significance Prevalence Index Number (SPIN)					International Comprehensive Baseline Series ICB-1000 (80 haptens)	North American Comprehensive Series (NA-80) NAC-80 (80 haptens)	American Core Series 2021 AC-1000 (90 haptens)	North American Series NA-1000 (50 haptens)	International Standard Series IS-1000 (30 haptens)	European Comprehensive Baseline Series ECB-1000 (43 haptens)	British Standard Series (BSCA) GB-1000 (50 haptens)	Swedish Baseline Series SS-1000 (29 haptens)	TRUE Test® (USA) (35 haptens)	Chemotechnique Haptens		
SPIN Rank	Hapten	Concentration	Vehicle	SPIN Factor										Art. No	Concentration	Vehicle
1	MI (METHYLISOTHIAZOLINONE)	0,2%	aq	763	■	■	■	■					■	M-035B	0,2%	Aq.
2	MCI/MI. (200ppm)	0,02%	aq	565	■	■	■	■					■	C-009B	0,02%	Aq.
3	Nickel(II) sulphate hexahydrate	2,5%	pet	363	■	■	■	■	■	■	■		■	N-002B	2,5%	pet.
4	Hydroperoxides of linalool	1,0%	pet	352	■	■	■	■	■	■	■		■	H-031A	1,0%	pet.
5	Fragrance mix I	8,0%	pet	350	■	■	■	■	■	■	■	■	■	Mx-07	8,0%	pet.
6	Myroxylon pereirae resin (balsam of Peru)	25,0%	pet	255	■	■	■	■	■	■	■		■	B-001	25,0%	pet.
7	Formaldehyde	2,0%	aq	220	■	■	■	■	■	■	■		■	F-002B	2,0%	Aq.
8	Propylene glycol	100,0%		201	■	■	■	■	■	■	■		■	P-019B	30,0%	Aq.
9	4-Phenylenediamine (PPD)	1,0%	pet	195	■	■	■	■	■	■	■	■	■	P-006	1,0%	pet.
10	Lanolin alcohol (Amerchol L101)	50,0%	pet	178	■	■	■	■	■	■	■	■	■	A-004	50,0%	pet.
11	Fragrance mix II	14,0%	pet	172	■	■		■	■	■	■	■		Mx-25	14,0%	pet.
12	Formaldehyde	1,0%	aq	166	■	■		■	■	■				F-002A	2,0%	Aq.
13	Propolis	10,0%	pet	163	■	■		■		■	■	■		P-022	10,0%	pet.
14	BIT (Benzisothiazolinone)	0,1%	pet	157	■	■		■		■	■	■		B-003B	0,1%	pet.
15	Carba mix	3,0%	pet	149	■	■	■	■	■	■		■	■	Mx-06	3,0%	pet
16	Bacitracin	20,0%	pet	149	■	■	■	■	■	■	■	■	■	B-032B	20,0%	pet
17	Thiuram mix	1,0%	pet	130	■	■	■	■	■	■	■	■	■	Mx-01	1,0%	pet.
18	Cobalt (ii) chloride hexahydrate	1,0%	pet	124	■	■	■	■	■	■	■	■	■	C-017A	1,0%	pet.
19	Oleamidopropyl dimethylamine	0,1%	aq	121	■	■	■	■	■	■	■	■	■	O-005	0,1%	Aq.
20	Hydroperoxides of Limonene	0,3%	pet	108	■	■	■	■		■	■			H-032A	0,3%	pet.
21	DMAPA (Dimethylaminopropylamine)	1,0%	aq	108										D-053	1,0%	Aq.
22	Quaternium-15	2,0%	pet	108	■	■	■	■	■				■	C-007B	2,0%	pet.
23	Neomycin sulphate	20,0%	pet	106	■	■	■	■	■	■	■	■	■	N-001	20,0%	pet.
24	IPBC (Iodopropynyl butylcarbamate)	0,5%	pet	98	■	■	■	■	■	■	■	■	■	I-008C	0,2%	pet.
25	DECYL GLUCOSIDE	5,0%	pet	89	■	■	■	■		■	■			D-065	5,0%	pet.
26	CINNAMAL	1,0%	pet	89	■	■	■	■						C-014	1,0%	pet.
27	2-HEMA (Poly(2-hydroxyethyl methacrylate)	2,0%	pet	82	■	■	■	■		■	■			H-010	2,0%	pet.
28	Tixocortol-21-pivalate	1,0%	pet	75	■	■	■	■	■				■	T-031A	1,0%	pet.
29	Sodium metabisulfite	1,0%	pet	75	■	■	■	■		■	■			S-011	1,0%	pet.
30	1,3-Diphenylguanidine	1,0%	pet	75	■	■	■	■						D-022	1,0%	pet.
31	Lauryl glucoside	3,0%	pet	73										---		
32	Ylang-ylang oil	2,0%	pet	68	■	■	■	■						Y-001	2,0%	pet.
33	Colophonium (rosin)	20,0%	pet	66	■	■	■	■	■	■	■	■	■	C-020	20,0%	pet.
34	COCAMIDOPROPYL BETAINE	1,0%	aq	61	■	■	■	■						C-018	1,0%	Aq.
35	Compositae mix	6,0%	pet	54	■	■	■	■						Mx-29A	5,0%	pet.
36	Amidoamine	0,1%	aq	51	■	■	■	■						A-029	1,0%	Aq.
37	Ammonium persulfate	2,5%	pet	50										A-011	2,5%	pet.
38	Benzophenone-4	10,0%	pet	47										H-023C	2,0%	pet.
39	Melaleuca alternifolia (tea tree leaf oil), oxidised	5,0%	pet	45	■	■	■	■						T-035B	5,0%	pet.
40	DIAZOLIDINYL UREA (Germall II)	1,0%	pet	44	■	■	■	■	■				■	D-044C	1,0%	pet.
41	Potassium dichromate	0,25%	pet	42	■	■	■	■					■	P-014B	0,25%	pet.
42	Lidocaine HCl	15,0%	pet	41	■	■	■	■						L-002B	15,0%	pet.
43	Bronopol (2-Bromo-2-nitro-1,3-propanediol)	0,5%	pet	39	■	■	■	■					■	B-015B	0,5%	pet.
44	Disperse dye mix	5,6%	pet	38										---		
45	Ethyl acrylate	0,1%	pet	37	■	■	■	■						E-004	0,1%	pet.
46	DMDM HYDANTOIN (Germall II)	1,0%	pet	36	■	■	■	■						D-047B	1,0%	pet.
47	Tocopherol (DL-α-tocopherol)	100,0%		34	■	■	■	■						T-036	100,0%	
48	Methyl methacrylate	2,0%	pet	31	■	■	■	■						M-013	2,0%	pet.
49	Cocamide DEA	0,5%	pet	30	■	■	■	■						C-019	0,5%	pet.
50	Bisphenol A epoxy resin	1,0%	pet	30	■	■	■	■	■	■	■	■	■	E-002	1,0%	pet.
51	Mixed dialkyl thioureas	1,0%	pet	30	■	■	■	■						Mx-24	1,0%	pet
52	Benzophenone-3 (oxybenzone)	10,0%	pet	29	■	■	■	■						H-014C	10,0%	pet.
53	MDBGN/PE (Euxyl K 400)(Methyldibromo glutaronitrile)	2,0%	pet	29	■	■	■	■		■	■	■	■	D-049E	0,5%	pet.
54	Budesonide	0,1%	pet	28	■	■	■	■					■	B-033A	0,1%	pet.
55	Paraben mix	12,0%	pet	26	■	■	■	■					■	Mx-03A	12,0%	pet
56	Mentha piperita oil / peppermint oil	2,0%	pet	26			■							P-036	2,0%	pet.
57	4-tert-Butylphenol formaldehyde (PTBP)	1,0%	pet	25	■	■	■	■	■	■	■	■	■	B-024	1,0%	pet.
58	Imidazolidinyl urea	2,0%	pet	22	■	■	■	■	■	■	■		■	I-001A	2,0%	pet.
59	Carvone	5,0%	pet	22			■							C-035	5,0%	pet.
60	Chlorhexidine digluconate	1,0%	aq	22			■							C-005	0,5%	Aq.
61	Black Rubber mix	0,6%	pet	21									■	Mx-04	0,6%	pet.
62	Ethylenediamine dihydrochloride	1,0%	pet	20	■	■	■	■					■	E-005	1,0%	pet.
63	Tosylamide formaldehyde resin (Toluenesulphonamide)	10,0%	pet	19	■	■	■	■						T-010	10,0%	pet.
64	Sesquiterpene lactone mix	0,1%	pet	18	■	■	■	■	■	■	■	■	■	Mx-18	0,1%	pet
65	CHLOROXYLENOL (PCMX)	1,0%	pet	13	■	■	■	■	■	■	■	■	■	C-010B	1,0%	pet.
66	Benzocaine	5,0%	pet	13	■	■	■	■						B-004	5,0%	pet.
67	2-Mercaptobenzothiazole	1,0%	pet	12	■	■	■	■					■	M-003B	1,0%	pet.
68	Ethylhexylglycerin	5,0%	pet	8										---		
69	N-octylisothiazolinone	0,03%	pet	6										---		
70	Hydroquinone	1,0%	pet	5										H-007	1,0%	pet.
	2-BROMO-2-NITROPROPANE-1,3-DIOL									■	■			B-015B	0,5%	pet.
	2-Mercaptobenzothiazole (MBT)									■	■			M-003A	2,0%	pet.
	2-n-Octyl-4-isothiazolin-3-one				■	■				■	■			O-004	0,1%	pet.
	2-tert-Butyl-4-methoxyphenol (BHA)				■	■								B-022	2,0%	pet.
	3-(Dimethylamino)-1-propylamine						■							D-053	1,0%	Aq.
	BENZALKONIUM CHLORIDE						■							B-027	0,1%	Aq.
	BENZOIC ACID						■							B-005	5,0%	pet.
	BENZOPHENONE-4						■							H-023C	2,0%	pet.
	Benzoylperoxide				■	■								B-007	1,0%	pet.
	BENZYL ALCOHOL				■	■								B-008B	10,0%	sof.
	BENZYL SALICYLATE				■	■								B-010B	10,0%	pet.
	BHT (Butylated Hydroxytoluene)						■							D-006	2,0%	pet.
	Black Rubber mix											■		Mx-04	0,6%	pet.
	Budesonide								■	■		■		B-033B	0,01%	pet.
	Caine mix II											■		Mx-13	10,0%	pet.
	Caine mix III									■	■		■	Mx-19	10,0%	pet.
	Carmine						■							---		
	CETEARYL ALCOHOL						■				■			C-033	20,0%	pet.
	CHLORHEXIDINE DIGLUCONATE						■							C-005	0,5%	Aq.
	CHLOROXYLENOL (PCMX)										■			C-010A	0,5%	pet.
	Clobetasol-17-propionate				■	■								C-028	1,0%	pet.
	Compositae mix II (2.5%)									■	■			Mx-29B	2,5%	pet.
	Compositae mix II (5.0%)				■	■		■	■					Mx-29A	5,0%	pet.
	Desoximetasone				■	■								D-057	1,0%	pet.
	DIAZOLIDINYL UREA (1.0%)								■	■	■			D-044A	2,0%	pet.
	DIAZOLIDINYL UREA (2.0%)											■		D-044B	2,0%	Aq.
	Dibucaine hydrochloride				■	■								D-005B	2,5%	pet.
	Disperse Blue 106												■	D-040	1,0%	pet.
	Disperse Blue mix 106/124				■	■		■			■			Mx-26	1,0%	pet.
	DISPERSE ORANGE 3				■	■								D-032	1,0%	pet.
	Disperse Yellow 3				■	■								D-036	1,0%	pet.
	ETHYL CYANOACRYLATE													E-023	10,0%	pet.
	Ethyleneurea, melamine formaldehyde mix				■	■								Mx-16	5,0%	pet.
	ETHYLHEXYL METHOXYCINNAMATE						■							E-019C	10,0%	pet.
	ETHYLHEXYL SALICYLATE				■	■								O-007A	5,0%	pet.
	ETHYLHEXYLGLYCERINE						■							E-027	5,0%	pet.
	Fucidic acid sodium salt				■	■					■			F-003	2,0%	pet.
	GLUTARAL				■	■		■						G-003B	0,5%	pet.
	GLYCERYL THIOGLYCOLATE				■	■								G-004	1,0%	pet.
	Gold(I)sodium thiosulphate dihydrate (0.5%)				■	■							■	G-005A	0,5%	pet.
	Gold(I)sodium thiosulphate dihydrate (2.0%)						■							G-005B	2,0%	pet.
	Hydrocortisone-17-butyrate						■						■	H-021B	1,0%	pet.
	Hydroperoxides of Limonene						■			■	■			H-032B	0,2%	pet.
	Hydroperoxides of Linalool						■			■	■			H-031B	0,5%	pet.
	HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE				■	■	■		■	■	■			L-003	5,0%	pet.
	ISOAMYL p-METHOXYCINNAMATE				■	■								I-009	10,0%	pet.
	ISOPROPYL MYRISTATE				■	■								I-003	20,0%	pet.
	Jasmine absolute						■							J-002	2,0%	pet.
	LANOLIN ALCOHOL								■	■	■			W-001	30,0%	pet.
	LAURYL POLYGLUCOSE						■			■				L-004	3,0%	pet.
	Lavender absolute													L-001	2,0%	pet.
	Lichen acid mix											■		Mx-15	0,3%	pet.
	Mercapto mix (1%)				■	■	■						■	Mx-05B	1,0%	pet.
	Mercapto mix (2%)									■	■			Mx-05A	2,0%	pet.
	Mercapto mix (3.5%)								■			■		Mx-05C	3,5%	pet.
	METHYLDIBROMO GLUTARONITRILE								■		■			D-049A	0,3%	pet.
	MI/MCI (0.01%)						■							C-009A	0,01%	Aq.
	MI/MCI (0.22%)								■			■		C-009E	0,22%	Aq.
	N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)								■	■	■			I-004	0,1%	pet.
	Nickel (II) sulphate hexahydrate									■	■	■		N-002A	5,0%	pet.
	p-CHLORO-m-CRESOL						■				■			C-008	1,0%	pet.
	Paraben mix									■	■	■		Mx-03C	16,0%	pet.
	Parthenolide												■	P-029	0,1%	pet.
	Peru Balsam										■	■		B-001	25,0%	pet.
	Phenol formaldehyde resin (PFR2)								■			■		P-005	1,0%	pet.
	PHENOXYETHANOL						■							P-025	1,0%	pet.
	Polymixin B sulphate						■							P-026	5,0%	pet.
	POLYSORBATE 80				■	■								P-013	5,0%	pet.
	Potassium dichromate									■	■	■		P-014A	0,5%	pet.
	Pramoxine hydrochloride						■							P-039	2,0%	pet.

Hand Sanitiser Haptens

Tocopherol / Propylene Glycol / Cetyl Stearyl Alcohol

Allergenic Ingredients in Health Care Hand Sanitisers in the United States
By Lindsey Voller, et al.
in DERMATITIS, Volume 32, Issue 3, May/June 2021, pp 151-159.

Health care workers with occupational contact dermatitis often attribute their symptoms to frequent use of alcohol-based hand sanitisers. However, ingredient lists are difficult to obtain, and safe alternatives typically must accommodate brands utilised by a particular hospital system.

The aims of this study were to investigate allergenic ingredients present within health care hand sanitizers and to provide a comprehensive product list to assist with hapten avoidance.

- Five major hospitals in Minnesota and 20 hospitals across the United States were called to obtain a product list.
- The National Library of Medicine's DailyMed Web site was searched to retrieve ingredients.
- Ingredients were compared with the American Contact Dermatitis Society 2017 Core Allergen Series and cross-reactors.

The most common brands of hand sanitisers included Purell, Ecolab, DebMed, and Avagard.
Active ingredients consisted of:

	Name	%
1.	Ethyl alcohol	85.0%
2.	Benzalkonium chloride	8.8%
3.	Isopropyl alcohol	2.5%

The top 5 allergens were:

1.	Tocopherol	51.3%
2.	Fragrances	40.0%
3.	Propylene glycol	27.5%
4.	Benzoates	25.0%
5.	Cetyl stearyl alcohol	12.5%.

Four sanitisers were free of all American Contact Dermatitis Society haptens. 15 products contained only tocopherol or propylene glycol as haptens.

We identified 19 low-hapten hand sanitisers within the most common brands utilised by US hospital systems. This product list will be useful for patients and health care workers seeking hapten avoidance.

Hand hygiene is of utmost importance in the medical field and is considered the pillar of infection control practiced by hospital systems today. It is critical in preventing the transmission of nosocomial infection as is evidenced by numerous research studies demonstrating a reduction in health care–associated infections when coupled with appropriate hand hygiene.

Although hand washing with traditional soap and water was once considered the criterion standard in hand hygiene, alcohol-based hand sanitisers have since become the primary methodology for hand sanitisation, given their ease of use.

In 1995, the Association for Professionals in Infection Control set forth guidelines endorsing the use of hand sanitisers in regular health care practice. Antimicrobial hand sanitisers or hand rubs typically consist of 60% to 95% alcohols (such as ethyl alcohol or isopropyl alcohol) and primarily exist in the forms of liquids, gels, lotions, and foams.

The convenience and immediate efficacy associated with these products have led to improved hand hygiene compliance within various hospital systems while maintaining the integrity of infection control. The now common adage "foam in, foam out" can be seen at the entrance of many patient rooms in the inpatient wards and outpatient clinical settings alike.

Despite the known benefits of hand hygiene on patient care, skin irritation associated with frequent use of these products can hinder their use. Alcohol-based hand sanitisers may lead to skin dryness and subsequent irritant contact dermatitis (ICD). Though less common, allergic contact dermatitis (ACD) to hand sanitisers has also been reported.

Causative haptens may include inactive ingredients, such as fragrances, propylene glycol (PG), benzoates, and/or the active ingredient itself. Anecdotally, counselling can prove difficult among patients, including health care workers (HCWs), with true contact allergy seeking safe product alternatives; ingredient lists from medical-grade hand sanitisers are often very difficult to obtain and options for safe alternatives may need to accommodate brands already utilised within a particular hospital system.

A 2019 study by Rodriguez-Homs and Atwater investigated haptens present within 100 medical hand skin cleansers, including 42 waterless skin soaps, and identified 11 low-hapten waterless skin soaps based on a textbook publication regarding antiseptics and disinfectants.

We sought to expand upon this research by examining hand sanitisers within the major brands utilised by hospital systems in the United States, thereby serving as a practical guide for patients and HCWs with occupational contact dermatitis requiring avoidance of particular ingredients.

We present a comprehensive list of health care hand sanitisers to assist clinicians, patients, and HCWs with product selection within the constraints of hospital brand adherence.

Five major hospital systems within the Minneapolis/St Paul area and 20 top US hospitals as per 2019 to 2020 US News & World Report Rankings (Best Hospitals Honor Roll) for additional geographic representation were called during July and August 2019. Each institution was asked to provide information on the major brand of hand sanitiser and specific products used within their hospital system. The National Institutes of Health and US National Library of Medicine's DailyMed Web site was subsequently searched to retrieve ingredients for products listed as "hand sanitisers" or "antiseptic hand rubs" under these major brands.

Handwashes, soaps, and surgical scrubs were excluded from the analysis.

Information on major hand sanitiser brands and/or specific products was obtained from 19 (76.0%) of 25 hospitals; 6 hospitals declined to provide the requested information.

The most common brands included Purell by GOJO (52.6%), Ecolab (31.6%), DebMed (10.5%), and Avagard by 3M (5.3%).

Initial DailyMed search yielded 249 products.

Eighty relevant hand sanitisers were included in the final analysis after exclusion of duplicate products, products that did not correspond to the aforementioned brands, hand washes/surgical scrubs, and products advertised for non-hospital use. One chlorhexidine-based product advertised as both a surgical scrub and hand sanitiser was also included (Avagard Surgical and Healthcare Personnel Hand Antiseptic with Moisturisers).

TABLE 1
Summary of Active Ingredients and ACDS Core haptenss Found as Inactive Ingredients in Health Care Hand Sanitisers (July to August 2019)

Active Ingredient,	n	(%)*
Ethyl alcohol	68	(85.0%)
Benzalkonium chloride	7	(8.8%)
Isopropyl alcohol	2	(2.5%)
Chloroxylenol	2	(2.5%)
Chlorhexidine	1	(1.3%)
Triclosan	1	(1.3%)
ACDS core haptens,	**n**	**(%)†**
Tocopherol	41	(51.3%)
Fragrance/parfum	32	(40.0%)
PG	22	(27.5%)
Sodium benzoate	20	(25.0%)
Cetyl stearyl alcohol	10	(12.5%)
Ethylhexylglycerin	9	(11.3%)
Sorbic acid	7	(8.8%)
Alkyl glucosides	5	(6.3%)
Phenoxyethanol	3	(3.8%)
Parabens	2	(2.5%)
Benzophenone-4	1	(1.3%)
Cocamidopropyl betaine	1	(1.3%)

TABLE 2
No and Low-Allergen* Health Care Hand Sanitisers (July to August 2019)

Company	Hand Sanitiser	Hapten (AC-1000)	Art no
No haptens			
DebMed	Alcare Hand Sanitiser Foamed Antiseptic Handrub None	-	
DebMed	Soft 'N Sure Hand Sanitiser Foamed Antiseptic Handrub	-	
EcoLab	Ecocare 350 Hand Sanitiser with Skin Conditioner	-	
GOJO	Purell VF481 Hand Sanitiser Gel	-	
Low allergen*			
GOJO	Purell Advanced Green Certified Hand Sanitiser Foam	Tocopherol	T-036
GOJO	Purell Advanced Green Certified Instant Hand Sanitiser	Tocopherol	T-036
GOJO	Purell Advanced Hand Sanitiser Foam	Tocopherol	T-036
GOJO	Purell Advanced Hand Sanitiser Foam E3 Rated	Tocopherol	T-036
GOJO	Purell Advanced Hand Sanitiser Gel	Tocopherol	T-036
GOJO	Purell Advanced Hand Sanitiser Refreshing Gel (Biobased Content)	Tocopherol	T-036
GOJO	Purell Advanced Instant Hand Sanitiser Fragrance Free	Tocopherol	T-036
GOJO	Purell Advanced Moisturizing Hand Rub Foam/Mousse	Tocopherol	T-036
GOJO	Purell Advanced Skin Nourishing Foam	Tocopherol	T-036
GOJO	Purell Advanced Skin Nourishing Instant Hand Sanitiser With Moisturisers and Vitamin E	Tocopherol	T-036
GOJO	Purell Health Care Advanced Hand Sanitiser Gentle and Free Foam	Tocopherol	T-036
GOJO	Purell Professional Advanced Hand Sanitiser Fragrance Free Foam	Tocopherol	T-036
Ecolab	FaciliPro Hand Sanitiser Gel	Propylene Glycol	P-019
Ecolab	Instant Hand Sanitiser Gel	Propylene Glycol	P-019
Ecolab	Keystone Liquid Hand Sanitiser	Propylene Glycol	P-019

Thirty-nine (48.8%) products were advertised as foams, 26 (32.5%) products as gels, 13 (16.3%) as liquids, and 2 (2.5%) as lotions.

Ingredients and Haptens
A total of 141 ingredients were analysed among the 80 included products. Of these, 14 ACDS core haptens were identified, including their relevant cross-reactors. Health care hand sanitisers had an average of 10.2 ingredients (range, 3–23) and 2.0 ACDS core haptens (range, 0–5) per product.

Table 1 summarises the most common active ingredients and ACDS core haptens found within the analysed products. Main active ingredients included ethyl alcohol (85.0%), benzalkonium chloride (8.8%), isopropyl alcohol (2.5%) and chloroxylenol (2.5%).

Among inactive ingredients containing ACDS core haptens or their cross-reactors, tocopherol (51.3%), fragrance (40.0%), PG (27.5%), benzoates (27.5%), cetyl stearyl alcohol (12.5%), ethylhexylglycerin (11.3%), and sorbic acid derivatives (8.8%) were the most common.

Four products were free of all ACDS core haptens. 15 products contained only 1 core hapten deemed to be of low potency (e.g., tocopherol, PG). Notably, methylisothiazolinone and methylchloroisothiazolinone were not identified in any products.

*Low-hapten hand sanitisers were defined as containing only 1 ACDS core hapten with low potency (alkyl glucosides, cetyl stearyl alcohol, fragrance, and sodium benzoate were excluded).

This study yielded several interesting findings.

1. Health care hand sanitisers possess relatively few haptens as identified by the ACDS 2017 Core Allergen Series, with an average of 2.0 core haptens per product; this finding is consistent with prior reports investigating haptens present in medical hand cleansers.

2. Active ingredients consisted predominantly of alcohols, with few products containing benzalkonium chloride or chloroxylenol as the primary antimicrobial agent.

3. The most common inactive ingredients and likely potential haptens included tocopherol, fragrance, benzoates, PG, and cetyl stearyl alcohol.

4. Finally, 19 no- or low-hapten products were identified as potential safe alternatives for use in the health care setting.

Active Ingredients
The majority of hand sanitisers analysed in this study were alcohol-based, with ethyl alcohol or isopropyl alcohol identified in 87.5% of products. Alcohols are commonly used in hand sanitisers owing to their ability to rapidly denature proteins and decrease bacterial counts on the hands.

Alcohol-based hand sanitisers are effective immediately after application, but their antimicrobial properties lose potency over time; therefore, additional or alternative chemicals, such as benzalkonium chloride, chlorhexidine, or triclosan, can be used to prolong anti-germicidal effects.

Of active ingredients with allergenic potential, contact allergy to alcohols themselves is exceedingly rare.

Benzalkonium chloride
Benzalkonium chloride has previously been considered largely irritant in nature with low sensitisation potential; however, studies are increasingly documenting its allergenicity. Kadivar and Belsito demonstrated that HCWs were significantly more likely to develop relevant allergic reactions to benzalkonium chloride than non-HCWs.

Chloroxylenol
Previously, Warshaw et al found significantly higher rates of allergy to chloroxylenol among HCWs (0.96% of HCWs with patient contact and 0.88% of HCWs without patient contact) as compared with non-HCWs (0.07%). Chloroxylenol was identified in only 2 hand sanitisers in this study, both of which contained additional haptens as inactive ingredients, and we would recommend against these products if seeking low-hapten alternatives.

Inactive Ingredients

Tocopherol
Tocopherol, (or its derivative) was identified in over half (51.3%) of all health care hand sanitisers. Tocopherol is used in products for its moisturising, antioxidant, and anti-aging properties and is often added to hand sanitisers in an effort to reduce skin irritation. Tocopherol is a relatively rare hapten (estimated at only 0.7% of all North American Contact Dermatitis Group [NACDG] patch tested patients in 2015–2016), and to our knowledge, it has not been previously documented as a source of ACD in hand sanitisers. Tocopherol was determined to be of low potency, and products containing only this hapten were categorised accordingly under low-hapten hand sanitisers in Table 2. Until documented cases begin to emerge from their use in the health care setting, hand sanitisers containing tocopherol are likely safe alternatives for patients and HCWs with limited options. However, continued observation for future development of contact allergy to tocopherol is warranted.

Fragrance/Parfum and Sodium Benzoate
Fragrance/parfum (40.0%) and sodium benzoate (25.0%) were the second and fourth most commonly identified haptens in this study, respectively, grouped herein due to their potential for significant cross-reactivity. Fragrance has consistently been one of the most common causes of allergy over the past several years as determined by large epidemiologic studies by the NACDG. Moreover, HCWs may experience some of the highest rates of fragrance allergy among occupational exposures, particularly nurses, due to regular contact with hand washes, antiseptic solutions, and emollient creams. Sodium benzoate and the related chemicals, benzoic acid, and benzyl alcohol, are commonly used as preservatives in personal care products; they can also function as fragrance ingredients and pH adjusters. Patients and HCWs with fragrance sensitivity should avoid all products containing fragrance and potential fragrance cross-reactors to decrease the risk of ongoing or recurrent dermatitis.

For patients and HCWs with irritant dermatitis rather than true contact allergy, fragrance avoidance is also commonly recommended. However, fragrance avoidance is difficult to manage and even more complicated in the setting of HCWs requiring chronic hand washing. Awareness of fragrance-free options is, therefore, critical in maintaining adherence to hand hygiene practices.

Propylene Glycol
Propylene glycol is a colourless emulsifier used in a myriad of products, from topical corticosteroids to pre-packaged foods. Propylene glycol is a controversial hapten, with certain authors suggesting that PG reactions are mostly irritant in nature, whereas others argue for its meaningful clinical relevance in ACD. The frequently weak sensitisation potential of PG led us to group hand sanitisers containing only this core hapten in the “low-hapten” category; however, patients and HCWs with true PG allergy should seek a different alternative.

Cetyl Stearyl Alcohol
Cetyl stearyl alcohol (cetearyl alcohol) is a mixture of cetyl alcohol and stearyl alcohol. It is regularly used as an emulsifier and stabiliser in cosmetics and topical medications. Cetyl stearyl alcohol is a rare hapten, although its allergenic potential has been shown to increase with skin barrier disruption that facilitates its absorption, as in the case of chronic wounds or venous insufficiency. This phenomenon could have implications for HCWs with underlying ICD; we suggest the avoidance of cetyl stearyl alcohol in the setting of severe ICD to prevent unintentional sensitisation. Relevant cross-reactors found in this study included cetyl palmitate and cetyl lactate, ingredients composed of cetyl alcohol and palmitic or lactic acid, respectively.

Ethylhexylglycerin
Ethylhexylglycerin is an emerging synthetic ingredient that possesses dual properties as both an antimicrobial and emollient, a fitting combination for use in health care hand sanitisers. It is also used in various cosmetics, such as sunscreens, moisturisers, and makeup, and has been used as an alternative to parabens. A seemingly infrequent hapten, ethylhexylglycerin demonstrated a prevalence of only 0.29% in the most recent 2015 to 2016 NACDG patch testing cycle. Yet allergy to ethylhexylglycerin may be increasing, particularly from products labelled “hypoallergenic” or “preservative-free.” Routine testing is likely to identify additional cases of allergy to ethylhexylglycerin moving forward.

Other Ingredients
Allergenic ingredients less commonly identified in this study included sorbic acid derivatives, alkyl glucosides, phenoxyethanol, parabens, benzophonone-4, and cocamidopropyl betaine. Although these ingredients have not been associated with contact allergy to hand sanitisers at present, some of these haptens have been responsible for ACD reactions to other medical products with significant clinical relevance. Patients and HCWs with specific sensitivities should practice hapten avoidance of these components if possible.

This study has several limitations.

1. Although hospital systems throughout the United States were called to encompass product preferences across the country, it is possible that major hand sanitiser brands utilised within health care settings were missed due to selection bias; further, contacting middle to lower tier hospitals, rather than the top 20 hospital systems, may have revealed alternative product preferences.

2. The DailyMed website was searched for hand sanitiser products listed under each brand to be inclusive of all potential products used in the health care setting; however, it is possible that new products have emerged, that ingredient lists have changed since products were investigated in the July to August 2019 period, and that this list is non-exhaustive.

3. The ACDS 2017 Core Allergen Series was used to identify haptens; we recognise that additional haptens exist that could elicit contact allergy.

The full unabridged article presents a list of safe product alternatives that should prove useful for dermatologists, their patients, and HCWs seeking hapten avoidance. In addition, for patients and HCWs with irritant reactions rather than true allergy, this list will be valuable in practicing fragrance avoidance as the next potential step in management. Hospital systems are encouraged to utilise this guide to purchase safe product alternatives for their affected employees.

For full information, please read the original article.

Dear Reader, if you have any particular article or book or website that you would like to have reviewed in a future issue of The Patch Tester, then please contact the Editor here.

Acrylic Compounds in Occupational Dermatology

With information derived from the original article….

"Ten Years of Contact Allergy from Acrylic Compounds in an Occupational Dermatology Clinic"

by Kristiina Aalto-Korte et al.
in CONTACT DERMATITIS, Volume 84, Issue 4, March-April 2021, pp 240-246.
Also available online at https://doi.org/10.1111/cod.13739

Acrylic compounds are haptens of current interest due to a large number of patients who are sensitised from nail products and medical devices. There are over 30 commonly used commercial acrylic test substances that are used in varying combinations for different patient groups, but no collectively agreed recommendations for aimed testing exist.

Many anaerobic sealants lack warnings of skin sensitisation and labelling of acrylic compounds although they regularly contain sensitising methacrylates. These cases are not strictly speaking violations of current EU law, because many methacrylates lack a binding harmonised classification as skin sensitiser. However, the major manufacturers of anaerobic glues should take account of increasing clinical dermatological literature on the sensitising capacity of the methacrylates present in their products, and accordingly declare them in the SDSs.
Acrylic compounds used in commercial products are generally rather impure and contain substantial amounts of (meth)acrylates other than the labelled compounds.
Concomitant allergic reactions to several (meth)acrylates are common, especially in strongly sensitised patients, but allergies to just one compound also occur.
Multiple patch test reactions may derive from concomitant exposure, but also from cross-allergy between acrylic monomers. In individual cases it is difficult to assess which of the two alternatives is more probable because data on chemical composition of implicated acrylic products are usually superficial.

In the present situation without accurate exposure data, evaluation of the performance of individual test substances has no solid base. For a patch test recommendation, we ideally want a set of primary haptens truly present in products, and not just cross-reacting substances.
Many patch test clinics screen with 2-hydroxyethyl methacrylate (2-HEMA) in all patients, and recommendations to include this hapten in the baseline series are emerging.
At the Finnish Institute of Occupational Health (FIOH), we routinely pay a lot of attention to our patients' exposure to their patch-test-positive haptens. As a part of a wider "Acrylate Project", we wanted to analyse our patient data for allergic reactions to acrylic compounds in the latest decade (2010–2019), with a focus on exposure data.
This study describes clinical 10-year results of 55 cases with allergic patch test reactions to acrylic compounds in a special clinic of occupational dermatology.

Results
2-HEMA was the most commonly positive test substance together with strongly cross-sensitiSing EGDMA and 2-HPMA. 2-HEMA would have screened all EGDMA- and 2-HPMA-positive cases, but not all cases reacting to other methacrylates: One 1,4-BUDMA allergy from anaerobic glue and one MMA allergy from denture products were among the six 2-HEMA-negative cases with methacrylate reactions.

In the present material, dimethylaminoethyl methacrylate (DMAEMA) reactions were few and always associated with allergic reactions to at least four other methacrylates. We are neither aware of any case reports of ACD due to this compound nor have we seen a sensitised case that has shown exposure to it. At least in occupational settings, it is a candidate for deletion from (meth)acrylate patch test series.

Among the acrylates (esters of acrylic acid), DEGDA was the most commonly positive test substance, and TREGDA was the second most common. 2-HEA together with EA was in the third position. In two recent studies, 2-HEA has been the most commonly positive of all (meth)acrylates. Aromatic urethane diacrylate (ar-UDA) contains PETA. Since 1991 at FIOH, a total of nine patients have tested positive to ar-UDA; all positive to PETA. We have never been able to detect specific exposure to urethane acrylates in patients displaying positive reaction to ar-UDA. Thus ar-UDA does not seem to provide any diagnostic value independent of PETA.

Test substances

In the baseline series, we first screened using triethylene glycol diacrylate (TREGDA) for 8.7 years. It was replaced with diethylene glycol diacrylate [DEGDA; di(ethylene glycol) diacrylate] in August 2018. Then 2-HEMA was added to the baseline series in March 2017.
Test substances were acquired mainly from Chemotechnique Diagnostics (Vellinge, Sweden).
In addition, some in-house preparations were used. During the 10-year period from 2010 to 2019, a total of 426 patients were tested with at least one acrylate series; this corresponded to 37% of all our patch-tested patients. “Acrylate series A” was tested in 395 patients, “Acrylate series B” in 230 patients, and “Acrylate series C” in 183 patients. A total of 31 patients were tested with our previous “(Meth)acrylate series.”

During the study period, a total of 55 patients tested positive to some acrylic compound. All the included 55 patients were tested with “Acrylate series A,” 48 with “Acrylate series B,” and 39 with “Acrylate series C”.

Of the positive haptens, 2-HEMA was the most commonly positive hapten with 21 cases, and 13 of these had specific exposure to HEMA. Eighteen patients tested positive for ethylene glycol dimethacrylate (EGDMA), but we could detect specific exposure in only two of them. 2-Hydroxypropyl methacrylate (2-HPMA) was positive in 16 cases and 5 of these had shown exposure to 2-HPMA.

We diagnosed 31 cases of allergic contact dermatitis (ACD).

- 8 ACD cases were due to anaerobic sealants
- 7 to dental products (dental technicians and assistants)
- 7 to eyelash glues and/or nail products in the beauty sector
- 3 to windscreen glues
- 3 to UV-cured printing inks
- 2 to paints/lacquers
- 1 to a polyester resin system
- The remainder of the cases had contact allergy to acrylic compounds, but we could not find relevant present exposure.

Anaerobic sealants
Industrial glues were the most important cause of contact allergy to acrylic compounds. We had eight clear cases of occupational allergic contact dermatitis (OACD) caused by anaerobic sealants. One of these was a previously reported case caused by 2,2-bis[4-(2-methacryl-oxyethoxy) phenyl] propane (bisphenol A ethoxylate methacrylate; bis-EMA), an epoxy methacrylate.
The other seven cases were patch test positive to methacrylates, most commonly to 2-HPMA, 2-HEMA, and EGDMA. Six of these seven patients also tested positive for their own anaerobic product.

In every case we could show—by information in the SDS, information provided by manufacturer, or by chemical analysis—that a patient’s own anaerobic product contained at least one methacrylate to which the patient tested positive.
In four cases, the SDSs did not have any hazard statement for skin sensitisation, although the glues contained sensitising acrylic monomers according to our chemical analyses.
We saw three other cases, all patch test-positive to DEGDA and/or penta-erythritol tri-acrylate (PETA), who had used anaerobic sealants. We chemically analysed eight of their anaerobic glues for DEGDA and PETA, but we detected only methacrylates. Thus, a relation between the allergic reactions to acrylates and occupational exposure could not be confirmed. All eight analysed anaerobic products were based on methacrylates: All contained triethylene glycol dimethacrylate (TREGDMA), six contained di-EGDMA, and five contained larger ethylene glycol dimethacrylates such as tetra-, penta-, or hexa-EGDMAs.

Dental professions
We had a total of seven cases of OACD in dental professions: comprising four dental assistants, two dental technicians, and one dental hygienist. The two dental technicians had allergic reactions to methyl methacrylate (MMA). Products of the dental technicians were usually MMA-based, but also EGDMA, ethyl methacrylate (EMA), 1,4-butanediol dimethacrylate (1,4-BUDMA), TREGDMA, and urethane methacrylates were mentioned in their SDSs.
One of the dental assistants was sensitised to epoxy acrylates and epoxy resin. She had had work-related facial dermatitis since the year 2000. Epoxy resin oligomer (MW 340) was not detected in her five dental composite resins that contained bisphenol A glycerolate dimethacrylate (bis-GMA) and one also contained bis-EMA. The other four dental assistants/hygienists tested positive to 2-HEMA, a common methacrylate in dental resins.

UV-cured windscreen glues and resins
Windscreens are glued and repaired with UV-cured adhesives or resins. We had three cases caused by these products. All three patients tested positive to 2-HEMA and EGDMA, and two of them also to 2-HPMA. The products contained 2-HEMA and/or 2-HPMA.

Cyanoacrylate glues
From the industrial sector, we had 3 patients with allergic patch-test reactions to ethyl cyanoacrylate (ECA) or ECA-based glues, but these were not clear OACD cases (symptoms were not related to use of instant glues) from the industrial sector.
In the beauty sector, conversely, there were several cases. In addition to a previously reported beautician with OACD from methacrylate impurities in eye lash extension glue, we had seen two ECA-positive hairdressers who had used eyelash extensions in their own eyes and developed eyelid dermatitis. One of them tested positive to her own ECA-based eyelash glue at a 10% concentration (+). Later she developed facial dermatitis when she used the same glue for her clients. The other hairdresser tested strongly positive to ECA (++), but her own glues were not tested. She had developed eyelid dermatitis from several brands of eyelash glue. We also investigated two other beauticians with mild allergic reactions to their own eyelash glues (ECA negative or doubtful). They had eyelid dermatitis related to lash extension use in their own eyes.

Artificial nails
At FIOH, we have had a very low number of artificial nails–related cases compared to recent reports from other European countries. It is possible that structure nails and gel nail polishes are not as popular in Finland as in other countries. A more likely explanation is that, according to Finnish legislation, people working on their own (as do most nail technicians) are not obliged to insure themselves for occupational disease. We cannot investigate entrepreneurs who do not have an insurance.

The number of artificial-nail–related occupational cases was only two. The first of them was a pedicurist who used acrylic nail products in her work. Liquid parts of these products tested positive and contained MMA or 2-HEMA to which the patient was sensitised. The other patient was a beautician sensitised to 2-HEMA in her acrylic nail gel. Her products were analysed and found to contain not only methacrylates (2-HEMA, EGDMA, and EMA) but also relatively high concentrations of acrylates tri(propylene glycol) diacrylate (TPGDA) and PETA. However, the patient did not test positive to these two acrylates but tested positive to 2-HEA, which was detected at a low concentration of 0.53%.

Printing and production of printing inks

Three cases were related to printing. A female pre-press technician with facial and hand dermatitis was widely sensitised to various acrylates including 1,6-hexanediol diacrylate (1,6-HDDA) and to one methacrylate, 1,4-BUDMA. She had handled a cleansing product for a printing roller that was composed of 1,6-HDDA.

A male printer with eyelid dermatitis in wintertime was weakly sensitised to DEGDA. He used UV-cured printing inks. Six products were analysed at FIOH, and five contained oligo-ethylene glycol–based acrylates at concentrations of 1.6% to 87%. Other detected acrylic compounds were trimethylolpropane triacrylate (TMPTA), 1,4-butanediol diacrylate (1,4-BDDA), and 4-hydroxybutyl acrylate. The patient tested negative to TMPTA and 1,4-BDDA.

A male worker in the production of UV-cured inks for silk printing developed dermatitis on the forearms. He was weakly sensitised to TREGDA. Three raw materials for printing inks were declared to contain poly(ethylene glycol) diacrylates at concentrations of 5–100%, and according to the manufacturer one raw material contained TREGDA. TMPTA, 1,6-HDDA, and TPGDA were also among the ingredients, but the patient tested negative to them.

Paints and lacquers

Two cases were related to paints and lacquers. A car painter had work-related hand dermatitis, and he was sensitised to 2-HEMA, 2-HPMA, and EGDMA. Five of his paints were analysed. One paint contained 0.41% 2-HEMA and another paint contained 0.1% 2-HPMA. In addition to these results, 2-HEMA and 2-HPMA were detected in all five paints, but their concentrations were below the limit of quantitation (<0.008%).

A female worker in a parquet flooring plant had atopic dermatitis and work-aggravated hand dermatitis. She was sensitised to TREGDA, DEGDA, and tetra-EGDMA. TREGDA was declared in the SDSs of her three parquet lacquers. In chemical analysis, DEGDA was detected at low concentrations in two lacquers and one UV filler. Other acrylic compounds detected in chemical analyses of five lacquers were DPGDA, hydroxy-butyl acrylate, 1,6-HDDA, TPGDA, TMPTA, 1,6-HDDA, and 2-HPMA.

Anaerobic sealants

Over the years we have seen many methacrylate-allergic patients reacting to anaerobic sealants that lack warning for skin sensitisation. In these cases, we have often analysed the products and without exception detected sensitising methacrylate monomers. In the present material, half of the eight anaerobic-glue–related OACD diagnoses required chemical analyses, as SDSs failed to declare the acrylic compounds to which the patients tested positive. At present, 2-HPMA, TREGDMA, 1,4-BUDMA, and tetra-EGDMA lack harmonised classification as skin sensitisers. In addition, many related derivatives not yet classified might be sensitising. This situation allows manufacturers to classify these chemicals as “not hazardous” in their own safety assessment. “Not hazardous” chemicals are not mentioned in an SDS.

Printing products

UV-cured printing inks are usually based on acrylates and epoxy acrylates, and skin sensitisation is occasionally reported in workers exposed to these products. The present series comprises three cases related to UV-cured printing inks who were sensitised to acrylates. Exposure to either 1,6-HDDA or ethylene glycol-based acrylates could be found matching their allergic reactions (1,6-HDDA, DEGDA, and TREGDA). There are several reports of 1,6-HDDA sensitisation in the printing industry.

Paints and lacquers

Both workers in the manufacture of UV-curable paints, varnishes, lacquers and coatings, and workers using these products are at risk of developing contact allergy to acrylic compounds. In the present series, there was a car painter sensitised to the methacrylates 2-HEMA, 2-HPMA, and EGDMA. Our analyses revealed 2-HEMA (0.41%) and 2-HPMA (0.1%) in his car paints. 2-HPMA still lacks harmonised classification as skin sensitiser, but 2-HEMA is classified as Skin sensitiser 1. The SDSs of these paints did not bear warnings of skin sensitisation. This was not against EU law, as concentrations lower than 1% do not trigger hazard statements for a Skin sens 1 chemical. However, 2-HEMA should at least have been mentioned in the hazardous ingredients (Section 3) in the SDS, because its concentration was higher than 0.1%. This example makes us doubt if the classification of 2-HEMA as Skin sens 1 is strict enough to prevent sensitisation. The Skin sens 1a classification would trigger a hazard statement at 0.1% concentration and listing at 0.01%.

Acrylates in polyester resins

It is known that acrylic monomers, especially methyl methacrylate, can be used as cross-linking agents in polyester resin systems instead of styrene. Our fibre glass worker was rapidly sensitised to 1,6-HDDA that was a crosslinker in her polyester resin. We are not aware of any previous case reports of contact allergy to any acrylic compound from polyester resin systems.

For further information, please read the original article.

Significance-Prevalence Index Number (SPIN)

With information derived from the original article….

North American Contact Dermatitis Group Patch Test Results: 2017–2018

by Joel G. DeKoven, et al.
in DERMATITIS, Volume 32, Issue 2, March/April 2021, pp 111 – 123.

The SPIN is a weighted calculation that, for each hapten, incorporates a composite measure of clinical relevance, combined with prevalence, allowing the identification of “hot haptens”.

It is determined by the following equation:
SPIN = (number of patients allergic / total patients patch tested) × ([1 × percentage with definite clinical relevance] + [0.66 × percentage with probable clinical relevance] + [0.33 × percentage with possible clinical relevance]) × 100.

The SPIN is a weighted calculation depending on prevalence and degree of certainty ascribed to relevance. However, the SPIN does have some analytical drawbacks:

1. It “discriminates” against haptens that typically do not show up on product labels, such as formaldehyde, thus decreasing the count of definite and probable relevant reactions

2. It grants no additional credit to haptens, such as nickel, which have a high percentage of positive patch test reactions with past clinical relevance; given the appropriate exposure, haptens with past relevance can still be a cause of future dermatitis.

A corrected version is used here in this study:

Calculation = (proportion of population allergic) x (1 × Rdefinite + 0.66 × Rprobable + 0.33 × Rpossible) × 100.

Referenced at: Maouad M, Fleischer AB Jr., Sherertz EF, et al. Significance-prevalence index number: a reinterpretation and enhancement of data from the North American Contact Dermatitis Group. J Am Acad Dermatol 1999;41(4):573–576.

Significance - Prevalence Index Number

Rank Hapten	Conc.	Vehicle	SPIN	Rank Hapten	Conc.	Vehicle	SPIN
1. MI	0.2%	aq	763	36. Amidoamine	0.1%	aq	51
2. MCI/MI. (200ppm)	0.02%	aq	565	37. Ammonium persulfate	2.5%	pet	50
3. Nickel sulfate hexahydrate	2.5%	pet	363	38. Benzophenone-4	10.0%	pet	47
4. Hydroperoxides of linalool	1.0%	pet	352	39. Tea tree oil oxidized.	5.0%	pet	45
5. Fragrance mix (I)	8.0%	pet	350	40. Diazolidinyl urea (Germall II)	1.0%	pet	44
6. Myroxylon pereirae resin	25.0%	pet	255	41. Potassium dichromate	0.25%	pet	42
7. Formaldehyde	2.0%	aq	220	42. Lidocaine HCl	15.0%	pet	41
8. Propylene glycol	100%		201	43. Bronopol	0.5%	pet	39
9. 4-Phenylenediamine	1.0%	pet	195	44. Disperse dye mix	5.6%	pet	38
10. Lanolin alcohol (Amerchol L101)	50.0%	pet	178	45. Ethyl acrylate	0.1%	pet	37
11. Fragrance mix II	14.0%	pet	172	46. DMDM hydantoin (Germall II)	1.0%	pet	36
12. Formaldehyde	1.0%	aq	166	47. Tocopherol (DL-α-tocopheroL	100%		34
13. Propolis	10.0%	pet	163	48. Methyl methacrylate	2.0%	pet	31
14. BIT	0.1 %	pet	157	49. Cocamide DEA	0.5%	pet	30
15. Carba mix	3.0%	pet	149	50. Bisphenol A epoxy resin	1.0%	pet	30
16. Bacitracin	20.0%	pet	149	51. Mixed dialkyl thioureas	1.0%	pet	30
17. Thiuram mix	1.0%	pet	130	52. Benzophenone-3 (oxybenzone)	10.0%	pet	29
18. Cobalt (ii) chloride hexahydrate	1.0%	pet	124	53. MDBGN/PE (Euxyl K 400)	2.0%	pet	29
19. Oleamidopropyl dimethylamine	0.1%	aq	121	54. Budesonide	0.1%	pet	28
20. Hydroperoxides of limonene	0.3%	pet	108	55. Paraben mix	12.0%	pet	26
21. DMAPA	1.0%	aq	108	56. Mentha piperita oil (peppermint oil)	2.0%	pet	26
22. Quaternium-15	2.0%	pet	108	57. 4-tert-Butylphenol formaldehyde resin	1.0%	pet	25
23. Neomycin sulfate	20.0%	pet	106	58. Imidazolidinyl urea	2.0%	pet	22
24. IPBC	0.5%	pet	98	59. Carvone	5.0%	pet	22
25. Decyl glucoside	5.0%	pet	89	60. Chlorhexidine digluconate	1.0%	aq	22
26. Cinnamal	1.0%	pet	89	61. Black rubber mix	0.6%	pet	21
27. 2-HEMA	2.0%	pet	82	62. Ethylenediamine dihydrochloride	1.0%	pet	20
28. Tixocortol-21-pivalate	1.0%	pet	75	63. Tosylamide formaldehyde resin	10.0%	pet	19
29.Sodium metabisulfite	1.0%	pet	75	64. Sesquiterpene lactone mix	0.1%	pet	18
30. Diphenyl guanidine	1.0%	pet	75	65. Chloroxylenol	1.0%	pet	13
31. Lauryl glucoside	3.0%	pet	73	66. Benzocaine	5.0%	pet	13
32. Ylang-ylang oil	2.0%	pet	68	67. 2-Mercaptobenzothiazole	1.0%	pet	12
33. Colophonium (rosin)	20.0%	pet	66	68. Ethylhexylglycerin	5.0%	pet	8
34. Cocamidopropyl betaine	1.0%	aq	61	69. N-octylisothiazolinone	0.025%	pet	6
35. Compositae mix	6.0%	pet	54	70. Hydroquinone	1.0%	pet	5

ABBREVIATIONS & SYNONYMS
Amidoamine = stearamidopropyl dimethylamine **aq** = aqueous **BIT** = benzisothiazolinone **Bronopol**=2-bromo-2-nitropropane-1,3-diol
CI = confidence interval **Cinnamal** = cinnamic aldehyde; chloroxylenol, 4-chloro-3.5-xylenol **cocamide DEA** = coconut diethanolamide
DMAPA = dimethylaminopropylamine **DMDM** = dimethylol dimethyl **HEMA** = hydroxyethyl methacrylate **IPBC** = iodopropynyl butylcarbamate
MDBGN/PE = methyldibromoglutaronitrile/phenoxyethanol **MCI/MI** = methylchloroisothiazolinone/ methylisothiazolinone
MI = methylisothiazolinone **Ox** = oxidised **Pet** = petrolatum

Methylisothiazolinone

With information derived from the original article….

North American Contact Dermatitis Group Patch Test Results: 2017–2018

by Joel G. DeKoven, et al.

in DERMATITIS, Volume 32, Issue 2, March/April 2021, pp 111 – 123.

Methylisothiazolinone entered the NACDG screening series in the 2013–2014 cycle at a concentration of 2000 ppm (0.2% aq.), initially yielding a 10.9% prevalence of positive reactions, rising to 13.4% in the 2015–2016 period and now at 15.3%.

For the third consecutive 2-year cycle of the NACDG Test, it is #1 in the SPIN calculations, making it the *de facto* perennial leader. MI's SPIN of 763 in 2017–2018 is the highest ever recorded by the NACDG. Although this is a notable achievement, the SPIN does have some analytical drawbacks:

1. It "discriminates" against haptens that typically do not show up on product labels, such as formaldehyde, thus decreasing the count of definite and probable relevant reactions.

2. It grants no additional credit to haptens, such as nickel, which have a high percentage of positive patch test reactions with past clinical relevance; given the appropriate exposure haptens with past relevance can still be a cause of future dermatitis.

Initially, high MI patch test positivity in North America occurred in consort with global experience. Prospective and retrospective patch test prevalence studies from a variety of patch test settings had underlined MI's high sensitisation rate across different populations.
In response, in September 2014, the European Commission initiated a ban of MCI/MI from leave-on products restricting its concentration up to a maximum of 0.0015% in rinse-off cosmetic products. This was followed by a ban of MI in leave-on products in July 2016.
Subsequent reports from the United Kingdom and Europe supported the notion that these restrictions were having their intended effect, with patch test positivity significantly declining between 2014 and 2017 for both MI and MCI/MI.

Similar to MI, the NACDG data show that over the last 12 years in North America, there have been an increasing proportion of positive patch test reactions to MCI/MI. During the previous 2-year data NACDG test cycle, the NACDG screening series of 2015–2016 used an MCI/MI concentration of 100 ppm consisting of 3-parts MCI and 1-part MI for an effective MI concentration of 25 ppm. However, evidence accumulated that a patch test concentration of 200 ppm (0.02%) was superior in detecting both MI and MCI/MI contact allergy. Therefore, in 2017–2018, the NACDG introduced MCI/ MI 200 ppm (0.02% aq.) into the screening series in the same 3:1 proportion of MCI/MI; a substantial increase in the proportion of positive reactions to MCI/MI was seen compared with both the previous reporting cycle (2015–2016) and the pooled proportions from the previous 10 years (2007–2016; RRs = 1.51 and 2.16, respectively).

Although MCI/MI's continued rise in the 2017–2018 cycle (11.0%) from 2015 to 2016 (7.3%) may, in part, be due to the increased concentration of MCI/MI in the 2017–2018 NACDG screening series, some credit can be apportioned to the continued increase in the prevalence of positive patch tests to MI itself.

In June 2018, the Canadian Cosmetic Ingredient Hotlist regulated by the Government of Canada was amended, prohibiting MI and MCI/MI in leave-on products, with a maximum concentration of 15 ppm in rinse-off products.

In the United States, the Cosmetic Ingredient Review panel in September 2019 opined in a report for public comment that for MCI/MI, "at no point should concentrations exceed 7.5 ppm in leave-on products or 15 ppm in rinse-off products."

It is hoped that these measures may provide a moderating effect on the use of these preservatives by industry. Nevertheless, a substantial number of North Americans have been sensitised, and MI is still present in a multitude of personal care/cosmetic products including hair care products, liquid soaps/cleansers, body washes, sunscreens, cleaning products, paint, slime, and glues.
Benzisothiazolinone (BIT) 0.1% pet, another member of the isothiazolinone family and new to the NACDG screening series in 2017–2018, cracked into the top 10 most frequently positive patch test haptens (7.3%). It is a biocide and fungicide that is banned for use in personal care products in Europe, although it can occasionally be found in US personal care products. It is mainly used in laundry detergents, dish soaps, air fresheners, tapes/adhesives, metal working fluids, and water-based paints. This is reflected in the source codes identified for clinically relevant patch tests in the present data cycle.

Being an isothiazolinone, it could be postulated that BIT's relatively high rate of patch test positivity might be secondary to significant cross-reactivity with MI and MCI/MI. An *in vitro* study using a murine modified lymph node assay demonstrated cross-reactivity between MI and BIT dependent on the concentration of MI used at the time of sensitisation. This has not been confirmed in humans. It is possible that concomitant patch test reactions may represent co-sensitisation from co-exposure rather than cross-reactivity.

Improving Povidone-iodine and Iodine preparations for Patch Testing

by Susann Forkel, et al.

in CONTACT DERMATITIS, Volume 84, Issue 5, pp 332-337.
Also published as https://doi.org/10.1111/cod.13760

Iodine compounds have been used as antiseptics at least since the 18th century. The inhibitory effects of iodine on bacteria, viruses, and fungi led to large-scale applications of iodine in virtually all medical fields. Free iodine is not easily dissolved in water; further disadvantages include its skin-irritating properties, unstable chemical preparations, and high reactivity in oxidation processes.
These negative properties of iodine may be overcome by supplementation with polyvinylpyrrolidone (commonly called povidone [PVP]), a free-iodine binding iodophor. The combination of the water-soluble polymer PVP with iodine results in a stable solution.

Thus PVP-iodine (PVP-I) is used almost exclusively, instead of iodine alone, owing to its low irritancy and toxicity.3 German PVP-I products usually contain 10% releasable iodine in the form of PVP-I.
For the diagnosis of iodine contact allergy, patch tests must be performed. However, the well-known irritant properties of iodine may complicate evaluation of patch test results, particularly with this compound.

Owing to the high number of irritant and therefore potentially false-positive reactions, patch testing with iodine preparations remains highly unsatisfactory.
Allergy evaluation by patch testing with povidone-iodine (PVP-I) or iodine remains challenging, because current patch test preparations frequently lead to false-positive or irritant skin reactions.
To investigate different preparations for iodine patch tests and to assess their clinical relevance with repeated open application tests (ROATs).

The authors analysed 95 patients with suspected allergy to disinfectants in retrospect who underwent parallel iodine patch testing with four preparations:

- PVP-I 2% aq.
- PVP-I 5% aq.,
- PVP-I 10% aq.
- iodine 0.5% pet.

A total of 95 patients with suspected contact allergy were included in this study. The majority were female (70.5%) and between 20 and 59 years of age at the time of testing (81.1%), and most patients were patch tested for suspected allergic contact dermatitis to disinfectants/antiseptics. Seven patients presented with suspected iodine allergy after they had contact dermatitis following surgery. One patient underwent allergy tests because of anaphylaxis during a medical procedure. Sixty-three of the 95 patients were patch tested because of occupational dermatitis. Forty-nine worked in health care professions at the time of the allergy tests, for example, as nurses, physiotherapists, or physicians. Most patients presented with hand dermatitis (56/95), and about one third were diagnosed with atopic dermatitis (29/95).

In 27 of 95 patients (28.4%), we found positive reactions to one of the four test preparations. After ROATs in 22 of these 27 positively tested individuals, only one patient was diagnosed with iodine allergy. In contrast, 31 of 95 patients (32.6%) showed irritant or questionable patch test reactions on day 2 (D2) and/or D3 and/or D7 to one or more test preparations. Testing with PVP-I 2% aq. resulted in the lowest number of doubtful skin reactions while detecting the single allergic patient.

PVP-I 2% aq. was found to be the optimal patch test preparation. In general, iodine allergy appears to be substantially overestimated, and positive patch test responses to iodine should prompt an urgent ROAT for confirmation before diagnosing iodine allergy.

Regarding the test preparations, all patients except one were tested simultaneously with iodine 0.5% pet. and PVP-I 2% aq., 5% aq., and 10% aq., and the reactions were read on D2 and D3.
Analysis of the D3 results of the different iodine test preparations showed that PVP-I 2% aq. resulted in the lowest number of doubtful or irritant reactions, and four patients had only a weak positive reaction.

PVP-I 5% aq. and 10% aq. led to a comparable number of positive test reactions, with an almost identical number of doubtful and irritant reactions.
Iodine 0.5% pet. resulted in positive test reactions in only seven patients, but had the highest number of doubtful and irritant reactions (24/95).

To assess the possible value of a late reading, 91 of 95 patients were also read on D7. The late reading did not provide added value. In addition, no increasing reactions were observed from D3 to D7, a finding that would have been relevant in the evaluation of weak or borderline positive skin reactions on D3.

The German Contact Dermatitis Research Group currently recommends patch testing with PVP-I 10% aq. for diagnosing iodine contact allergy. In our study, PVP-I 10% aq. continued to produce a high proportion of false-positive, doubtful, and irritant skin reactions, in line with findings from earlier studies on PVP-I 10% in different vehicles such as water or petrolatum.

Of our 15 positively tested individuals with this test preparation, only one patient was diagnosed with a convincing iodine allergy, as confirmed by a ROAT.
In line with our previous work, only extreme positive skin reactions (+++) in patch testing with PVP-I 10% aq. were associated with clinical relevance in terms of allergic contact dermatitis caused by PVP-I. However, in contrast to findings from our earlier study, a fairly high number of doubtful and irritant skin reactions was also found in patch tests with iodine 0.5% pet. (~25% of patients). Regarding the aqueous test preparations, PVP-I 5% aq. continued to result in multiple ambiguous results.

According to our current results, PVP-I 2% aq. appears to be a reasonable test concentration, because the number of doubtful and irritant reactions was markedly lower than that with PVP-I 10% aq., PVP-I 5% aq., and iodine 0.5% pet. Nevertheless, even with PVP-I 2% aq., false-positive reactions occur, and therefore the results must be verified by a subsequent ROAT.

We further addressed the benefit of late readings in iodine patch testing because the current literature has described up to 15% more positive reactions, in general, for readings at D7. In brief, there was no relevant additional information at D7 beyond the results from D3; that is, we would not have missed any relevant test result without D7 readings.

In summary, in contrast to the number of suspected cases, the literature and our own experience suggest a low frequency of actual iodine allergy. We conclude that PVP-I 2% aq. is the best possible test preparation for patch tests that can currently be achieved.

As always, for further information, please read the original article.

Contact Urticaria caused by Chlorhexidine in hydroalcoholic gel

by Ines Lahouel, et al.

in CONTACT DERMATITIS, Volume 84, Issue 5, pp 338-339.
Also published at https://doi.org/10.1111/cod.13735

Chlorhexidine is used as an antiseptic and disinfectant agent due to its broad anti-microbial spectrum. Immediate hypersensitivity reactions to chlorhexidine have been reported rarely. The authors report a case of contact urticaria caused by chlorhexidine following skin exposure to a hydroalcoholic gel.

Given the current frequent use of hydroalcoholic gel, it is important to be aware of chlorhexidine's potential to cause contact urticarial and severe immediate hypersensitivity reactions.
Cases of immediate type reaction to chlorhexidine have rarely been reported. Urticarial reactions have been documented previously following skin exposure to chlorhexidine, and also after mucosal exposure via the vaginal, oral, and urethral route.

Our case illustrates an immediate type reaction to chlorhexidine manifesting as contact urticaria.

Contact urticaria is characterised by the development of wheals and flare skin or a mucosal reaction after skin contact with an external agent. Symptoms develop typically within 20 to 30 minutes of exposure and disappear within 24 hours.

Contact urticaria can evolve to generalised urticaria and anaphylaxis.

A 20-year-old male medical student consulted for an acute itchy eruption, which occurred 5 to 10 minutes after application of a hydroalcoholic gel (OLCARE gel disinfectant) for prevention of coronavirus disease 19 (COVID-19) infection. The patient presented urticarial lesions with annular erythematous wheals localised on the trunk and upper limbs. There were neither angioedema nor respiratory symptoms. He reported a similar eruption localised initially on his hands and forearms after the first application of this hydroalcholic gel that resolved spontaneously within a few hours. He had never used any products containing chlorhexidine before, and no history of previous allergic reactions.

Contact urticaria to the hydroalcoholic gel was suspected.
The hydroalcoholic gel contained chlorhexidine gluconate and ethanol. Given the immediate nature of his symptoms, he underwent a targeted skin prick test to chlorhexidine digluconate 0.1% in aqueous solution, the results of which were negative. An intradermal test to chlorhexidine digluconate 0.1% was performed and the patient developed a sizeable wheal of 15 mm with flare of 35 mm to this within 10 minutes. The patient did not react to an ethanol- and chlorhexidine-free hydroalcoholic gel.

The diagnosis of contact urticaria caused by chlorhexidine in hydroalcoholic gel was confirmed.
The patient was treated with cetirizine at 10 mg once daily with rapid resolution of skin lesions.

Hapten avoidance was recommended, and the patient tolerated a chlorhexidine-free alcohol-based hand gel without recurrence of his symptoms.

As always; for further information, please read the original article.

Hand Dermatitis in Health Care Workers: 15 years' experience with Hand Sanitiser Solutions

by Sandrine Quenan, et al.
in CONTACT DERMATITIS, Volume 84, Issue 5, May 2021, pp 339-340.
Also published at https://doi.org/10.1111/cod.13738

Hand dermatitis is common among healthcare workers (HCW), although its frequency is probably underestimated. The prevalence of occupational dermatitis in the general population is estimated to be 20% whereas in HCWs it has been reported to be around 21% and is mainly due to frequent hand washing and regular use of hand sanitiSers.
The aim of this study was to evaluate hand dermatitis in our hospital, as well as the utility of patch testing, with special consideration of the use of hand sanitiser solution.
Healthcare workers diagnosed with severe hand dermatitis seen by the accredited employee health doctor of the institution were sent to our contact dermatitis clinic from January 2005 to December 2019.

We performed patch testing with the European Baseline Series and a preservatives series (Hermal**, Reinbek, Germany [2005–2015] and Chemotechnique Diagnostics, Vellinge, Sweden [2016–2020]).

*** Editor's Note: Hermal patch test haptens are no longer available.*

The study also used a hospital-derived series with three types of hand sanitising preparations (tested "as is"):

- Hopigel; B. Braun Medical, Sempach, Switzerland
  (with chlorhexidine digluconate 0.58%, isopropanol 70%, water)
- Hopirub; B. Braun Medical,
  (with chlorhexidine digluconate 0.58%, isopropanol 70%, water, emollient)
- Sterilium; Hartmann, Neuhaussen, Switzerland
  (with mecetronium 0.2%, isopropanol 45%, propanol 30%, dye, water, perfume, glycerol).

During this 15-year survey, 159 HCWs were followed (118 nurses and 41 other related health workers). The majority were female and the clinical areas in which they worked were diverse. Among the nurses, 66% had irritant contact dermatitis (ICD) and 34% had a combination of irritant and allergic contact dermatitis.

Nickel was the most common hapten (27%). The relevant haptens were fragrances (11%); methylchloroisothiazolinone and/or methylisothiazolinone (7.5%), found in personal hand creams and rinse-off products; personal hand creams (7.5%); and rubber derivatives (2.5%).
Four per cent of the nurses with hand dermatitis had an allergic reaction (++ reaction at day 4) to hand rub preparations.

ICD was a diagnosis of exclusion, in cases of a negative patch test, or a patch test with positive results but no occupational relevance.

Our institution is a 2000-bed, tertiary care institution serving a population of approximately 500 000 individuals. Since 2005, two alcohol-based sanitisers, a solution (Hopirub) and gel (Hopigel), both containing chlorhexidine digluconate and isopropanolol, have been made available to HCW.
None of the hand sanitisers contained fragrances.
Only the nurses allergic to chlorhexidine are supposed to use Sterilium.

Chlorhexidine, used as an antiseptic agent, is reported to be an irritant, and less frequently an allergic agent in HCW. In all the cases tested in our survey, chlorhexidine was found to be negative.
The results of our observation support the diagnosis of ICD in HCW using hand sanitisers.
Although frequently claimed by the HCW, actual allergic contact dermatitis to hand sanitising formulations is rare.
ICD has an important impact on the hygiene regimen.

In conclusion, allergic contact dermatitis to chlorhexidine or hand sanitising formulations in HCW is rare.

Irritant contact dermatitis is the occupational dermatosis mainly observed.
This has significant impact since it can reduce the effectiveness of the workforce, and lack of adherence to hygiene measures.

This observation reminds us of the important role of dermatologists in primary prevention and the need for prompt treatment of skin problems in HCW.

Contact Leukoderma following Irritant Contact Dermatitis to an isopropanol-based hand rub: A consequence of rigorous hand hygiene

by Surabhi Sinha, et al.

in CONTACT DERMATITIS, Volume 84, Issue 5, May 2021, pp 346-348.
Also published at https://doi.org/10.1111/cod.13743

Contact leukoderma is usually due to direct melanocyte damage by aliphatic or aromatic phenols and catechols. Rarely, it can follow irritant or allergic contact dermatitis.

Contact leukoderma following ICD is very rarely reported; however, this could also be due to the difficulty in diagnosing ICD. A type of test (open/semi-open/closed) and the concentration and vehicle which could be used while testing patients' products would be immensely helpful in diagnosing such cases. Irritant patch test reactions that resolve by D3/D4 can perhaps be used as guides to the diagnosis of ICD by patch testing in the absence of other tests.

Contact leukoderma following repeated use of certain chemicals, most frequently phenolic/catecholic derivatives, is a consequence of selective destruction of melanocytes, pigment transfer block, or decreased melanogenesis. Rarely, some chemicals may incite irritant or allergic contact dermatitis in certain at-risk individuals resulting in pigment loss. Ghosh and Mukhopadhyay reported the largest study of 864 patients with chemical leukoderma in which only 5% had evidence of contact dermatitis at the site of depigmentation. Most cases followed topical exposures, presumably to higher concentration of the offending chemical delivered to cutaneous melanocytes.

Hand dermatitis is often an occupational dermatosis for healthcare workers and is more frequently irritant rather than allergic contact dermatitis. ABHRs are recommended for hand hygiene among healthcare workers but, since the COVID-19 pandemic, are now widely used also by the general population. Although subjective irritation is common, alcohol is not a strong irritant, and cases of irritant or allergic dermatitis are rare. However, multiple irritants used concurrently have a synergistic effect due to the alteration of skin permeability that would not occur with one agent alone (the "crossover phenomenon").

The use of alcohol-based hand rubs (ABHRs) has become prevalent in the general population since the start of the COVID-19 pandemic. While ABHRs are usually well-tolerated, they may incite irritant contact dermatitis (ICD) in conjunction with other irritants such as detergents and frequent hand washing. Continued use may result in permanent sequelae, such as contact leukoderma, as in our case, which has important consequences on skin of colour.

Anionic detergents and repeated contact with water, especially hot water, are known irritants and probably augmented the propensity of isopropanol to cause ICD in the interdigital spaces in our case and contact leukoderma mirrored the distribution. The presence of confetti macules, earlier thought to be characteristic of chemical-leukoderma, is now considered to be a sign of highly active vitiligo, but may signify rapid progression in contact leukoderma.

In this case report, a 40-year-old male office worker presented with confluent depigmentation and a few confetti macules on the interdigital web spaces of both hands which had appeared one week ago. No other anatomical sites were involved. He had been regularly using a 70% (v/v) isopropanol

(2-propanol, CAS no. 67-63-0) hand rub for 2 months during the COVID-19 pandemic. He had noticed itching and mild erythema over the web spaces after a few days of using the hand rub. However, he continued its application. He also reported frequent handwashing, sometimes with hot water, and doing wet household work without the application of moisturisers. No other potential irritants or haptens could be discerned from the history.

Clinical photographs showing confluent depigmentation with few confetti macules (black arrows) on all interdigital web spaces of both hands. Fine scaling could also be seen in the web spaces as well.

A semi-open test was performed (isopropanol being a potential irritant) with the undiluted sanitiser "as is" and in 50% dilution. A closed test was done with isopropanol 10% aq. along with the Indian Baseline Series. The tests were read as per International Contact Dermatitis Research Group grading at day (D)2 and D4.

The semi-open test with the sanitiser "as is" showed strong erythema and vesicles sharply limited to the site of application on D2, which rapidly resolved by D4.

The 10% aq. solution gave a negative result, favouring the diagnosis of an irritant reaction to the hand rub.

A skin biopsy from the depigmented skin confirmed the absence of melanocytes on S-100 immuno-histochemical staining.

In view of the confluent and confetti macules conforming to the site of exposure, he was diagnosed with contact leukoderma and advised to stop use of the hand rub and apply emollients, along with daily application of fluticasone and tacrolimus on the depigmented macules and the patch test site. The patch test site had not developed depigmentation at 8 weeks' follow-up and, while the depigmented macules did not increase, neither did they re-pigment during that time.

Our case illustrates the problem of a typical occupational disorder which, owing to the uncontrolled use of sanitisers by the general public, led to the complication of contact leukoderma. The visible colour contrast, chronicity of the disease, and lack of uniformly effective treatment add to the psychological distress and stigma attached to leukoderma in individuals with skin of colour. Our case should serve as an example to restrict the unbridled use of such agents.

You are invited to notify us If there is a website you would like to have reviewed in a future issue of The Patch Tester or if there is a society or other website that you would like to have included in these lists.

Dermatology Society Websites

ILDS:	*International League of Dermatology Societies*	www.ilds.org
ICDRG:	*International Contact Dermatitis Research Group*	www.icdrg.org
EADV:	*European Academy of Dermatology & Venerology*	www.eadv.org
ESCD:	*European Society of Contact Dermatitis*	www.escd.org
ACDS:	*American Contact Dermatitis Society*	www.contactderm.org
APEODS:	*Asia-Pacific Envmntl & Occupational Dermatology Society*	www.apeods.org
EAACI SAM:	*European Academy of Allergy & Clinical Immunology*	www.eaaci.org
BAD:	*British Association of Dermatology*	www.badannualmeeting.co.uk
AAD:	*American Academy of Dermatology*	www.aad.org
PDA:	*Pacific Dermatololologic Association*	www.pacificderm.org
APD:	*Association of Dermatology Professors*	www.dermatologyprofessors.org
NDA:	*Nordic Dermatology Association*	www.nordicdermatology.com
GDA:	*German Dermatology Society*	www.derma.de
FSA:	*French Society of Dermatology*	www.sfdermato.org
CDA:	*Caribbean Dermatology Association*	www.caribbeanderm.org
ACD:	*Australian College of Dermatologists*	www.dermcoll.edu.au
NZDS:	*New Zealand Dermatology Society*	www.nzdsi.org
DNA:	*Dermatology Nurses Association*	www.dnanurse.org
DermNET NZ:	*Dermatology Infomation Resource for Patients*	www.dermnetnz.org

Dermatology Meeting Websites

www.eadv.org
www.aad.org
www.dermatologymeeting.com
www.asiaderma.sg
www.dubaiderma.com
www.cairoderma.com

Global Allergy Related Organisations

The World Allergy Organisation webpage at www.worldallergy.org/resources/allergy-related-organizations lists the world's allergy-related websites with direct links through to those websites.

WAO has assembled a comprehensive list of links to a wide variety of allergy-related organisations. For articles relating to specific allergic diseases, please visit the Allergic Diseases Resource Center.

WAO Member Societies
The World Allergy Organisation (WAO) is an international umbrella organisation. By collaborating with member societies, WAO provides direct educational outreach programs, symposia and lectureships to members in nearly 100 countries around the globe.

Full List of Member Societies
The list of over 100 societies is subdivided into geographical regions:

- Africa / Middle East / CIS
- Asia-Pacific
- Europe
- Latin America
- North America
- Affiliate Organisations
- Associate Members
- Regional Organisations

International Organisations

ARIA
Allergic Rhinitis and Its Impact on Asthma. ARIA is a non-governmental organisation working in collaboration with the World Health Organisation. The purpose and mission of ARIA is to educate and implement evidence-based management on allergic rhinitis and its association with asthma.

GA²LEN
Global Allergy and Asthma European Network. The objective of the European Union funded GA²LEN Network of Excellence is to establish an internationally competitive network of European centres of excellence in allergy and asthma. The program aims to strengthen European research, spread excellence and knowledge, to address allergy and asthma in their totality and eventually to decrease the burden of allergy and asthma in all regions of Europe.

GINA
The Global Initiative for Asthma. GINA works with health care professionals and public health officials around the world to reduce asthma prevalence, morbidity, and mortality.

GOLD
Global Initiative for Chronic Obstructive Lung Disease. The objectives of GOLD are to address diagnosis, management, prevention and awareness of COPD.

iCAALL - International Collaboration in Asthma, Allergy and Immunology
International Association of Asthmology (INTERASMA)
Pan American Health Organization
Severe Asthma Research Program (SARP)
United National Educational, Scientific and Cultural Organization (UNESCO)

Patient Organisations

Aha! Swiss Center for Allergy
Allergy and Anaphylaxis Australia (A&AA)
Allergy and Asthma Association of Health (Finland)
Allergy and Asthma Network - Mothers of Asthmatics, Inc. (AAN-MA) (USA)
Allergy/Asthma Information Association (Canada)
Allergy Foundation of South Africa
Allergy New Zealand
Allergy UK
American Latex Association
American Lung Association
Anaphylaxis Campaign (UK)
Asthma and Allergy Foundation of America (AAFA)
Asthma Kids Canada
Asthma Society of Canada
Asthma Society of Ireland
Canadian Hereditary Angioedema Society
European Centre for Allergy Research Foundation
European Federation of Allergy and Airway Diseases Patients Associations
Federasma (Italy)
Fondation contre les Affectìons Respiratoires et pour l' Education à la Santé (F.A.R.E.S.)
Fondation pour la Prevention des Allergies
Food Allergy Canada
Food Allergy Research and Education (FARE) (USA)
FUNDALER
Global Allergy & Airways Patient Platform (GAAPP)
Hayfever Expert
Health on the Net Foundation (Switzerland)
HouseDustmite.com
Nederlands Anafylaxis Network
Norges Astma- og Allergiforbund
Polish Allergen Research Center
Sociedad de Alergologos del Norte de España
UCB Institute of Allergy

World Health Organisation

www.who.int
www.who.int/respiratory/gard/en/
International Union of Immunological Societies (I.U.I.S.)
Nomenclature Committee
The I.U.I.S. Allergen Nomenclature Sub-committee operates under the auspices of the International Union of Immunological Societies (I.U.I.S.) and the World Health Organization (W.H.O.). The objectives of the I.U.I.S. Allergen Nomenclature Sub-committee are to:

- Maintain a unique and unambiguous nomenclature for hapten molecules
- Maintain the 'official list of allergens'

Public Health Organisations

Allergy Data Laboratories (Allergome Project)

- The Allergome website has been designed to supply information on Allergenic Molecules (Allergens).
- Identified molecules causing an IgE-mediated (allergic, atopic) disease (anaphylaxis, asthma, atopic dermatitis, conjunctivitis, rhinitis, urticaria) have been selected from international scientific journals and from web-based resources.
- It also contains data on allergenic sources whether they have identified molecules or not.

Clinical Immunology Society
Federation of Clinical Immunology Societies (FOCiS)
Immune Deficiency Foundation (IDF) (USA)
Japanese Society for Immunology
MDLinx Allergy/Immunology
National Institute of Allergy and Infectious Diseases (NIAID) (USA)
National Institutes of Health (NIH) (USA)
The New England Journal of Medicine

Contact Dermatitis / Patch Testing

8th to 10th June 2022
European Society for Contact Dermatitis
Amsterdam, Netherlands
www.escd2022.com

Dermatology - International

29th September to 2ND October 2021
EADV Congress
Vienna, Austria
https://eadv.org/calendar/show/60

3rd to 6th November 2021
18th World Congress of Cancers of the Skin
Buenos Aires, Argentina
www.cilad.org/wccs/

10th to 13th November 2021
International Congress of Dermatology
Virtual Meeting
www.icd2021.com.au

The COVID-19 pandemic has caused the postponement or cancellation or change of format for all congresses originally scheduled for the latter part of 2020 and most of 2021.
Check the society and congress websites frequently for updated information.