

ORIGINAL ARTICLE

Is a specific eyelid patch test series useful? Results of a French prospective study

Haudrey Assier¹  | Florence Tetart² | Martine Avenel-Audran³ | Annick Barbaud⁴  | Marie-Christine Ferrier-le Bouëdec⁵ | Françoise Giordano-Labadie⁶ | Brigitte Milpied⁷  | Emmanuelle Amsler⁴ | Evelyne Collet⁸ | Pascal Girardin⁹ | Angèle Soria⁴ | Julie Waton¹⁰  | François Truchetet¹¹ | Jean-Luc Bourrain¹²  | Gwendeline Gener¹ | Claire Bernier¹³ | Nadia Raison-Peyron¹²  | for the Dermato-Allergology Group of the French Society of Dermatology (DAG)

¹Department of Dermatology, CHU Henri-Mondor, Créteil, France

²Department of Dermatology, CHU Rouen, Rouen, France

³Department of Dermatology, CHU Angers, Angers, France

⁴Department of Dermatology and Allergy, Hôpital Tenon, Sorbonne Université, AP-HP, Paris, France

⁵Department of Dermatology, CHU Clermont-Ferrand, Clermont-Ferrand, France

⁶Department of Dermatology, Hôpital Larrey, CHU Toulouse, Toulouse, France

⁷Department of Dermatology, Hôpital St André, Bordeaux, France

⁸Department of Dermatology, Hôpital le Bocage, Dijon, France

⁹Department of Dermatology, CHRU Besançon, Besançon, France

¹⁰Department of Dermatology, CHRU Nancy, Nancy, France

¹¹Department of Dermatology, CHR Metz-Thionville, Thionville, France

¹²Department of Dermatology, CHU Montpellier, Montpellier, France

¹³Department of Dermatology, CHU Nantes, Nantes, France

Correspondence

Dr. Haudrey Assier, Department of Dermatology, Hôpital Henri-Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, France.
Email: haudrey.assier@hmn.aphp.fr

Background: Eyelids are frequent sites of contact dermatitis. No prospective study focused on eyelid allergic contact dermatitis (EACD) has yet been published, and this topic has never been studied in French patients.

Objectives: To prospectively evaluate the usefulness of an eyelid series in French patients patch tested because of EACD, and to describe these patients.

Methods: We prospectively analysed standardized data for all patients referred to our departments between September 2014 and August 2016 for patch testing for suspected EACD as the main reason. All patients were patch tested with an eyelid series, the European baseline series (EBS), the French additional series, and their personal products. Patch testing with additional series and repeated open application tests (ROATs) or open tests were performed if necessary. A standardized assessment of the relevance was used, and the analysis of the results was focused on patients having positive test results with a current certain relevance.

Results: Two-hundred and sixty-four patients (238 women and 26 men) were included. Three-hundred and twenty-two tests gave positive results in 167 patients, 84 of whom had currently relevant reactions: 56 had currently relevant positive test reactions to the EBS, 16 had currently relevant positive test reactions to their personal products, 8 had currently relevant positive test reactions to the French additional series, and 4 had currently relevant positive test reactions to the eyelid series. Sixty-seven per cent of all relevant cases were related to cosmetic products. The most frequent allergens with current relevance were methylisothiazolinone (10.2%), fragrance mix I (3%), nickel (2.7%), hydroxyperoxides of linalool (2.7%) and limonene (2.3%), and *Myroxylon pereirae* (2.3%). Current atopic dermatitis was found in 9.5% of patients. The duration of dermatitis was shorter (23.2 vs 34.2 months; $P = .035$) in patients with currently relevant test reactions. The percentage of currently relevant tests remained the same when atopic patients or dermatitis localized only on the eyelids were taken into account.

Conclusion: In French patients, testing for EACD with the extended baseline series and personal products, also including ROATs and use tests, appears to be adequate, considering the currently relevant positive test reactions. The regular addition of an eyelid series does not seem to be necessary.

KEYWORDS

eyelid dermatitis, eyelid series, French population, patch test, prospective study

1 | INTRODUCTION

Allergic contact dermatitis is the main cause of eyelid dermatitis, and affects 5% to 20% of the patients referred for patch testing.^{1–4} Many studies on eyelid allergic contact dermatitis (EACD) have already been published, but all were retrospective and did not use any targeted allergens, and none included French patients. The primary objective of this prospective study was to assess the usefulness of a specific eyelid series in addition to the European baseline series (EBS) and the French additional series in the diagnostic work-up of patients with EACD. The secondary objectives were to describe the features of eyelid dermatitis in these patients.

2 | PATIENTS AND METHODS

The study was carried out for 2 years (September 2014 to August 2016) by the members of the Dermato-Allergology Group of the French Society of Dermatology (DAG). All adult patients presenting for patch testing with eyelid dermatitis as the main reason for consulting were included. For each patient, the dermatologist had to complete a form with detailed information about the patient and the dermatitis: age, sex, history, detailed clinical symptoms, presence or history of atopy, duration of dermatitis, trigger factors, topically applied cosmetics and medications, everyday life, and habits (Annex 1 in File S1). Atopy status was assessed according to usual validated criteria⁵ and prick tests with aeroallergens.

Each patient was patch tested with the EBS,⁶ the French additional series of the vigilance network in Dermato-Allergology (REVIDAL-GERDA), and an eyelid series. The French additional series is systematically added to the EBS in our French centres, and comprises 12 allergens chosen according to data from the literature and/or a suspicion of emerging importance.⁷ This series is re-evaluated each year according to the proportion of positive results over the past year, and allergens are retained if $\geq 1\%$ positive reactions are observed. The 9 allergens of the French additional series used during this 2-year study are shown in Table 1. The eyelid series was established according to data from the literature and the experience of DAG members (Table S1). Other series were also applied if necessary, and patch tests with the patients' own suspected products were performed according to their history. These were followed by a

TABLE 1 French additional series

Allergen	Concentration (%) and vehicle
Amerchol L 101	50 pet.
3-Dimethylamino-1-propylamine	1 aq.
Benzalkonium chloride	0.1 aq.
Lauryl glucoside	3 pet.
Propolis	10 pet.
Hydroxyperoxides of linalool	0.5 pet.
Hydroxyperoxides of limonene	0.2 pet.
Benzyl alcohol	10 sof.
Sorbitan oleate	5 pet.

sof, Softisan.

repeated open application test (ROAT) or a use test in cases of doubtful reactions.

Patch testing was performed according to ICDRG guidelines, with 2 readings on day (D) 2 and D3 or D4.⁸ The relevance was assessed with a simplified method adapted from Lachapelle.⁹ We used only 3 possibilities for current relevance: (1) certain relevance, namely, certainty that eczema was attributable to the use of a product that certainly contained the allergen found to be positive on patch testing; (2) doubtful relevance, namely, it was deemed plausible, possible or probable that contact with a product likely to contain the allergen had occurred, or eczema had resulted from a product in which the presence of the allergen was uncertain; and (3) absence of relevance.

In order to assess our eyelid series as validly as possible, we decided to focus the analysis of our results and the discussion only on patients having positive test reactions with certain current relevance. Regarding statistical analysis, the χ^2 test was used for qualitative data, and Student's t-test was used for quantitative data.

3 | RESULTS

Between September 2014 and August 2016, 264 patients were included in 14 centres (2–60 cases per centre). The clinical characteristics of the French patients and their habits are summarized in Table 2. The population comprised 238 (90%) females and 26 males, with an age range of 18 to 98 years (median 50 years). In 71 cases, the dermatitis was chronic; in the other cases, it was recurrent. The mean

TABLE 2 Characteristics of the 264 patients in relation to the results of the tests. G1, patients with at least 1 certain relevant positive patch test reaction; G2, other patients

	All	G1	G2
Female	238	77	161
Male	26	7	19
Age (years), median	50.5	51	50
Duration (months), mean	31.4	23.2	34.9 (P = .035)
Atopy background	107	30 (36.6%)	77 (42.3%)
Current atopic dermatitis	25	4 (4.9%)	
Permanent eyelid dermatitis	71	24 (29.2%)	47 (25.8%)
Eyelids involved			
Unilateral	4	1 (1.2%)	3 (1.6%)
Upper eyelids	47	15 (18.2%)	32 (17.6%)
Lower eyelids	18	2 (2.4%)	16 (8.8%)
4 eyelids	185	62 (75.6%)	123 (6.6%)
Dermatitis restricted to eyelid(s)	110	33 (40.2%)	77 (42.3%)
Description of the dermatitis			
Erythema	259	84 (100%)	175 (97.2%)
Pruritus	213	68 (82.9%)	144 (79.7%)
Oedema	189	59 (70.2%)	128 (71.1%)
Scaling	187	63 (75%)	126 (70%)
Crusting	43	9 (10.7%)	34 (18.9%)
Oozing	26	10 (12.2%)	16 (8.8%)
Sharply demarcated	146	40 (47.6%)	107 (59.4%)
Associated with conjunctivitis	74	21 (25%)	53 (29.4%)

duration of eyelid dermatitis was 31.4 months (1-360 months; median 12 months), but it was <6 months in 69 cases.

One hundred and eleven patients (42%) had a background of atopy; 71 (26.9%) of these had a history of atopic dermatitis, which was active in 25 (9.5%). The eyelid dermatitis was attributed to atopy alone in 30 patients (14 certain; 16 possible). There was no difference in the frequency of positive patch test reactions of any relevance between atopic and non-atopic patients. One hundred and sixty-seven patients (63.3%) had positive test results (patch test, ROAT or use test). Eighty-eight patients had several positive reactions, so there were 322 positive test reactions in total. According to the history of the patient, positive test reactions were of certain current relevance in 84 (31.8%) patients, and of possible current relevance in 65 (24.6%) patients; no current relevance could be found for 43.6% of patch test reactions. There was no statistically significant difference with regard to the percentage of currently relevant positive test reactions between dermatitis restricted to the eyelids (40.2%) and dermatitis with lesions elsewhere (42.3%); this was also true when the currently and the possibly relevant positive test reactions (39.4% and 44.1%, respectively) were considered. The only statistically significant finding with regard to clinical or demographic data concerning the patients with at least 1 positive patch test reaction of current relevance was a shorter duration of the dermatitis (23.2 vs 34.2 months) than in those without any currently relevant reaction ($P = .035$) (Table 3).

There were 257 positive patch test reactions in 149 patients to haptens of the EBS and French additional series (Table 4). For 56 patients, the currently relevant positive test reactions to the EBS were sufficient to determine the cause of EACD. Eight patients had currently relevant positive test reactions only to the French additional series (there were none to the other series). Only 5 of the 9 allergens of the French additional series gave positive test reactions with current relevance: hydroxyperoxides of limonene and linalool, lauryl glucoside, diethylaminopropylamine, and propolis (Table 4). Interestingly, because of the presence of hydroxyperoxides of limonene or linalool in the French additional series, it detected 7 patients allergic to fragrances not detected by the fragrance allergens of the EBS.

There were 53 positive patch test reactions in 41 patients to haptens contained in the eyelid series (Table 4). Only 4 patients had currently relevant positive test reactions (2 positive test reactions in a same patient): 3 to allergens from cosmetics (*tert*-butylhydroquinone, octyl gallate, dodecyl gallate, and benzophenone-4) and 1 to benzoyl peroxide present in swimming goggles. Benzoyl peroxide in 1 patient's swimming goggles was considered to be currently relevant, because this hapten had already been incriminated in a similar case, avoidance of goggles led to recovery, and a rechallenge test gave a positive result. The 4 above-mentioned patients had no other currently relevant positive test reactions.

The most frequent allergens leading to currently relevant positive reactions were from the EBS and French additional series: methylisothiazolinone (MI), fragrance mix I, nickel sulfate, hydroxyperoxides of linalool and limonene and *Myroxylon pereirae* in, respectively, 10.2%, 3%, 2.7%, 2.7%, 2.3% and 2.3% of the patients. Fragrance allergies were mostly attributable to direct contact with cosmetics, and rarely to airborne contact dermatitis caused by home perfumes (2 cases). Thiuram contact allergy was detected in

TABLE 3 Positive test reactions to the extended baseline series (European baseline series [EBS] and French additional series [FAS])

	Allergen	Relevance		
		Current	Possible	None
EBS	MI or MI/MCI	27	8	1
	Fragrance mix I	8	10	2
	Nickel sulfate	7	36	25
	<i>Myroxylon pereirae</i>	6	5	3
	Thiuram mix	2	1	2
	Epoxy resin	2	2	2
	Budesonide	2		
	Potassium dichromate	1	5	2
	Fragrance mix II	1	3	1
	Colophonium	1	4	
	Hydroxyisohexyl 3-cyclohexene carboxaldehyde	1	2	1
	Neomycin sulfate	1		1
	Lanolin alcohol		6	2
	Cobalt chloride		5	5
	Formaldehyde		1	
	Methyldibromo glutaronitrile		3	1
	Sesquiterpene lactone mix		1	
	Benzocaine		1	
	Quaternium 15		1	
	Tixocortol 21-pivalate			1
FAS	Hydroxyperoxides of linalool	7	8	3
	Hydroxyperoxides of limonene	6	7	1
	Lauryl glucoside	3	1	
	Dimethylaminopropylamine	2	1	
	Propolis	1	4	4
	Amerchol L 101		4	1
	Benzalkonium chloride		2	
Total		78	121	58

Abbreviations: MI, methylisothiazolinone; MCI, methylchlorisothiazolinone.

2 patients: 1 hand-borne allergy through a fingerstall, and 1 after contact with a cosmetic puff.

Thirty-seven patients had positive test reactions to their own products. In 16, the reactions to personal products were the only currently relevant positive reactions. Nine were to eye drops (2 different eye drops gave positive reactions in the same patient), 5 were to face creams, 2 were to nail varnishes, and 1 was to mascara. Among the eye drops, 5 were β -blockers, 2 were dorzolamide, 1 was azithromycin, and 1 was ketotifen. ROATs and use tests were the only tests to give positive results in 4 of the 16 cases: 2 with eye drops, 1 with a face cream, and the 1 with a mascara.

Overall, in 57 (67.9%) of the 84 patients with currently relevant positive test reactions, the dermatitis was attributable to cosmetics. In 11 patients, an eyelid treatment was responsible for the eyelid dermatitis: 8 eye drops, and 3 creams containing budesonide² or neomycin.¹ In 3 patients (all men), the eyelid dermatitis was attributable to an occupational allergen. One refrigeration engineer was allergic to potassium dichromate from cement, 1 gardener was allergic to colophonium from pine trees, and 1 resin floor installer was allergic to epoxy resin.

TABLE 4 Positive test reactions to the eyelid series

Allergens	Relevance		
	Current	Possible	None
2-Bromo-2-nitropropane-1,3-diol		1	
Chlorhexidine digluconate		1	
Sodium metabisulfite		6	5
Dodecyl gallate	1 ^a	1	2
Octyl gallate	1 ^a	2	3
<i>tert</i> -Butylhydroquinone	1	1	1
Triethanolamine			
Sorbitan sesquioleate		1	
Turpine oil, oxidized			1
Toluenesulfonamide formaldehyde resin		1	
Hydroabietyl alcohol		1	
Propylene glycol		1	1
Cocamide DEA			1
Cocamidopropylbetaine		1	
Sodium benzoate		1	
Shellac		6	2
Benzoyl peroxide	1	2	2
Benzophenone-3		1	1
Benzophenone-4	1	2	
Total	5	29	19

^a Same patient.

4 | DISCUSSION

This study is the first prospective study focused on the assessment of a specific eyelid series, the aim of which was to improve the diagnosis of relevant allergens in EACD. It is also the first study on eyelid dermatitis in a French patient population. From the results of our prospective study, when taking into account only the positive test reactions of current relevance, 95% of these were to allergens from the EBS and the French additional series associated with personal products, whereas our eyelid series was useful for only 4 patients, with 4 allergens: benzoyl peroxide, gallates, benzophenone-4, and *tert*-butylhydroquinone. Appropriate targeted tests based on an accurate investigation could have led to the identification of these 4 allergens even without using the eyelid series. Therefore, it appears that the usefulness of our eyelid series is too limited to warrant systematic use in the investigation of EACD.

Comparison between the different published studies on eyelid dermatitis is difficult, because they have different objectives. Some have focused on the causes of periorbital dermatitis,^{3,4,10} some on eyelid-limited contact dermatitis without any other skin involvement,¹ and some on only patients with positive test results¹¹ or even only on currently relevant test results.¹² One Italian prospective study concerned not only eczema but also other inflammatory dermatitis located on the eyelids, and was mainly a descriptive study.⁴ In this study, the series used and the results of patch testing were not outlined. All of the other studies were retrospective. A special eyelid series has already been suggested in 2 studies; however, they were based on retrospective data, they concerned only dermatitis limited to the eyelids, and most of the allergens were already contained in the

EBS.^{11,12} These recommendations have not been used in further studies.

The high proportion of women in our study (90%) is similar to the percentage (70-90%) reported in previous studies in other countries.^{1-4,13-15} It is higher than the 70% proportion of females in French patients patch tested for eczema with various localizations.⁷ This difference is usually attributed to higher cosmetic use among women, which is also supported by our study, in which 67.9% of the EACD cases were attributable to cosmetics. As observed in other studies, the proportion of atopic dermatitis, either past (26.9%) or current (9.5%), was high in our population, and higher than in the French patch test population.^{1-4,13,16} However, no statistically significant association was found between the test results and atopic dermatitis status. This is in accordance with a recent meta-analysis concerning the relationship between contact sensitization and atopic dermatitis.¹⁷

The most frequent allergens of current relevance in our study were MI, fragrance mix I, nickel sulfate, hydroxyperoxides of linalool and limonene, and *M. pereirae*. These allergens are the same as those reported most frequently in the population patch tested for eczema with various localizations.^{4,7,14} The very high prevalence of positive test reactions to MI (10.2%) can be explained by the worldwide outbreak of contact sensitization to this allergen, in which the eyelids are a classic localization, but the mixture MI/methylchloroisothiazolinone was already recognized as a main allergen in EACD before the MI sensitization outbreak.^{2,10,12,18-20} In our study, the sources of MI were cosmetics, household products, and paint. In most studies on EACD performed before the MI sensitization outbreak, nickel sulfate and fragrance allergens were, as in our study, the most frequently identified allergens, in addition to eye drop preservatives, which may vary according to the country and years of the studies.^{1-4,11-14,16,21-23}

Our French additional series appeared to be very useful for EACD evaluation, as it helped to identify 9.8% of the patients with currently relevant positive patch test reactions. Interestingly, hydroxyperoxides of linalool and limonene included in the French additional series gave positive reactions in 7 patients without positive reactions to any other fragrance allergens and, for 4 of them, no other relevant positive test reaction was observed. This high percentage of positive reactions to hydroxyperoxides is consistent with a recent Spanish study suggesting the inclusion of limonene and linalool hydroxyperoxides in the EBS.²⁴

In our study, 19% of the allergic patients (16/82) were only identified by testing with their personal products, and 4 of them only with a ROAT or a use test. These results support the usefulness of testing with patients' own products, particularly to detect allergens that are not present in the standardized series, such as drugs, and, particularly important for EACD, topical ophthalmic drugs.^{12,25} As these ophthalmic topicals may give false-negative results when patch tested on the back, a ROAT or a use test may be required.

One limitation of our study could be our choice to restrict our analysis to only currently relevant positive test reactions, but this, in our opinion, made the results more convincing. The second limitation could be the fact that we included EACD as the main reason for patch testing, but EACD did not need to be the sole site of dermatitis; however, this seemed to us to better reflect the real-life situation in our patients.

To conclude, patch testing with the EBS, 3 allergens of the French additional series (hydroxyperoxides of limonene and linalool and lauryl glucoside) and patients' own products seems to be useful for investigating EACD. The addition of an eyelid series did not greatly increase the percentage of positive relevant patch test reactions, and therefore its usefulness is too limited to justify systematic testing in cases of suspected EACD. Conversely, our French additional series could be recommended to be added to the EBS for improving the detection of allergens responsible for EACD. In cases of negative patch test results, ROATs and use tests with strongly suspected products remain absolute necessary.

Conflict of interest

The authors declare no potential conflict of interests.

ORCID

Haudrey Assier  <http://orcid.org/0000-0003-0465-1241>

Annick Barbaud  <http://orcid.org/0000-0001-8889-1589>

Brigitte Milpied  <http://orcid.org/0000-0003-3679-6613>

Julie Waton  <http://orcid.org/0000-0003-4791-5120>

Jean-Luc Bourrain  <http://orcid.org/0000-0002-9501-9331>

Nadia Raison-Peyron  <http://orcid.org/0000-0002-7991-3165>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Online supplemental table S1: Eyelid series

Allergen	Concentration (%) Vehicle	
2-bromo-2-nitropropane-1,3-diol	0.5 pet.	
Imidazolidinyl urea	2.0 pet.	
Diazolidinyl urea	2.0 pet.	
Chlorhexidine digluconate	0.5 aq.	
Sorbic acid	2.0 pet.	
Chloracetamide	0.2 pet.	
DMDM hydantoin	2.0 pet.	
Cetylpyridium chloride	0.1 pet.	
Phenoxyethanol	1.0 pet.	
Sodium metabisulfite	1.0 pet.	
BHT	2.0 pet.	
BHA	2.0 pet.	
Dodecyl gallate	0.25 pet.	
Octyl gallate	0.25 pet.	
<i>tert</i> -Butylhydroquinone	1.0 pet.	
Triethanolamine	2.0 pet.	
Sorbitan sesquioleate	20.0 pet.	
Cetearyl alcohol	20.0 pet.	
Iodopropynyl butylcarbamate	0.2 pet.	
Polyethene glycol 400	100	
Isopropyl myristate	20.0 pet.	
Turpentine oil, oxidized	0.4 pet.	
Tosylamide formaldehyde resin	10.0 pet.	
Hydroabietyl alcohol	10.0 pet.	
Propylene glycol	5.0 pet.	
Cocamide DEA	0.5 pet.	
Cocamidopropyl betaine	1.0 aq.	
Sodium benzoate	5.0 pet.	
Shellac	20.0 alc.	
Benzoyl peroxide	1.0 pet.	
Benzophenone-3	10.0 pet.	
Benzophenone-4	2.0 pet.	

pet : petrolatum, aq: aqua,

Form to be filled in by the practitioner

Check the correct items and specify when necessary

DATE:

PATIENT : Name (3 first letters) _ _ _ First name

Gender:

Birth date : / /

Exclusion criterion

- ☐ Suspicion of eyelid contact dermatitis is not the main purpose of the consultation
- ☐ No health care service
- ☐ Patient under the age of 18
- ☐ Pregnancy
- ☐ No respect of recommendations for patch testing
- ☐ Treatment modifying the tests interpretation
- ☐ Bad understanding of the questions

CLINICAL DATA

How was the diagnosis of the eyelid dermatitis made? (Check one of the 3 items)

- ☐ Present at the consultation
- ☐ Described by the patient
- ☐ Made by another dermatologist

Duration (months):

The dermatitis is (Check one of the 3 items)

- ☐ Chronic
- ☐ Acute
- ☐ Chronic recurring

Eyelid(s) involved

- ☐ Upper right
- ☐ Upper left
- ☐ Lower right
- ☐ Lower left

Description of the dermatitis

- ☐ Erythema
- ☐ Edema
- ☐ Scaling
- ☐ Scabby
- ☐ Pruritus
- ☐ Oozing
- ☐ Sharp limited
- ☐ Associated with conjunctivitis
- ☐ Face involvement (other than eyelids)
- ☐ Body involvement

Specify where:

Specify where:

☐ Photos of the eyelid dermatitis

Medical history

- ☐ Past history of contact dermatitis Specify the known allergen:
- ☐ Current atopic dermatitis Specify localizations:
- ☐ Past history of atopic dermatitis
- ☐ Past history of atopic symptoms Specify: ☐ conjunctivitis, ☐ asthma, ☐ hay fever
- ☐ Past history of face dermatitis Specify: ☐ psoriasis, ☐ rosacea, ☐ seborrheic dermatitis
- ☐ Important past history (other than dermatitis) Specify :

ENVIRONMENTAL SURVEY

Is eyelid dermatitis recurrence linked to?:

- ☐ Occupation
- ☐ Season Specify:
- ☐ A specific activity Specify:

Which activities are done?

- ☐ Profession Specify:
☐ Sport Specify:
☐ Manual hobbies Specify:
☐ Playing music Specify:

Environmental encounters

- ☐ Work in the personal or professional environment before the onset of the dermatitis Specify:
☐ Use of fragrance diffuser (at home or at work) including essential oils, scented candle, toilet spray...
☐ Pets Specify:
☐ Smoking (cigarette, cigar, pipe) ☐ electronic cigarette

Ophthalmic contacts

- ☐ Eye drop utilisation Current ☐ Specify which one:
Past ☐ Specify which one:

- ☐ Glasses How are they cleaned:
☐ Ophthalmic lens How are they cleaned:
☐ Ophthalmic examination before the onset of the dermatitis
☐ Swimming goggles

COSMETIC HABITS

What are the facial hygiene products used?

- ☐ Cleansing bar
☐ Shower gel
☐ Facial cleanser

What are the face creams used?

- ☐ Day cream Specify:
☐ Night cream Specify:
☐ Anti-aging cream Specify:
☐ Eyelid cream Specify:

What are the hair care products used?

- ☐ Shampoo
☐ Conditioner
☐ Hair spray
☐ Hair dye ☐ Colored locks
☐ Gel, mousse, mask..

What are the hand care products used?

- ☐ Cream
☐ Nail varnish
☐ Acrylic nails

What are the eyelids make-up used?

- ☐ Mascara
☐ Eye liner
☐ Eye pencil
☐ Eye shadow
☐ Eye removing make-up
☐ Cleansing wipe

Are some of these products used?

- ☐ Perfume Specify: ☐ Spray ☐ Hand application
☐ Body deodorant Specify: ☐ Spray ☐ roll-on ☐ stick

- ☐ Topical treatment used for the eyelid dermatitis Specify: