Anton C. de Groot

ADVERSE REACTIONS TO COSMETICS

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Stellingen

1. De hoeveelheid vrije formaldehyde in cosmetische producten die geconserveerd worden met DMDM hydantoin is voldoende om bij sommige individuen met contactallergie voor formaldehyde dermatitis te induceren (A.C. de Groot et al. Contact Dermatitis 1988; 18: 197)

2. Pre-marketing onderzoek naar irritatieve effecten van cosmetische producten dient bij voorkeur bij atopici te worden uitgevoerd.

3. Om onnodige angst bij de gebruiker te voorkomen, dient de informatie over mogelijke bijwerkingen, vermeld op de bijsluiter van geneesmiddelen, meer genuanceerd te worden weergegeven.

4. Het idee, dat voor het ontstaan van "allergie" nieuwe contactstoffen geïntroduceerd dienen te zijn, blijkt onder leken, maar ook onder huisartsen, wijdverbreid.

5. Het is dringend noodzakelijk, dat de vermelding van alle bestanddelen van cosmetica op de verpakking in EEG verband wettelijk verplicht wordt gesteld.

6. Lokaal toegepast minoxidil heeft bij mannelijke patienten met alopecia androgenetica zelden een cosmetisch acceptabele mate van nieuwe haargroei tot gevolg.

7. De consequente afwijzing door een aantal "bewuste" moeders van corticosteroiden-bevattende zalven is nadelig voor hun kinderen met ernstig atopisch eczeem.

8. Het College Ter Beoordeling van Geneesmiddelen (Rijswijk) dient over meer wettelijke bevoegdheden te beschikken om registratie van nieuwe geneesmiddelen te weigeren.

9. Methyl(chloor)isothiazolinon (Kathon CG) 100 ppm in water dient aan de Europese standaardreeks van veel voorkomende contactallergenen te worden toegevoegd (A.C. de Groot en J.D. Bos. Brit J Derm 1987; 116: 289).

10. Opschriften op cosmetica als "zuiver plantaardig", "zonder chemische toevoegingen", "gaat rimpelvorming tegen", duiden erop dat het beleid van de Nederlandse overheid ten aanzien van Artikel 6.2 van de EEG cosmetica wetgeving (Cosmetic Directive 76/768/EEC) niet het gewenste effect heeft.

11. De diagnose "compound allergie" verbergt vaak inadequate diagnostiek.

12. Gegevens over bijwerkingen van cosmetica, aan de Keuringsdienst van Waren gemeld door medici en consumenten, zijn epidemiologisch gezien van geen waarde.

13. Nu blijkt dat irritatie de meest voorkomende bijwerking van cosmetica is, kan op korte termijn de introduktie van *"hypo-irriterende"* produkten tegemoet gezien worden.

14. Dermatologische studies over bijwerkingen van cosmetica dienen door de cosmetische industrie gebruikt te worden ter optimalisering van de produkt-veiligheid, en niet opgevat te worden als een aanval op hun branche.

15. Toepassen van parabenen in cosmetica is relatief veilig.

16. De aanwezigheid van formaldehyde in nagelverharders die tolueensulfonamide/formaldehyde hars bevatten, verhoogt mogelijk de kans op sensibilisatie voor de hars (FS de Wit et al. Contact Dermatitis 1988; 18: 280).

17. Het "moment" van telefonistes doet vermoeden dat zij een andere tijdsrekening hanteren dan gebruikelijk is.

18. Voor verdergaande bezuinigingen in de Gezondheidszorg ontbreekt een breed maatschappelijk draagvlak.

19. Partnerruil komt in bridgekringen niet zelden voor.

RIJKSUNIVERSITEIT GRONINGEN

ADVERSE REACTIONS TO COSMETICS

PROEFSCHRIFT

ter verkrijging van het doctoraat in de

GENEESKUNDE

aan de Rijksuniversiteit Groningen op gezag van de Rector Magnificus Dr. L.J. Engels in het openbaar te verdedigen op woensdag 21 december 1988 des namiddags te 4.00 uur

door

ANTON CORNELIS DE GROOT

geboren te Deventer

Promotores:	Prof. Dr. J.P. Nater
	Prof. Dr. E. Bleumink
Referent:	Dr. P.J. Coenraads

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Prof. Dr. M.N.G. Dukes
Prof. Dr. H. Wesseling
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(Thesis, State University of Groningen, The Netherlands, 1988)

Aan mijn ouders
Aan Janny, Elleke en Suzan

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Aims of the studies

Cosmetics and toiletry products are used by everyone for the daily care and hygiene of the body, to enhance attractiveness, to obtain a pleasant smell, for protection, or for masking skin defects.
Vast sums of money are involved in cosmetics and toiletries, and the use of these products still increases. A broad spectrum of adverse reactions to cosmetics has been observed including irritant effects, contact allergy, photosensitivity, contact urticaria, acne/folliculitis, discoloration of the skin and appendages, and systemic side effects.
Although many studies have reported on cosmetic-related side effects, a number of aspects still need to be clarified, e.g. the frequency of adverse reactions from cosmetics and toiletries, their nature, the profile of consumers liable to develop such reactions, and the products and ingredients responsible. Such data are essential to provide the information necessary to optimise the safety-profile of cosmetics and toiletries.

Several factors account for the relative paucity of available data:
1. Most patients who experience adverse effects from cosmetics or toiletries merely cease to use the offending product, and do not seek medical attention.
2. The lack of information on the ingredients of cosmetic products (the USA excepted) has discouraged dermatologists from further investigations in patients with diagnosed cosmetic allergy.
3. Most research has been done in selected groups of patients seen in dermatological clinics; epidemiological studies have rarely been performed.

We therefore planned a number of investigations aiming to answer the following questions:
1. What is the frequency of side effects from cosmetics and toiletries ?
2. How often are cosmetic-related adverse reactions caused by contact allergy ?
3. Which ingredients are the most frequent causes of cosmetic allergy?

The ultimate goal, of course, is to make a contribution to the development of safer cosmetic products.

Chapter 1 Introduction

1.1 COSMETICS: WHAT THEY ARE AND WHAT THEY DO

A "cosmetic product" means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours (Cosmetic Directive 76/768/EEC, Article 1). The products to be considered as cosmetic products within the meaning of this definition are shown in the following illustrative list by category:

- Creams, emulsions, lotions, gels and oils for the skin (hands, face, feet, etc.)
- Face masks (with the exception of peeling products)
- Tinted bases (liquids, pastes, powders)
- Make-up powders, after-bath powders, hygienic powders, etc.
- Toilet soaps, deodorant soaps, etc.
- Perfumes, toilet waters and eau de Cologne
- Bath and shower preparations (salts, foams, oils, gels, etc.)
- Depilatories
- Deodorants and anti-perspirants
- Hair care products:
  - hair tints and bleaches
  - products for waving, straightening and fixing
  - setting products
  - cleansing products (lotions, powders, shampoos)
  - conditioning products (lotions, creams, oils)
- Shaving products (creams, foams, lotions, etc.)
- Products for making up and removing make-up from the face and the eyes
- Products intended for application to the lips
- Products for care of the teeth and the mouth
- Products for nail care and make-up
- Products for external intimate hygiene
- Sunbathing products
- Products for tanning without sun
- Skin-whitening products
- Anti-wrinkle products

Cosmetics have been used for millennia to embellish the physical, mental, and spiritual well being of mankind. These products are used with one or more of the following purposes:

- for the daily care and hygiene of the body (soap, shampoo, toothpaste, moisturising and cleansing cream)
- to enhance attractiveness (makeup, hair colour, permanent wave, setting and styling gel, nail lacquer)
- to obtain a pleasant smell (deodorant, perfume, aftershave, mouth-freshener)
- for protection (sunbathing products)
- for the masking of skin defects, e.g. vitiligo, wine spots

Recent studies have indicated that cosmetics can bring substantial psychological benefits (61).

1.2 COSMETICS: THE EXTENT OF THEIR USAGE

Cosmetic products are used by everyone. In 1974, a consumer panel of 10,050 family units (35,490 persons) located throughout the USA was interviewed on personal cosmetic usage pattern (Westat Report, see Chapter 2.2). The results are shown in Table 1.

Table 1. Number of panel members using at least one cosmetic brand at least one time during September 1974 by product category (Westat report, chapter 2.2)

Product category	Number of panel members	% (N=35,490)
Toothpaste/polish/whitener	29,163	82%
Mouthwash/breath freshener	16,983	48%
Deodorant/antiperspirant	21,703	61%
Soap	30,819	87%
Suntan/sunscreen	6,449	18%
Talcum/bath powder/spray	15,925	45%
Feminine hygiene deodorant	2,168	6%
Douche	1,958	6%
Foot powder/spray	7,518	21%
Bath bubble/oil/capsule	9,203	26%
Hand/body lotion	15,347	43%
Colognes	12,117	34%
Hair spray/lacquer	8,763	25%
Hair colour/bleach	2,943	8%
Shampoo	28,287	80%
Hair dressing	5,008	14%
Setting/waving gel/solution	3,307	9%
Home permanent	1,466	4%
Hair relaxer/straightener	132	<1%

Table 1. (continued)

Product category	Number of panel members	% (N=35,490)
Cream rinse/conditioner	9,544	27%
Aftershave	8,709	25%
Shave cream	8,237	23%
Beard softener	615	2%
Depilatory	1,133	3%
Mascara	6,623	19%
Eye shadow	6,272	18%
Eyeliner	3,190	9%
Cleanser/makeup remover	3,968	11%
Eye cream	1,438	4%
Eyebrow pencil	4,426	12%
Lipstick	9,517	27%
Face powder/blusher/rouge	6,828	19%
Foundation/base/lightener	5,902	17%
Facial skin cream/cleaner	7,100	20%
Moisturiser/lotion	6,128	17%
Skin freshener/adstringent	3,799	11%
Night cream	3,774	11%
Nail polish	7,666	22%
Hardener/extender	2,881	8%
Nail undercoat/base coat	2,094	6%
Polish remover	7,267	20%
Cuticle remover/softener	2,898	8%

The product categories used by the largest number of consumers were soap (87%), toothpaste/polish/whitener (82%), shampoo (80%), deodorant/antiperspirant (61%), mouthwash/breath freshener (48%), talcum/bath powder/spray (45%) and hand/body lotion (43%). The cosmetic categories used by the smallest number of consumers were hair relaxer/straightener (<1%), beard softener (2%), depilatory (3%), eye cream (4%), and home permanent (4%).

We have conducted a survey on cosmetic usage pattern in 811 (regular) female clients of beauticians (62). The results are shown in Table 2. Obviously this group of consumers is a very attractive target population to the cosmetic industry. Toothpaste, shampoo, facial cream /lotion and perfume/toilet water were used by more than 90% of the 811 women. Between 80-90% of the clients interviewed used deodorant/antiperspirant, eye shadow, lipstick, soap, and body lotion. Mascara, facial tonic/milk, facial mask, bath/shower foam, hand lotion/cream, and nail lacquer were used by 70-80% of these women (62).

Table 2 lists the number of clients using one or more products of a certain cosmetic category only, without reference to their frequency of usage. Detailed information on this is shown in Appendix 1.

Table 2. Cosmetic usage pattern in 811 female clients of beauticians

Product category	No. of clients using products of this category	%
Toothpaste	781	96%
Mouthfreshener	177	22%
Deodorant/antiperspirant	669	82%
Shampoo	798	98%
Colour shampoo	195	24%
Hair lacquer	413	51%
Hair dye/bleach	241	30%
Hair conditioner	447	55%
Dry shampoo	60	7%
Cream rinse	496	61%
Permanent (at home)	45	6%
Permanent (hairdresser)	430	53%
Mascara	600	74%
Eye shadow	667	82%
Eyeliner	151	19%
Eye cream	193	24%
Eye pencil	418	52%
Brow pencil	256	32%
Eye cosmetics remover	391	48%
Facial cream/lotion	753	93%
Facial powder	205	25%
Rouge	558	69%
Facial tonic/milk	629	78%
Liquid makeup	435	54%
Facial mask	640	79%
Camouflage stick	158	19%
Makeup remover	427	53%
Lipstick	703	87%
Soap	705	87%
Body powder	114	14%
Bath/shower foam	583	72%
Bath oil	310	38%
Bath salt	137	17%
Body lotion	662	82%
Hand lotion/cream	598	74%
Perfume/toilet water	741	91%
Depilatory cream	262	32%
Nail lacquer	570	70%

Table 2. (continued)

Product category	No. of clients using products of this category	%
Nail lacquer remover	562	69%
Nail hardener (conditioner)	121	15%
Artificial nail	33	4%
Foot powder	100	12%

Vast sums of money are involved in cosmetics and toiletry products. In the USA, over 800 million dollars were spent in 1981 on over-the-counter moisturisers alone (63). In 1986, the sales (at factory prices) by the members of the Dutch Cosmetics Association amounted to 910 million Dutch guilders, an increase of 10% over 1985 (64). This represents approximately 80% of the entire Dutch market. The shares of the various product categories are shown in Table 3.

Table 3. 1986 Sales of the members of the Dutch cosmetics association. Shares of various product categories and % increase over 1985 (64)

Product category	Sales 1986 (millions)	% of total	(% increase)
Hair care products	204.5	22.5%	(12.2%)
Perfumes, Colognes	95.3	10.5%	(3.4%)
Products for oral hygiene	92.0	10.1%	(9.0%)
Baby products	31.0	3.4%	(4.4%)
Skin care products	152.3	16.7%	(12.0%)
Beautifying cosmetics	90.5	9.9%	(9.4%)
Bath cosmetics & Deodorants	135.9	14.9%	(11.3%)
Men's cosmetics	53.0	5.8%	(16.0%)
Soap (luxury products)	30.9	3.4%	(3.0%)
Other, incl. Sun cosmetics	24.4	2.7%	(10.9%)
TOTAL	909.8	100 %	(10.0%)

Until recently, marketing efforts have been directed mainly at women. Presently, there is an increase in the usage of cosmetic products by men.

1.3 THE INGREDIENTS OF COSMETICS

Cosmetics are complex mixtures of chemical compounds. It has been estimated (30) that about 8,000 vehicle raw materials and fragrance ingredients are available to the cosmetic chemist. Though the rational approach to formulation is fairly logical and simple, the abundance of

available ingredients has created endless variety in cosmetic formulations. An illustrative example is moisturising cream:

MOISTURISING CREAM (11)

Lipid	500
Surfactant; emulsifier	1000
Polyol; humectant	20
Thickener	30
Moisturising agent	50
Antioxidant	40
Preservative	150
Colour	500
Fragrance	3500
Total	5790

Thus, nearly 6000 ingredients are available to a chemist wanting to formulate a moisturising cream. The substances used in cosmetic products may (arbitrarily) be divided into six functional classes: antimicrobials and antioxidants, fragrance materials, colours, sunscreens, lipids and surfactants, and miscellaneous cosmetic ingredients. A tabulation of these classes, their subclasses, and some examples are provided below (adapted from ref. 11). The examples mentioned in each class are usually either frequently used in cosmetic products, or known causes of cosmetic sensitisation.

ANTIMICROBIALS AND ANTIOXIDANTS

This functional group of cosmetic ingredients may be divided as follows (some examples given for each category):

1. *Antioxidants and chelating agents*
   - BHA (Butylated hydroxyanisole)
   - BHT (Butylated hydroxytoluene)
   - *ditert*-Butyl hydroquinone
   - *t*-Butyl hydroquinone
   - EDTA (Ethylene diamine tetra acetic acid)
   - Gallates (cetyl, dodecyl, octyl, propyl)
   - Nordihydroguaiaretic acid
   - Tocopherol
   - *o*-Tolyl biguanide

2. *Antimicrobials: acids (salts) – esters – alcohols -amides*
   - Benzoic acid
   - Benzyl alcohol
   - Dehydroacetic acid

- Parabens (benzyl-, butyl-, ethyl-, methyl-, propyl-)
- Phenoxyethanol
- Potassium sorbate
- Sodium benzoate
- Sorbic acid

3. *Formaldehyde and donor compounds*
   - 2-Bromo-2-nitropropane-1,3-diol
   - Diazolidinyl urea
   - DMDM hydantoin
   - Formaldehyde
   - Imidazolidinyl urea
   - Methenamine
   - Quaternium-15

4. *Mercurials*
   - Phenylmercuric salts (acetate, borate, chloride, nitrate)
   - Thimerosal

5. *Phenols – halogenated phenols – organohalogen compounds*
   - Chlorhexidine (diacetate, digluconate, dihydrochloride)
   - Chloroacetamide
   - Chlorobutanol
   - *p*-Chloro-*m*-cresol
   - Chloroxylenol
   - Cloflucarban
   - Hexachlorophene
   - Kathon CG
   - *o*-Phenylphenol
   - Triclocarban
   - Triclosan

6. *Cationic compounds*
   - Benzalkonium chloride
   - Benzethonium chloride
   - Cetrimonium bromide
   - Cetrimonium chloride
   - Cetylpyridinium chloride

7. *Other antimicrobials*
   - Dimethoxane
   - Glutaral
   - Quinoline-derivatives
   - Sulfur
   - Zinc pyrithione

FRAGRANCE MATERIALS

This is the largest group of cosmetic ingredients, consisting of thousands of fragrances of natural origin and synthetic materials. The Research Institute for Fragrance Materials (RIFM) has investigated over 800 fragrance materials for their sensitising potential (11).
Some examples are (see also Appendix 2):

Acetyl cedrene
Amyl cinnamate
α-Amylcinnamic alcohol
α-Amylcinnamic aldehyde
Anisic aldehyde
Balsam Peru
Benzaldehyde
Benzyl acetate
Benzyl alcohol
Benzyl benzoate
Benzyl salicylate
D- and L-Carvone
Caryophyllene
Cassia oil
Cinnamic alcohol
Cinnamic aldehyde
Citral
Citronellal
Citronellol
Coumarin
Diethyl phthalate
Ethyl acetate
Eugenol
Geranial
Geraniol
Heliotropin
Hexylcinnamic aldehyde
Hydroxycitronellal
Isoeugenol
Lilial
D- & L-Limonene
Linalool
Lyral
γ-Methylionone
Musk ambrette
Musk ketone
Oak moss
Phenylethyl alcohol
α- & β-Pinene
Spearmint oil
Terpineol
Terpinyl acetate

COLOURS

Colours are classified as follows:

Dyes	*Colour Index Numbers*
Nitroso	10000-10299
Nitro	10300-10999
Azo	
Monoazo	11000-19999
Disazo	20000-29999
Trisazo	30000-34999
Polyazo	35000-36999
Azoic	37000-39999

Stilbene	40000-40799
Carotenoid	40800-40999
Diphenylmethane	41000-41999
Triarylmethane	42000-44999
Xanthene	45000-45999
Acridine	46000-46999
Quinoline	47000-47999
Methine and Polymethine	48000-48999
Thiazole	49000-49399
Indamine and Indophenol	49400-49999
Azine	50000-50999
Oxazine	51000-51999
Thiazine	52000-52999
Sulfur	53000-54999
Lactone	55000-55999
Aminoketone	56000-56999
Hydroxyketone	57000-57999
Anthraquinone	58000-72999
Indigoid	73000-73999
Phthalocyanine	74000-74999
Natural organic colouring matters	75000-75999
Oxidation bases	76000-76999
Inorganic colouring matters	77000-77999

Some frequently used colours are:

CI 12075 (D&C Orange no. 17)
CI 13065 (Acid Yellow 36)
CI 14700 (FD&C Red no. 4)
CI 15510 (D&C Orange no. 4)
CI 15585 (D&C Red no. 8 & 9)
CI 15630 (Pigment Red 49 Barium lake)
CI 15850 (D&C Red no. 6 and 7 lakes)
CI 15985 (FD&C Yellow no. 6, Sunset Yellow)
CI 16185 (Amaranth)
CI 17200 (D&C Red no. 33)
CI 19140 (FD&C Yellow no. 5)
CI 26100 (D&C Red no. 17)
CI 42053 (FD&C Green no. 3)
CI 42090 (FD&C Blue no. 1)
CI 45170 (D&C Red no. 19)
CI 45370 (D&C Orange no. 5)
CI 45380 (D&C Red no. 21)
CI 45430 (FD&C Red no. 3)

CI 47000 (D&C Yellow no. 11)
CI 47005 (D&C Yellow no. 10)
CI 61565 (D&C Green no. 6)
CI 61570 (D&C Green no. 5)
CI 75470 (Carmine)
CI 77004 (Aluminum silicate, Bentonite, Kaolin)
CI 77007 (Ultramarine Blue/Red/Violet)
CI 77019 (Mica)
CI 77163 (Bismuth oxychloride)
CI 77220 (Calcium carbonate)
CI 77267 (Carbon Black)
CI 77288 (Chromium oxide Greens)
CI 77289 (Chromium hydroxide Green)
CI 77510 (Ferric ferrocyanide)
CI 77742 (Manganese Violet)
CI 77891 (Titanium dioxide)
CI 77947 (Zinc oxide)

Frequently used colour ingredients of *hair dye* preparations include:

m-Aminophenol
o-Aminophenol
p-Aminophenol
2-Methoxy-*m*-phenylenediamine sulfate
4-Nitro-*o*-phenylenediamine
2-Nitro-*p*-phenylenediamine
p-Phenylenediamine
Pyrogallol
Resorcinol
Toluene-2,5-diamine (sulfate)

SUNSCREENS

This group of cosmetic ingredients, which are used for both protecting the skin and products themselves against UV-light may be divided as follows (examples for each category provided):

1. PABA derivatives
- Amyl dimethyl PABA
- Glyceryl PABA
- Octyl dimethyl PABA
- PABA

2. *Anthranilates*
   - Glyceryl-3-(glyceroxy)anthranilate
   - Homomenthyl *N*-acetyl anthranilate
   - Menthyl anthranilate

3. *Salicylates*
   - Benzyl salicylate
   - Homosalate
   - Octyl salicylate
   - Phenyl salicylate

4. *Cinnamates*
   - Cinoxate
   - Isopropyl-*p*-methoxycinnamate
   - Octyl *p*-methoxycinnamate

5. *Benzophenones*
   - Benzophenone-1 – 12

6. *Camphoric UV-absorbers*
   - 3-Benzylidene camphor
   - 3-(4'-Methylbenzylidene) camphor

7. *Other UV-absorbers*
   - Butyl methoxydibenzoylmethane
   - Dianisoyl methane
   - Digalloyl trioleate
   - Drometrizole
   - 4-Isopropyl-dibenzoylmethane
   - 2-Phenylbenzimidazole-5-sulfonic acid

LIPIDS AND SURFACTANTS

This group of cosmetic ingredients may be classified as follows (examples of frequently used ingredients are provided for each category):

1. *Lipids*
   - Beeswax
   - Castor oil
   - Cetyl alcohol
   - Cetyl palmitate
   - Corn oil
   - Dibutyl phthalate
   - Glyceryl oleate
   - Mineral oil
   - Octyl palmitate
   - Oleyl alcohol
   - Ozokerite
   - Paraffin
   - Petrolatum
   - Propylene glycol

- Glyceryl stearate
- Isopropyl myristate
- Isopropyl palmitate
- Lanolin (derivatives)
- Microcrystalline wax
- Spermaceti
- Squalane
- Stearic acid
- Stearyl alcohol
- Wheat germ glycerides

2. *Anionic surfactants*
   - Ammonium lauryl sulfate
   - Disodium cocamido sulfosuccinate
   - Disodium oleamido sulfosuccinate
   - Sodium laureth sulfate
   - Sodium lauryl sulfate
   - Sodium stearate
   - Sulfated castor oil
   - Triethanolamine lauryl sulfate

3. *Cationic surfactants*
   - Benzalkonium chloride
   - Benzethonium chloride
   - Cetrimonium bromide
   - Cetylpyridinium chloride
   - Oleamidopropyl dimethylamine
   - Quaternium-1 – 54
   - Stearalkonium chloride

4. *Nonionic surfactants*
   - Cocamide DEA
   - Laneth-5 – 40
   - Lauramide DEA
   - Laureth-3 – 23
   - Nonoxynol-2 – 14
   - Oleth-2 – 25
   - PEG derivatives
   - Polysorbate-20 – 85
   - PPG derivatives
   - Sorbitan laurate
   - Sorbitan sesquioleate
   - Sorbitan stearate

5. *Amphoteric surfactants*
   - Amphoteric-1 – 20
   - Cocamidopropyl betaine
   - Cocobetaine

6. *Amines – Aminoalkanols*
   - Aminomethyl propanol
   - Diisopropanolamine

7. *Polyols (polyalcohols)*
   - Butylene glycol
   - Ethoxydiglycol
   - Glycerol
   - Hexylene glycol
   - PEG-4 - 150
   - Polypropylene glycol (PPG)
   - Sorbitol

MISCELLANEOUS COSMETIC INGREDIENTS

These include a variety of cosmetic ingredients that may be divided in the following (functional) classes:

Acidic agents
Adhesive aids
Adsorbents
Adstringents
Aerosol propellants
Alcohol denaturants
Alkaline agents
Aminoacids
Antiperspirants
Antiseborrhoeic agents
Buffering salts
Counterirritants
Depilating agents
Hair waving agents
Humectants
Natural ingredients
Oxidising agents
Perfume carriers
Plasticisers
Polymers
Powder fillers
Skin abrasives
Skin healing agents
Solvents
Suspending agents
Sweeteners
Thickeners
Vitamins

THE FREQUENCY OF USAGE OF COSMETIC INGREDIENTS

No data exist on the frequency of usage of the various ingredients in cosmetics and toiletries in the EEC. In the USA, the Food and Drug Administration (FDA) in 1986 had approximately 19,000 cosmetic formulas of wholesale products on file. The 100 ingredients found most frequently to be present in these formulas (fragrances and flavours not included) are listed in Table 4, together with the number of products containing them. It should be appreciated, that the ingredients used by cosmetic chemists/companies in the USA and the EEC may differ considerably. Nevertheless, most ingredients on this list will probably be also in the list of "Top-100" in the EEC.

Table 4. The 100 most frequently used ingredients in 19,000 cosmetic formulas on file with FDA (March 1986); number of products containing the chemicals

No. of Products	Name	Function (65)
6787	Methylparaben	Preservative
5911	Propylparaben	Preservative
4073	Mineral oil	Emollient
3503	Propylene glycol	Solvent
3449	Titanium dioxide	Opacifier
3121	Iron oxides	Colourant
2937	Alcohol, denatured	Solvent, Preservative
2584	Triethanolamine	Neutraliser
2453	Talc	Powder
2336	Stearic acid	Emollient, Emulsifier
2309	Cetyl alcohol	Emulsifier, Emollient
2048	BHA	Antioxidant
1759	Beeswax	Emulsifier
1749	Glycerin	Humectant
1719	EDTA (sodium salts)	Chelate, Preservative, Antioxidant
1676	FD&C Yellow no. 5	Colourant
1655	Lanolin	Emollient, Emulsifier
1574	Isopropyl myristate	Emollient, Solvent
1531	Glyceryl stearate (SE)	Emollient, Opacifier, Emulsifier
1393	Zinc stearate	Anti-caking
1352	Castor oil	Pigment dispersant, Emollient
1337	Ultramarine Blue	Colourant
1319	FD&C Blue no. 1	Colourant
1263	Carnauba	Wax
1240	Petrolatum	Moisturiser
1235	Candelilla wax	Wax
1198	Mica	Powder, Pearlant
1178	Ozokerite	Wax
1146	Citric acid	Acidulent
1105	D&C Red no. 7 Calcium lake	Colourant
995	Paraffin	Moisturiser
960	Imidazolidinyl urea	Preservative
959	Lanolin oil	Emollient, Lubricant
900	Isopropyl lanolate	Lubricant, Emollient
895	Kaolin	Absorbent, Anti-caking
877	Quaternium-15	Preservative
777	Butylparaben	Preservative
773	Oleyl alcohol	Emollient, Lubricant
752	Bismuth oxychloride	Pearlant
725	Allantoin	Skin protectant
714	Isopropyl palmitate	Emollient, Solvent
710	Isopropyl alcohol	Solvent

Table 4. (continued)

No. of Products	Name	Function (65)
701	Magnesium aluminum silicate	Thickener
696	Microcrystalline wax	Emollient
679	FD&C Red no. 4	Colourant
665	Dimethicone	Emollient, Silicone, Antifoam
661	D&C Red no. 6 Barium lake	Colourant
634	Ammonium hydroxide	Neutraliser
607	Sodium chloride	Thickener
606	Sodium lauryl sulfate	Detergent, Foamer
596	BHT	Antioxidant
590	Camphor	Soothing agent
587	Boric acid / Sodium borate	Antiseptic
587	FD&C Yellow no. 6	Colourant
563	Formaldehyde	Preservative
561	Polysorbate 20	Emulsifier, Solubiliser, Thickener
557	Ethyl acetate	Solvent
545	Butyl acetate	Solvent
531	Acetylated lanolin alcohol	Emollient
522	Toluene	Solvent
518	Resorcinol	Hair dye
514	Magnesium carbonate	Powder
512	*p*-Phenylenediamine	Hair dye
512	Polysorbate 60	Emollient, Emulsifier, Stabiliser
509	Hydrolyzed animal protein	Protein
507	Lecithin	Emulsifier, Conditioner, Wetting agent
505	D&C Red no. 19	Colourant
496	Dibutyl phthalate	Insect repellent
489	Lauramide DEA	Foam stabiliser, Thickener, Emulsifier
482	Lanolin alcohol	Emulsifier
470	Panthenol	Humectant, Vitamin
467	Cocamide DEA	Foam booster, Thickener, Emulsifier
467	D&C Red no. 33	Colourant
464	Carbomer 934	Thickener
449	Stearyl alcohol	Emulsifier, Emollient
436	D&C Red no. 9 Barium lake	Colourant
434	Carbomer 940	Thickener
430	Oleic acid	Emulsifier, Intermediate
429	*p*-Aminophenol	Hair dye
429	Sorbitan sesquioleate	Emollient
424	Sorbic acid	Preservative

Table 4. (continued)

No. of Products	Name	Function (65)
409	D&C Yellow no. 10	Colourant
404	Manganese Violet	Colourant
403	Squalane	Emollient
394	Cellulose gum	Thickener
394	Dehydroacetic acid (sodium salt)	Preservative
388	Octyl palmitate	Emollient
380	Hydroxyethylcellulose	Thickener
377	Octyldodecanol	Emulsifier, Emollient
362	Phosphoric acid	Buffer
354	Propylene glycol stearate	Opacifier, Emulsifier, Pearlant
352	Chromium hydroxide Green	Colourant
347	Acetyl triethyl citrate	
339	Ferric ferrocyanide	Colourant
334	Carmine	Colourant
333	Chromium oxide Greens	Colourant
327	Sodium sulfite	Depilating agent
324	FD&C Blue no. 1 Aluminum lake	Colourant
324	PVP	Resin, Fiber, Thickener, Binder
323	D&C Yellow no. 5 Aluminum lake	Colourant

1.4 ADVERSE REACTIONS TO COSMETICS AND TOILETRIES

Cosmetics have often been denigrated as insignificant and frivolous. Also, many dermatologists believed that these products did more harm than good. An illustrative discussion took place in a meeting of the American Medical Association in the year 1925, in connection with a presentation on cosmetic side effects (60):

Dr. Harold N. Cole, Cleveland: It is well for our members to keep this before the profession and before the public. I hope the American Medical Association will see that this matter is circularized through the newspapers again. In that way we shall do much toward letting the *senseless women* know what they are doing in using dyes in their hair, rouge and other cosmetics.

Dr. Lulu Hunt Peters, New York: I am one of the senseless women who have been addicted to powder and rouge for some years, but I have never had a dermatitis. I wonder whether the percentage is not rather small.

It should be appreciated that in those days some hazardous materials were used in cosmetic products, such as lead carbonate, bismuth and mercurials.

Unwanted effects of cosmetics can be classified as follows:

1. Irritation (objective and/or subjective)
2. Contact allergy
3. Photosensitivity
4. Contact urticaria
5. Acne/folliculitis
6. Colour changes of the skin and appendages
7. Other local side effects
8. Systemic side effects

1. IRRITATION

Subjective irritation may be defined as chemically induced burning, stinging, itching, or other skin discomfort *without* visible, obvious signs of inflammation (4). It is estimated that between 1 and 10% of all cosmetic users note and often complain of this discomfort, primarily on the face (4). *Objective irritation* is defined as non-immunologically mediated inflammation of the skin. Its signs usually are mild erythema and scaling, but frank dermatitis may occur. Irritation may be observed with cosmetic products containing detergents such as soap, shampoo, and bath/shower foam. The humid climate in, and anatomical occlusion of the axillae favour irritant responses to deodorants and antiperspirants (5). Surfactants and emulsifiers present in moisturising or emollient creams may cause irritation, especially when applied to facial skin. Daily application of eye makeup cosmetics and removal with cleansing products often irritate the sensitive skin of the eyelids.

2. CONTACT ALLERGY

Allergic reactions to cosmetic products are often unrecognised, both by the patient and by the physician. Several factors are involved:

a. Frequently patients have used the causative cosmetics for many years; the development of skin problems from such products conflicts with the consumer's perception of allergy, which is based on the assumption, that a *new* cosmetic has to be introduced.
b. Cosmetic allergy is sometimes manifested by mild reactions only, e.g. itching, erythema and scaling of the eyelids.
c. Cosmetic dermatitis may sometimes be noticed, but wrongly interpreted. Psoriasis of the face may be exacerbated by cosmetic dermatitis (12); dermatitis caused by emollient creams interpreted as worsening of dry skin or atopic dermatitis for which it was applied; and contact allergy

to sunscreens as failure of the product to adequately protect the skin against the sun-rays. The literature on cosmetic allergy is surveyed in Chapter 3.2.

3. PHOTOSENSITIVITY

Contact photosensitivity (CPS) implies chemical photosensitivity resulting from UV-induced excitation of a chemical applied to the skin. Traditionally, CPS has been divided into phototoxic and photoallergic reactions; however, in practice, it is often difficult to categorise the individual photochemical reaction in vivo.

Phototoxic reactions may be experienced by any individual, provided that the ultraviolet light contains the appropriate wave-lengths to activate the compound, and that the UV dose and the concentration of the photoreactive chemical are high enough. For photoallergic reactions, which are rare compared to both contact allergic and to phototoxic reactions, a sensitisation period is required. The reactions are usually delayed, becoming manifest days or weeks after the UV exposure. A major problem with photoallergy is that the patients often remain photosensitive for many years, even when contact with the offending chemical is meticulously avoided ("persistent light reactions") (13).

With the exception of the epidemic caused by the halogenated salicylanilides in the 1960s (Chapter 3.2), photosensitivity has accounted for only a small proportion of cosmetic-related side effects. In a study from the USA (7), photoallergy and phototoxicity were responsible for only 9 reactions in 713 patients investigated for cosmetic dermatitis. Currently, musk ambrette, a fragrance in some aftershaves, has been reported as a major cause of cosmetic photosensitivity reactions (14).

Cosmetic ingredients which have caused photosensitivity reactions (not necessarily by their presence in cosmetic products) are listed in Table 5.

Table 5. Cosmetic ingredients that have caused photosensitivity (adapted from ref. 11)

	Ref.
6-Acetoxy-2,4-dimethyl-*m*-dioxane	(15)
Amyl dimethyl PABA	(16)
Balsam Peru	
Benzophenone-3	(16)
Benzophenone-10	
BHA (Butylated hydroxyanisole)	(20)
BHT (Butylated hydroxytoluene)	(20)
Bithionol	
5-Bromo-4'-chlorosalicylanilide	
Buclosamide	

Table 5. (continued)

	Ref.
Butyl methoxydibenzoylmethane	(19,21)
Carotene	
Chlorhexidine	
Chlormercaptodicarboximide	
p-Chloro-*m*-cresol	(20)
4-Chloro-2-phenylphenol	
Cinnamal (Cinnamic aldehyde)	
Cinoxate	(21)
D&C Orange no. 17	
D&C Red no. 31	
Dibromosalicylanilide	
Dichlorophene	(20)
Digalloyl trioleate	
Dimethoxane	
Essential oils	
Formaldehyde	
Furocoumarines	
Glyceryl PABA	
Hexachlorophene	
4-Isopropyldibenzoylmethane	(19,21)
p-Methoxy-isoamylcinnamate	
6-Methylcoumarin	
Musk ambrette	
Oak moss	
Octyl dimethyl PABA	(17)
PABA (derivatives)	
2-Phenylbenzimidazole-5-sulfonic acid	(15)
p-Phenylenediamine	(18)
Pigment Red 49, calcium lake (CI 15630:2)	
Tetrachlorosalicylanilide	
Toluidine Red (CI 12120)	
Tribromsalan	
Triclocarban	
Zinc pyrithione	

4. CONTACT URTICARIA

On the basis of the action mechanisms involved, contact urticaria may be divided into non-immunological and immunological reactions. On a clinical basis, the following division has been suggested (22):

Cutaneous reactions only
Stage 1: Localised urticaria
Dermatitis/dermatosis
Non-specific symptoms (e.g. itching, tingling, burning)

Stage 2: Generalised urticaria

Extracutaneous reactions
Stage 3: Bronchial asthma
Rhinoconjunctivitis
Otolaryngeal symptoms
Gastrointestinal symptoms

Stage 4: Anaphylactoid reactions

Contact urticaria is infrequently described as a cause of cosmetic-related adverse reactions. However, many cases of "irritation" (itching, burning, tingling) may actually represent contact urticarial responses, especially non-immunological contact urticaria from sorbic acid (29), benzoates and cinnamic aldehyde. Cosmetic products that have been reported to induce contact urticaria include (11): deodorant, fixation fluid for permanent wave, hair bleach, hair spray, nail lacquer, perfumes, permanent wave fluid, rouge, shampoo (23), and toothpaste (66). Cosmetic ingredients that have caused contact urticarial reactions (not necessarily by their presence in cosmetic products) are listed in Table 6.

Table 6. Cosmetic ingredients that have caused contact urticarial reactions (adapted from ref. 11)

	ref.
Alcohol	
Ammonium persulfate	
α-Amylcinnamic alcohol	(30)
Anisyl alcohol	(30)
Balsam Peru	
Benzaldehyde	
Benzoic acid	
Benzophenone-4	
Benzyl alcohol	(30)
BHA (Butylated hydroxyanisole)	
BHT (Butylated hydroxytoluene)	
2-Bromo-2-nitropropane-1,3-diol	(30)
Butyl alcohol	
Camphor	
Caraway oil	
Cetyl alcohol	
p-Chloro-*m*-cresol	
Cinnamal (Cinnamic aldehyde)	
Cinnamic acid	
Cinnamic alcohol	(30)
Cinnamon oil	
Coumarin	(30)
Ethylvanillin	

Table 6. (continued)

Eugenol	
Formaldehyde	
Geraniol	(30)
Henna	(26)
Imidazolidinyl urea	(30)
Isopropyl alcohol	
Kathon CG	(30)
Lanolin alcohol	
MEK (Methyl ethyl ketone)	(25)
Menthol	
Oleum menthae piperitae	(66)
Parabens	
PEG-400	
Phenol	
p-Phenylenediamine	
Phenylmercuric compounds	
o-Phenylphenol	(28)
Polysorbate 60	
Propyl alcohol	
Propylene glycol	
Salicylic acid	
Sodium benzoate	
Sorbic acid	
Sorbitan laurate	(27)
Stearyl alcohol	
Sulfur	
Terpinyl acetate	
Tocopherol	

5. ACNE/FOLLICULITIS

For follicular eruptions caused by cosmetic products the term *acne cosmetica* has been coined (31). They consist mainly of closed comedones. Blackheads are scarce, sometimes papulo-pustules may be seen over the cheeks and the chin. The eruption is seen in adult women and is attributed to the comedogenic properties of cosmetics, mainly facial creams. It must be appreciated that cosmetics are weakly comedogenic. Daily use, year after year, may induce acne in predisposed subjects. Assays on the rabbit ear suggested the following cosmetic ingredients to be comedogenic (11):

Acetylated lanolin alcohols
Butyl stearate
Caprylic alcohol
Cetyl alcohol
Methyl oleate
Myristyl myristate
Oleic acid
Olive oil

Cocoa butter
Coconut oil
Corn oil
Hexylene glycol
Isopropyl isostearate
Isopropyl myristate
Lanolin
Lanolin polyoxyethylene ether
Lauryl alcohol
Linseed oil
Peanut oil
PEG-300
Petrolatum (32,33)
Pine tar
Safflower oil
Sesame oil
Sodium lauryl sulfate
Stearic acid
Sulfur

6. COLOUR CHANGES OF THE SKIN AND APPENDAGES

Most colour changes as a result from contact with cosmetic products are intentional. However, sometimes cosmetics cause discoloration of the skin, nails or hair as an unwanted effect. With some exceptions (dihydroxyacetone, glutaral, monobenzone, resorcinol) such side effects are rare. Table 7 lists cosmetic ingredients that have been reported to cause discoloration as a side effect (not necessarily by their presence in cosmetic products).

Table 7. Cosmetic ingredients that have caused (unintentional) discoloration (adapted from ref. 11)

Cosmetic ingredient	Side effects
BHA (Butylated hydroxyanisole)	Depigmentation
BHT (Butylated hydroxytoluene)	Depigmentation (?)
Chlorhexidine	Discoloration of the teeth and the tongue
Cinnamal (Cinnamic aldehyde)	Depigmentation
Cloflucarban	Pigmented cosmetic dermatitis
Coal tar dyes (Chapter 3.2)	Pigmented cosmetic dermatitis
Dihydroxyacetone	Brown discoloration
Essential oils (lemon, lime, orange, mandarin, juniper)	Red discoloration of the skin caused by terpenes
Formaldehyde	Brown discoloration of nails
Glutaral	Brown discoloration of nails and skin
Hydroquinone	(De)pigmentation; brown discoloration of the nails
Monobenzone	(De)pigmentation
Monomethyl ether of hydroquinone	Depigmentation
Perfume ingredients – benzyl alcohol – benzyl salicylate – cananga oil – cinnamic alcohol – geraniol	Pigmented cosmetic dermatitis

Table 7. (continued)

Cosmetic ingredient	Side effects
– hydroxycitronellal	
– jasmine absolute	
– lavender oil	
– methoxycitronellal	
– red zig	
– sandalwood oil	
– ylang-ylang oil	
Petrolatum	Hyperpigmentation
Resorcinol	Darkens fair hair; orange-brown discoloration of (lacquered) nails
Triclocarban	Pigmented cosmetic dermatitis
Zinc pyrithione	Postinflammatory hypo- and hyperpigmentation

7. OTHER LOCAL SIDE EFFECTS

A variety of other local effects have rarely been reported from cosmetic products (11). Overuse of soap on the female external genitals may cause dysuria (34). Excessive use of bubble baths may also lead to urinary tract irritation, especially in children. Cetrimonium bromide in shampoo may cause irreversible matting of scalp hair (Bird's nest hair) (35). Selenium sulfide shampoo has been blamed for irreversible hair loss. The hair strengthener Ineral has caused nail dystrophy with onycholysis. Formaldehyde, phenolformaldehyde resin and toluenesulfonamide/formaldehyde resin in cosmetic nail products have caused a variety of nail abnormalities including paronychia, subungual hyperkeratosis, subungual hemorrhages, leukonychia, and onycholysis. Ochronosis and colloid milia have been caused by topical application of hydroquinone for whitening of the skin. Chlorhexidine in mouthwashes has caused disturbance of taste sensations (also with hexetidine mouthwash), ulceration of the oral mucosa, and reversible swelling of the parotid glands. Conjunctival pigmentation may be a consequence of applying eyeliner to the conjunctival side of the eyelid (36). Corneal ulcers have been associated with mascaras contaminated with Pseudomonas (37).

8. SYSTEMIC SIDE EFFECTS

Systemic reactions from percutaneous absorption of cosmetic ingredients are rare. Some reported serious adverse effects have been due to formulation errors (hexachlorophene) or inappropriate use (henna and *p*-phenylenediamine) (11).

Hair dyes

A number of constituents of semi-permanent and permanent hair dyes have been shown to be mutagenic in bacteria, to induce mutation, chromosome breakage, sister chromatid exchanges and malignant transformation in mammalian cells, to cause mutation in Drosophila, to induce mitotic recombination in yeast and to induce tumours in rodents. Some hair dye ingredients and commercial dyes have been shown to give rise, in the urine of treated rats, to metabolites which are also mutagenic in bacteria (50). It has been attempted (51-52) to assess the potential increase of cancer among occupational groups, e.g., hairdressers and beauticians, and – by inference – to associate this risk with hair dye use. The results of these studies have only raised suspicions of an increased risk. Lack of adequate demographic and exposure information prevents the interpretation that increased risks are associated with any chemicals to which such people are occupationally exposed.

In case-control studies of bladder and breast cancer either no increased risk was found with hair dye use or conflicting evidence was reported. In the current climate, the mutagenicity and animal carcinogenicity data available for hair dyes and their ingredients suggest that they may have the potential to constitute a human health risk. However, epidemiological and human monitoring studies have not detected such risk in exposed human populations (50-52). There have been a few reports of other systemic effects attributed to hair products in women, but none have been generally accepted. Examples are toxic nephritis and fetal death after a permanent dye shampoo; jaundice; meningeal hemorrhage; and fever (53).

Henna and p-phenylenediamine

The use of a henna dye is traditional in Islamic communities. Dyeing hair with powdered henna is a somewhat lenghthy procedure, and in order to speed up this process, Sudanese women mix a "black powder" (which is *p*-phenylenediamine) with henna. The combination of henna and "black powder" is particularly toxic, and over 20 cases of intoxication, some fatal, have been noted in Khartoum alone in a period of 2 years. Initial symptoms are angioneurotic oedema with massive oedema of the face, lips, glottis, pharynx, neck and bronchi. These occur within hours of the application of the dye-mix to the skin. The symptoms may then progress on the second day to anuria and acute renal failure with death occurring on the 3rd day (38,39).

Hexachlorophene

In 1972, in France, accidentally 6.3% of hexachlorophene was added to batches of baby talcum powder (40). 204 babies fell ill and 36 died from respiratory arrest. Symptoms of intoxication included a severe rash in the diaper area, gastroenteritis, pronounced hyperexcitability and lethargy.

High blood levels of hexachlorophene were demonstrated. Animal experiments subsequently confirmed the neurotoxic potential of the antimicrobial. The FDA in 1972 banned all non-prescription use of hexachlorophene, restricting it to prescription use only, as a surgical scrub and handwash product for health care personnel. Hexachlorophene was excluded from cosmetics except as a preservative in levels not exceeding 0.1%. The EEC guidelines prohibit the use of hexachlorophene (Council Directive 87/137/EEC).

Mercury

Mercury compounds have been used with varying success to lighten skin pigment. The use of mercury in bleaching creams has been banned in many countries (including the EEC) because of percutaneous absorption and potential nephrotoxicity (41-44,49).

Monobenzone (monobenzyl ether of hydroquinone)

Depigmentation of skin distant from the sites of application of monobenzone has suggested that percutaneous absorption occurs (45-46). A patient who had applied a cosmetic cream containing monobenzone for 1 year had an anterior linear deposition of pigment in both corneas. Of 15 additional patients with vitiligo, 11 of whom were using monobenzone, acquired conjunctival melanosis in two patients and pingueculae in 3 may have been related to monobenzone use (47). The EEC guidelines prohibit the use of monobenzone.

Selenium sulfide

One case of systemic effects from the antidandruff agent selenium sulfide in a shampoo has been reported (48). A woman who had been shampooing her hair with selenium sulfide shampoo 2 or 3 times weekly for 8 months noticed a tremor of the arms and hands one hour after a shampoo.

This was followed by severe perspiration and an increasingly severe generalised tremor. Two hours after the shampoo she noticed a metallic taste in her mouth. The tremor lasted for 8 hours and was followed by a dull continuous pain in the lower abdomen. For the next 3 days she felt quite weak, lethargic and anorectic, and occasionally vomited. The patient had an excoriated lesion 5 by 12 cm on the scalp, which may have facilitated percutaneous absorption of selenium (48).

Sex hormones

Oestrogens present in hair lotions have caused pseudoprecocious puberty in young girls and gynecomastia in young and adult male patients (11).

Miscellaneous

Percutaneous absorption of alcohol from a beer-containing shampoo has caused an antabuse effect in a patient taking disulfiram for alcoholism (54). Aerosol propellants have been linked with cardiac arrhythmias (55).

Hair spray has been associated with alteration in pulmonary fuction in persons with preexisting disease such as asthma (56) and in healthy individuals (57). Hair spray polymers were (probably incorrectly) blamed for thesaurosis of the lung (58,59).

1.5 LEGISLATION IN THE EUROPEAN ECONOMIC COMMUNITY

The EEC legislation on cosmetics (Cosmetic Directive 76/768/EEC) contains 15 regulatory articles and 7 annexes.
Some of the more important articles of the Directive are the following:

Article 2 Cosmetic products put on the market within the Community must not be liable to cause damage to human health when they are applied under normal conditions of use.

Article 3 Member States shall take all necessary measures to ensure that only cosmetic products which conform to the provisions of this Directive and its Annexes may be put on the market.

Article 6.2 Member States shall take all measures necessary to ensure that in the labelling, presentation for sale and advertising of cosmetic products, the wording, use of names, trade marks, images or other signs, figurative or otherwise, suggesting a characteristic which the products in question do not possess, shall be prohibited.

Article 7.3 Furthermore, a Member State may require, for purposes of prompt and appropriate medical treatment in the event of difficulties, that adequate and sufficient information regarding substances contained in cosmetic products is made available to the competent authority, which shall ensure that this information is used only for the purposes of such treatment.

Article 12.1 If a Member State notes, on the basis of a substantiated justification, that a cosmetic product, although complying with the requirements of the Directive, represents a hazard to health, it may provisionally prohibit the marketing of that product in its territory or subject it to special conditions. It shall immediately inform the other Member States and the Commission thereof, stating the grounds for its decision.

Annex I is an illustrative list by category of cosmetic products (see Chapter 1.1).

Annex II is a list of 372 substances which are *not* permitted as ingredients of cosmetic products.

Annex III part 1 is a list of 52 substances which are *not* allowed in cosmetic

products, except under to the restrictions and conditions laid down. These restrictions refer to field of application and/or use, maximum authorised concentration in the finished products, and "other limitations and requirements" (e.g. "not to be used for children under three years of age"). The presence of several of the ingredients mentioned in this list must be declared on the label ("contains ..."). This applies to: thioglycolate, ammonia (above 2%), phenylenediamines, diaminophenols, dichlorophen, hydrogen peroxide, hydroquinone, potassium or sodium hydroxide ("contains alkali"), formaldehyde (above 0.05%), α-naphthol, phenol, pyrogallol, resorcinol, monofluorophosphates, fluorides, fluorosilicates, 1,3-bis(hydroxymethyl)-imidazolidene-2-thione, silver nitrate, and selenium disulphide. Sometimes, conditions of use and warnings must be printed on the label, e.g. "can cause an allergic reaction. Sensitivity test advisable before use" (phenylenediamines and diaminophenols), "keep out of reach of children", "avoid contact with the eyes", "do not apply to irritated or damaged skin" (aluminum zirconium complexes).

Annex III part 2 is a list of 160 colouring agents which can be contained in cosmetic products, subject to the provisions and conditions laid down.

Annex IV part 1 is a list of 4 substances *provisionally* allowed: 1,1,1-trichloroethane, 3,4',5-tribromosalicylanilide, dithio-2,2'-bispyridine dioxide 1,1' (pyrithione disulfide + magnesium sulfate), and phenoxypropanol.

Annex IV part 2 is a list of 24 colouring agents *provisionally* allowed for use in cosmetic products.

Annex V is a list of 8 substances excluded from the scope of the directive: lead acetate, hormones, strontium (compounds), zirconium (compounds), thimerosal and phenylmercuric compounds, lidocaine, and tyrothricin. Some aspects of a number of these compounds are discussed elsewhere in the Directive.

Annex VI part 1 is a list of 39 preservatives allowed, subject to the provisions and conditions laid down.

Annex VI part 2 is a list of 22 preservatives *provisionally* allowed, subject to the provisions and conditions laid down. The presence of chlorobutanol, thimerosal, hexachlorophene, phenylmercuric compounds, chloroacetamide, dichlorophen, 1,3,5-tris(2-hydroxyethyl)hexahydro-1,3,5-triazine must be indicated on the products ("contains .....").

Annex VII is a list of 6 UV-filters which cosmetic products may contain (within the limits and under the conditions laid down), and a list of 31

UV-filters which are *provisionally* allowed, under the same conditions.

The information presented here incorporates the amendments of the original Directive 76/768/EEC until the Ninth Amendment (Council Directive 87/137/EEC) of februari 2, 1987.

1.6 REFERENCES

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Chapter 2 Adverse reactions to cosmetics: frequency, nature, and products involved

This chapter is based on the following publications:

1. de Groot AC, Liem DH, Nater JP, van Ketel WG. Patch tests with fragrance materials and preservatives. Contact Dermatitis 1985; 12: 87-92
2. de Groot AC, Weyland JW, Bos JD, Jagtman BA. Contact allergy to preservatives (I). Contact Dermatitis 1986; 14: 120-122
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4. de Groot AC, Nater JP, van der Lende R, Rijcken B. Een retrospectief bevolkingsonderzoek naar bijwerkingen van cosmetica. Ned T Geneeskd 1987; 131: 863-865
5. de Groot AC, Coenraads PJ, Nater JP. Adverse effects of cosmetics: A survey among clients of beauticians. J appl Cosmetol 1987; 5: 104
6. de Groot AC, Beverdam EGA, Tjong Ayong C, Coenraads PJ, Nater JP. The role of contact allergy in the spectrum of adverse effects caused by cosmetics and toiletries. Contact Dermatitis 1988; 19: 195-201
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Chapter 2 Adverse reactions to cosmetics: frequency, nature, and products involved

2.1 INTRODUCTION

Reported adverse reactions to cosmetics and toiletry products have included (1,2): irritant effects (both subjective and objective), allergic contact dermatitis, phototoxic and photoallergic reactions, contact urticaria, pigmentary disorders, and (rarely) systemic side effects (Chapter 1.4). Most studies of side effects caused by cosmetics have related to patients seen in dermatological clinics. The frequency of adverse effects of cosmetics and toiletries *in the general population* is unknown.

There are two reasons for this:

1. The patients usually identify the offending product, and solve the problem themselves without consulting their physician.
2. Few studies (3,4) have investigated cosmetic-related adverse reactions in the general population.

In this chapter, the results of a series of investigations into the frequency and the nature of side effects of cosmetics and toiletries are reported:

1. A group of 1609 individuals selected only on age was interviewed on cosmetic-related side effects (Chapter 2.3).
2. A group of 982 female clients of beauticians was interviewed on cosmetic-related side effects. Clients who claimed to have experienced such reactions were patch tested with cosmetic allergens, in order to quantify the role of contact allergy in the spectrum of adverse effects caused by cosmetics and toiletries (Chapter 2.4).
3. 179 patients suspected to suffer from cosmetic-related allergic contact dermatitis were patch tested with fragrances and preservatives used in cosmetics. The aims were to investigate the prevalence of contact allergy to these cosmetic ingredients, and to identify allergens suitable for inclusion in a "cosmetic screening series" (Chapter 2.5).
4. Two groups of 627 and 501 patients suspected to suffer from allergic contact dermatitis were patch tested with preservatives used in cosmetics. The aims were to investigate the prevalence of contact allergy to these cosmetic ingredients, and to identify allergens suitable for inclusion in a "cosmetic screening series" (Chapter 2.6).

A summary of the literature data on the frequency and nature of cosmetic-related adverse reactions in the general population and in dermatological patients, and on the product categories that are the cause of such reactions, is provided (Chapter 2.2).

2.2 LITERATURE SURVEY

INVESTIGATIONS IN THE GENERAL POPULATION

UK CONSUMERS' ASSOCIATION (3)

The UK Consumers' Association in 1978 performed a study aimed at determining the incidence of adverse reactions of the skin to cosmetics and toiletry products in the adult population of the United Kingdom. The research was carried out in three stages:

Stage I Omnibus survey

A commercial market research omnibus survey was used to contact a representative sample of the population. The total number of people interviewed was 11,062. All were asked if they had experienced any kind of "allergy" or "reaction" as a result of using a cosmetic or toiletry product in the 12 months before the interview.

Stage II Postal follow-up survey

A more detailed questionnaire was sent to each person who claimed (in Stage I) to have experienced an allergic reaction and who had agreed to provide further information. This questionnaire sought details of the product involved, the nature, severity and duration of the reaction and action taken by the person.

Stage III Second follow-up survey

A sample was drawn which was designed to be representative of one particular parliamentary constituency. 1297 people were selected and 1022 were actually interviewed. All the people in the sample were interviewed with the basic questionnaire used in Stage I of the study. Those people who claimed to have had an adverse reaction were asked to fill in the Stage II questionnaire and were invited to participate in a patch testing programme. They were patch tested with their suspected products, and at least 25 cosmetic allergens.

Results

In the omnibus survey (Stage I), 1321 individuals (12%) of the adult population (16 years and older) interviewed claimed to have experienced some sort of adverse reaction of the skin to cosmetic or toiletry products in the preceding 12 months. In the second follow-up survey (Stage III), 8% of the sample apparently had had an adverse reaction within the preceding 12 months. The differences between the results of the 2 investigations were attributed to selection procedures. Of the 85 people who claimed adverse reactions in Stage III, 44 attended the patch test clinic. The results are shown in Table 1.

Table 1. Results of patch testing in the study of the UK Consumers' Association (3)

	No. of people	% of total sample	% of claimants	% of those patch tested
Patch tested	44	4.3	52	100
Total with positive reaction	34	3.3	40	77
Contact allergy	11	1.1	13	25
Irritant reaction	23	2.3	27	52
Not a cosmetic problem	10	1.0	12	23

In 34 of the 44 patients patch tested (77%), a positive reaction "of some kind" to cosmetics or cosmetic ingredients was found. In 11 patients (25%) the cosmetic-related side effects were considered to have been caused by contact allergy. In 23 patients (52%) irritation was considered to be the cause. In the other 10 patients (23%) the reactions were considered not to have been a cosmetic problem.

The cosmetic products held responsible for the perceived adverse reactions are summarised in Table 2.

Table 2. Cosmetic categories causing side effects

	% of all respondents claiming an adverse reaction		
Category	Stage I	Stage II	Stage III
Soap	25	12	18
Deodorant/antiperspirant	18	25	14
Moisturising/skin cream	11	7	14
Eye makeup	13	14	12
Aftershave	9	5	6
Shampoo	8	3	7
Lipstick	7	3	6
Hair dye	3	2	4
Perfume	9	5	2

In each case the 4 products mentioned most frequently as causing an adverse reaction were the same: soap, deodorant, moisturising/skin cream and eye makeup.

Comment:

This study shows that in any year approximately 10% of the adult population

may suffer from cosmetic-related side effects. However, the conclusions of the patch testing programme are invalidated by an obvious misinterpretation of patch test results. If a patient had an irritant patch test reaction to a cosmetic/ingredient, the side effect experienced was interpreted as having been caused by irritation. If a patient did not react to the suspected products or the other allergens tested, it was concluded that the patient had *not* suffered from a genuine reaction to cosmetics.
These data raise serious doubts about the expertise with which the study was conducted; consequently, no valid conclusions can be drawn from it. In addition, in the study by the UK Consumers' Association, the section on products involved contains some major mistakes. These have been corrected where possible in Table 2, but approximately 20% of products in Stages II and III have not been accounted for.

WESTAT REPORT (4)

In 1974, a consumer panel of 10,050 family units (35,490 persons), located throughout the USA, was recruited to: (a) provide personal medical information; (b) participate in the collection of individual family members' use of cosmetics; and (c) participate in a system for the reporting of self-perceived adverse reactions from the use of cosmetics. The participants were instructed to report on cosmetic usage patterns and perceived injuries during a 3-month period. These adverse reactions were assessed by project dermatologists concerning their relationship to cosmetics and the severity of the reactions. In the period of 3 months, 701 reactions were reported by the participants. The dermatologists considered 589 of these (84%) genuine reactions to cosmetic products: 505 (86%) were graded as "mild", 63 (11%) as "moderate" and 13 (2%) as "severe". Most reactions were caused by deodorant/antiperspirant (28%), followed by soap (16%), skin care products (10%), eye cosmetics (7%), hair spray (6%), and shampoo and bath cosmetics (both 5%).
It was stressed that the findings should not be generalised beyond the study population.

INVESTIGATIONS IN SELECTED GROUPS OF DERMATOLOGICAL PATIENTS

USA (6)
70 patients with allergic cosmetic dermatitis were investigated (6). The total number of patients tested in the study period was not specified. The products involved are shown in Table 3.
Most reactions were caused by skin care products (44%), followed by fragrance products (12%), hair colours (8%), deodorants/antiperspirants (8%) and eye makeup (7%).

Sweden (7)
35 patients with allergic cosmetic dermatitis were investigated (7). This represented 0.05% of the number of patients seen during the period of the investigation. The products involved are shown in Table 3. Most reactions were caused by eye makeup products (23%), followed by deodorants/antiperspirants (17%), skin care products (14%), hair colours (9%), and fragrance products (9%).

Spain (8)
195 patients with allergic cosmetic dermatitis were investigated (8). This represented 0.3% of the total number of patients seen and 3.5% of the number of patients patch tested during the period of investigation.
The products involved are shown in Table 3.
Most reactions were caused by nail cosmetics (23%), followed by skin care products (19%), fragrance products (18%), facial makeup (10%), and shaving cosmetics (5%).

France (9)
91 patients with allergic cosmetic dermatitis were investigated (9). This represented 4% of the patients patch tested during the period of investigation. The products involved are shown in Table 3.
Most reactions were caused by skin care products (31%), followed by nail cosmetics (21%), hair colours (10%), eye makeup products (10%), and deodorants/antiperspirants (8%).

USA (10)
578 patients with allergic cosmetic dermatitis were investigated (10). This represented 0.2% of the number of patients seen, and 4.4% of the number of patients patch tested during the period of the investigation. The products involved are shown in Table 3. Most reactions were caused by skin care products (29%), followed by hair products (colours excluded) (16%), facial makeup products (10%), nail cosmetics (9%), and hair colours (8%).

Belgium (11)
156 patients with allergic cosmetic dermatitis were investigated (11). This represented 3.0% of the patients patch tested during the period of the investigation.
Most reactions were caused by soaps and shampoos (41%), followed by makeup and skin care products (37%), hair dyes and other hair preparations (27%), fragrance products (14%), and shaving preparations (13%).
Comment: It seems highly unlikely that rinse-off products such as soaps and shampoos could be responsible for 41% of all cosmetic allergic reactions.

The Netherlands (Chapter 3.3)
49 patients with allergic cosmetic dermatitis were investigated (Chapter 3.3). This represented 0.3% of all patients seen, and 3.5% of the number of patients patch tested during the period of the investigation. The products involved are shown in Table 3.
Most reactions were caused by skin care products (45%), followed by shaving preparations (10%), nail cosmetics (8%), deodorants/antiperspirants (7%), and eye makeup products (7%).

The Netherlands (Chapter 3.4)
119 patients with allergic cosmetic dermatitis were investigated (Chapter 3.4). This represented approximately 0.6% of the number of patients seen, and 5.4% of the number of patients patch tested during the period of the investigation. The products involved are shown in Table 3.
Most reactions were caused by skin care products (51%), followed by nail cosmetics (12%), fragrance products (8%), hair cosmetics (5%), and deodorants/antiperspirants (5%).

2.3 ADVERSE EFFECTS OF COSMETICS AND TOILETRIES: A retrospective study in the general population (12)

SUMMARY

Of 1609 individuals who were interviewed on adverse reactions to cosmetics or toiletry products in the preceding 5 years, 196 (12.2%) claimed to have experienced some such reaction. Women (n=124) mostly attributed their complaints to soap (41%), facial creams (33%), deodorant (25%), shampoo (16%) and eye shadow (11%). Men (n=72) complained about adverse effects from soap (49%), aftershave (22%), deodorant (19%) and shower foam (12%). Both in women and in men, most reactions were localised on the face (60% resp. 33%), followed by the hands (19% resp. 21%) and the axillae (18% resp. 14%). The majority of patients could solve the problem by stopping the use of the suspected product and purchasing a different brand. Nevertheless, medical consultation was sought by more than 30% of all patients.
Presumably the majority of all adverse effects were caused by irritation; contact allergic reactions are infrequent.

INTRODUCTION

Side effects of cosmetics and toiletry products reported (Chapter 1.4) have included irritation, contact allergy, contact urticaria, photosensitivity and pigmentary changes (1,2). Most relevant studies have related to contact

Table 3. Products involved in allergic cosmetic dermatitis

Product categories	USA (6) patients: 70 products: 73			Sweden (7) patients: 35 products: 35			Spain (8) patients: 195 products: 210			France (9) patients: 91 products: 96			USA (10) patients: 578 products: 600			The Netherlands # patients: 49 products: 60			The Netherlands @ patients: 119 products: 131		
	No.	%	rank	No.	%	rank	No.	%	rank	No.	%	rank	No.	%	rank	No.	%	rank	No.	%	rank
Skin care products	32	44	1	5	14	3	39	19	2	30	31	1	175	29	1	27	45	1	67	51	1
Nail cosmetics	1	1	9	2	6	7	49	23	1	20	21	2	53	9	4	5	8	3	16	12	2
Hair colours	6	8	3	3	9	4	10	5	6	10	10	3	45	8	5	2	3	8			
Deodorants/ antiperspirants	6	8	4	6	17	2	10	5	7	8	8	5	?*			4	7	4	6	5	5
Fragrance products	9	12	2	3	9	5	38	18	3	4	4	6	43	7	6	3	5	7	10	8	3
Shaving preparations	3	4	7	3	9	6	11	5	5	1	1	9	21	4	7	6	10	2	3	2	7
Eye makeup products	5	7	5	8	23	1	9	4	8	10	10	4	18	3	8	4	7	5	3	2	8
Facial makeup products	5	7	6	1	3	9	21	10	4				61	10	3	1	2	9	1	1	9
Other hair products	2	3	8	2	6	8	2	1	9	3	3	7	98	16	2	4	7	6	7	5	4
Lip cosmetics							1	<1	10	3	3	8				1	2	10	5	4	6
Other products	4	5		2	6		20	10		7	7		86	14		3	5		13	10	

* possibly included in "personal cleanliness products" (N =36)
# chapter 3.3
@ Chapter 3.4

allergic reactions in selected groups of patients (Chapter 2.2). Epidemiological surveys into adverse effects from cosmetic and toiletry products *among consumers* have only been conducted in 2 studies from the UK (3) and the USA (4) (Chapter 2.2).
This section discusses the results of an enquiry into side effects of such products in a population of 1609 adults.

POPULATION AND METHODS

The population studied consisted of participants in a prospective epidemiologic study on Chronic Obstructive Pulmonary Disease, conducted since 1967 by the Department of Social Medicine and Epidemiology of the University of Groningen (5). All inhabitants of the community of Sellingen, born between 1921 and 1951 were invited to participate in the 1985 follow-up study.
At the end of the regular COPD protocol, 1609 of the 1818 individuals (838 men, 771 women, aged 33-64 years, average age 47.5 years) were asked the following question: "Have you experienced side effects of cosmetics or toiletries in the preceding 5 years ?". It was explained that everyday products such as soap, shampoo and toothpaste were to be included, and that also mild reactions such as itching or dryness of the skin were to be reported.
Individuals who claimed to have experienced adverse effects were subsequently interviewed in more detail.
Attention was focused on the following relevant data:
- nature of the adverse reaction (subjective symptoms, description of possible skin eruption, extracutaneous symptoms)
- localisation(s) of the adverse effect
- what type(s) of cosmetics or toiletries were considered to be the cause
- what action was undertaken and with what result
- was the family physician and/or the dermatologist consulted
- had patch tests been performed
- the (family) history of atopic diseases
- any other information the patient felt to be important

RESULTS

Of the 1609 subjects who were interviewed, 196 (12.2%) claimed to have suffered from side effects of cosmetics or toiletries in the preceding 5 years: 124 women (63%) and 72 men (37%). The percentages of men and women having experienced adverse reactions were 8.6% and 16.1%, resp. The most frequently reported subjective symptom was itching (71%), followed by a feeling of dryness (63%), burning of the skin (50%) and prickling sensations (44%). 23 subjects (12%) had had no visible skin changes. The others

described their skin eruptions as redness, "spots", blisters, scales and chaps. Some complained of burning and watery eyes, and 3 patients had experienced shortness of breath (1 caused by perfume, 2 by their wives' hair lacquer). 1 patient had ascribed swelling of lymph nodes to the use of deodorant; another patient repeatedly started to sneeze when using an aftershave spray; and a third patient claimed that perfumes made her dizzy and nauseated. The products that were blamed for the adverse reactions are summarised in Table 4. Women ascribed most reactions to soap, facial cream, deodorant, shampoo and eye shadow. Among men soap also ranked first, followed by aftershave, deodorant and shower foam.

Table 4. Cosmetics to which side effects were attributed

women (n=124)			men (n=72)		
cosmetic	number	(%)	cosmetic	number	(%)
soap	51	(41%)	soap	35	(49%)
facial cream	41	(33%)	aftershave	16	(22%)
deodorant	31	(25%)	deodorant	14	(19%)
shampoo	20	(16%)	shower foam	9	(12%)
eye shadow	14	(11%)	massage oil	2	(3%)
bath/shower foam	9	(7%)	(wife's) hair lacqer	2	(3%)
facial makeup	8	(6%)	shaving soap	1	(1%)
perfumes	8	(6%)			
mascara	5	(4%)			
depilatory cream	3	(2%)			
other *	18	(15%)			

* Product categories implicated by 1 or 2 women only

NB The number of products exceeds the number of patients, as many mentioned more than 1 product

The localisations of the side effects are summarised in Table 5. In both the men and the women, most reactions were localised on the face, the hands and in the axillae. In women, the face was far more frequently involved (60%) than in men (33%).

The majority of patients (124 = 63%) could solve the problem by stopping the use of the suspected products and using a different brand instead. About 1 in every 6 patients stopped using cosmetics of the incriminated product category altogether. 14 patients could prevent the side effects by decreasing the frequency of use of the suspected products. In 3 patients the symptoms disappeared despite continuation of the cosmetics; in 5 the symptoms continued despite using a different brand.
62 patients (32%) consulted the family physician for the cosmetic-related

Table 5. Localisations of skin changes / complaints

women (n=124)			men (n=72)		
localisation	number	(%)	localisation	number	(%)
face	75	(60%)	face	24	(33%)
hands	24	(19%)	hands	15	(21%)
axillae	22	(18%)	axillae	10	(14%)
"all-over"	12	(10%)	arms	8	(11%)
neck	8	(6%)	legs	8	(11%)
groins / genitals	7	(6%)	head	4	(6%)
head	5	(4%)	"all-over"	4	(6%)
lips	5	(4%)	back	4	(6%)
arms	5	(4%)	other *	10	(14%)
legs	4	(3%)			
chest	4	(3%)			
back	4	(3%)			
other *	6	(5%)			

* These localisations were mentioned only 1-3 times

problems; 27 of them (14% of the 196 with side effects) were referred to a dermatologist. Of these 62 patients, 35 had solved the problem by stopping the use of the incriminated product and buying another cosmetic. In 20 of the 27 patients consulting the dermatologist, patch tests had been performed. In only 2, contact allergies were found which might indicate cosmetic allergy (wood tars, balsam Peru).
The personal history of atopic diseases of the 196 patients was positive in 59 (30%); they (had) suffered from atopic dermatitis and/or asthmatic attacks and/or hay fever. The family history of atopic diseases in parents, brothers and sisters was positive in 85 patients (43%).

DISCUSSION

This study shows that adverse effects from cosmetics and toiletries are by no means rare in The Netherlands. About 1 in every 8 of the 1609 subjects interviewed stated that he or she had suffered from such reactions in the preceding 5 years. It may be argued that 5 years is rather long for reliable recollection. However, a relatively long recall period would result in "underreporting" rather than in "overreporting" of adverse effects. In addition, only those patients were considered to have suffered from reactions to cosmetic products, who were quite certain and specific about it. Even when a certain degree of "over-claiming" cannot be excluded (we could not verify the adverse effects), the results of an American study suggest that in the great majority of cases, the consumer/patient correctly interprets the adverse reaction (4).

We do not pretend that our study is representative for the entire Dutch population, and generalisation to other countries may not be appropriate. However, most reactions were attributed to very widely used products such as soap, deodorant, shampoo and aftershave. It may be assumed that the usage pattern of these products in the population investigated will not differ in essence from that of the population as a whole. Also it seems unlikely that the results have been biased by investigating only a certain age group (33-64 yr).

Therefore, we feel that the results of our investigation may be considered a fairly reliable indication for the occurrence of cosmetic-related reactions in the adult population.

It is noteworthy that many patients (62 = 32%) consulted the family physician. This suggests that many complaints were of a more than trivial nature. Nevertheless, 35 of these patients had been able to solve the problem by discontinuation of the suspected products.

In not one patient had patch testing detected allergy to cosmetics or cosmetic ingredients. This, together with the type of complaints suggests that *contact allergic* reactions to cosmetics, contrary to widely held beliefs, constitute a minority of all adverse events.

30% of the 196 patients who reported adverse effects of cosmetics had an atopic diathesis as determined by a positive (family) history of atopic dermatitis and/or asthmatic attacks and/or hay fever. Of these patients, 18 (9%) (had) suffered from asthmatic attacks and 27 (14%) from hay fever, compared to 68 (4%) and 70 (4%) respectively in the total population at the time of the survey.

These differences are statistically significant (Chi square test; $p < 0.01$). This suggests that atopics in our population were at a higher risk of developing cosmetic-related side effects. Our history-taking was not exactly identical to that in the COPD study; thus, these data must be interpreted with care. It is well-established that an atopic diathesis predisposes to an increased susceptibility to irritant stimuli, such as the effects of water and products such as soap, bath foam, dish washing products and cleaning products (13).

Due to different methods used, comparisons between our study and the other 2 investigations in the general population (3,4; Chapter 2.2) are difficult to make. Still, it seems justifiable to draw some tentative conclusions from these 3 studies:

- Side effects of cosmetics and toiletries are by no means rare.
- Most reactions are mild, but nevertheless, 30% of our patients consulted a physician.
- Product categories causing most reactions in women are: soap, deodorant, (facial) creams, shampoo, eye cosmetics and shower foam. In men most reactions are caused by: soap, aftershave, deodorant and shower foam.

- Women report side effects nearly twice as frequently as men; this difference is largely due to products applied to the face.
- The majority of adverse effects are caused by irritation; contact allergic reactions constitute a minority. Atopic individuals may be at greater risk of developing side effects from cosmetics and toiletries caused by irritation.

2.4 THE ROLE OF CONTACT ALLERGY IN THE SPECTRUM OF ADVERSE EFFECTS CAUSED BY COSMETICS AND TOILETRIES (18)

SUMMARY

Of 982 clients of beauticians interviewed, 254 (26%) claimed to have experienced an adverse reaction to cosmetics and/or toiletry products in the preceding 5 years. Most reactions were caused by skin care products (37%), followed by personal cleanliness products (30%), eye cosmetics (24%), deodorant/antiperspirant (13%) and facial makeup products (8%). 150 women were patch tested. In the European standard series, only a few positive reactions were seen to allergens which may be present in cosmetics: fragrance mix (n=3), wool alcohols (n=3), formaldehyde (n=2), balsam Peru (n=1), and rosin (n=1). In the cosmetic series only Kathon CG elicited positive patch test reactions (n=3). Cosmetic allergy was considered to be "proven" in 3 patients (2%), and "possible" in 7 (5%). It is concluded that contact allergy is responsible for a minority (<10%) of all reactions to cosmetics/toiletries. The majority of reactions are due to irritation from personal cleanliness products such as soaps, shampoos, bath foams and from deodorants, and by worsening of preexisting dermatoses such as seborrhoeic dermatitis and acne.

INTRODUCTION

In a recent epidemiological survey (12, Chapter 2.3), 12.2% of an unselected population of 1609 individuals aged 33-64 years claimed to have experienced an adverse reaction to cosmetics or toiletries in the preceding 5 years. The most frequently reported side effect of such products in patients seen in dermatological clinics is contact allergy (2,10,11,14; Chapter 2.2). However, only the more serious and persistent reactions come to the attention of the dermatologist. It is generally assumed that irritation is the most common side effect of cosmetic products (2,12,15,16), but data to substantiate this are lacking. The contribution of contact allergic reactions to the spectrum of cosmetic-related adverse events has only been investigated in one previous, relatively small study (3; Chapter 2.2).

We have tried to quantify the role of contact allergy by patch testing 150 consumers who claimed to have experienced side effects from cosmetics or toiletry products.

POPULATION AND METHODS

The target population was formed by regular clients of beauticians, as from an epidemiological point of view it it appealing to investigate a group which is more than averagely exposed to cosmetic products.
Twenty-five beauticians were informed about the purpose of the study, and invited to participate. They were requested to interview unselected female clients on cosmetic usage pattern (product categories used, frequency of use), and possible experience of adverse effects from cosmetics and/ or toiletries.
The clients who claimed to have suffered from cosmetic-related side effects in the preceding 5 years were subsequently interviewed in more detail; the results were verified by one of the authors (18).
Attention was focused on the following data :

- nature of the adverse reaction (subjective symptoms, description of possible skin eruption, extracutaneous symptoms)
- localisation(s) of the adverse effect
- what type(s) of cosmetics of toiletries were considered to be the cause
- what action was undertaken and with what result
- was the family physician and/or the dermatologist consulted
- had patch tests been performed
- the (family) history of atopic diseases
- had the patient informed the person who had sold her the suspected products and/or the manufacturer and/or the governmental agency responsible for the quality control of cosmetics and toiletries about the adverse event

On the basis of these interviews, an attempt was made to assess whether the symptoms described by the clients had indeed been cosmetic-related. Individuals who were considered to have actually experienced an untoward effect due to cosmetics or toiletries were invited to participate in a patch test study. They were tested with the European standard series (Appendix 3) and a "cosmetic series" (Table 8), based on literature data (1,10,14,15). Patch test procedures were carried out according to internationally accepted recommendations (17).

RESULTS

Over a 5-month period a total of 982 clients were interviewed. 254 (26%) claimed to have experienced cosmetic-related adverse events during the preceding 5 years. This number excludes 23 clients who did claim adverse

reactions, but in whom the authors judged the symptoms to be of non-cosmetic origin.
The average age of the 254 clients who had experienced side effects was 35.5 years (range 16-66) , that of the group that had no side effects was 39.2 years (range 14-78).
The results of enquiries into the details of the cosmetic-related adverse reactions were as follows: itching was the most frequently reported subjective symptom (69%), followed by a feeling of dryness (56%), burning (48%) and prickling of the skin (36%). 29 individuals (11%) reported no visible skin changes. The most frequently reported objective symptom was redness (61%), followed by scaling (19%), pimples (14%), dry skin (9%) and swelling (7%). Extracutaneous symptoms were claimed by 22 patients (9%). Most complained of eye inflammation or misty eyes (n=10), some of swollen painful lymph nodes, fever or headache. Chest pain, nausea and tiredness were reported each by one patient.
The adverse effect was by far the most frequently localised on the face (71%); next were arms + hands (17%), followed by the axillae (15%), neck (9%), legs + feet (9%) and the trunk (8%).
The cosmetic categories blamed for the adverse reactions experienced are shown in Table 6: most reactions were attributed to skin care products (creams, lotions, tonics, milks) (37%). Next were personal cleanliness products (soap, bath and shower foam, shampoo) (30%), followed by eye cosmetics (24%), deodorants & antiperspirants (13%), and facial makeup products (8%). In 12 patients (5%) the symptoms disappeared despite continuation of the incriminated product(s). In 38 patients (15%) the symptoms persisted, despite discontinuation of the suspected cosmetic and the use of another product. 33 patients (13%) stopped using products of the category incriminated altogether, often after first trying many brands of that category, without alleviation of the symptoms. 143 patients (56%) solved the problem by stopping the use of the suspected products and using other brands instead.

76 patients (30%) consulted the family physician. Of these, 43 (17%) had been referred to the dermatologist.
The results of (family) history of atopic diseases are summarised in Table 7. The 254 clients who claimed adverse effects were overrepresented for all parameters (personal / family history of atopic eczema, asthma, hay fever) compared with clients that had not experienced side effects. For personal history of hay fever, and family history of asthma, the differences were statistically significant (Chi-square test; $p < 0.05$).

Of the 254 clients that had suffered from cosmetic-related side effects, 172 were invited to participate in the patch test study. The other 82 lived too far from the hospital to justify such a request.

Table 6. Cosmetic categories held responsible for adverse reactions experienced

Category	No.	% (N=254)
skin care products (cream, lotion, milk, tonic)	93	37%
personal cleanliness products (soap, foam, shampoo)	75	30%
eye cosmetics	61	24%
deodorant / antiperspirant	32	13%
facial makeup products	21	8%
hair cosmetics (shampoo excl.)	8	3%
sunscreens	8	3%
masks	8	3%
depilatory creams	8	3%
"various cosmetics"	7	3%
other products	17	7%

Table 7. (Family) history of atopic diseases

	SIDE EFFECTS CLAIMED: (N=254)		NO SIDE EFFECTS CLAIMED:	
THE CLIENT HERSELF HAS OR HAD:				
	No.	%	No.	%
atopic eczema	32	13%	19	7%
asthma	13	5%	9	3%
hay fever	48	19%	29	11%
PARENTS, BROTHERS OR SISTERS HAVE OR HAD:				
atopic eczema	36	14%	32	12%
asthma	47	19%	25	10%
hay fever	49	19%	34	13%

160 consented, and 150 actually came. Reasons for refusal were: pregnancy (n=5), already been tested (n=1), too busy (n=3), and not interested (n=3). The results of patch testing in 150 patients are summarised in Table 8. To the following allergens in the European standard series which may also be incorporated in cosmetic products were positive reactions observed: fragrance mix (n=3), wool alcohols (n=3), formaldehyde (n=2), balsam Peru (n=1), rosin (n=1). No patient reacted to the parabens, quaternium-15, or *p*-phenylenediamine dihydrochloride. In the cosmetic series only Kathon CG elicited positive patch test reactions (n=3).

Table 8. Results of patch testing (n=150)

	concentration and vehicle	positive reactions No.	%
EUROPEAN STANDARD SERIES *			
p-Phenylenediamine dihydrochloride	0.5 % pet.	–	–
Rosin (colophony)	60 % pet.	1	1%
Paraben mix	15 % pet.	–	–
Wool alcohols	30 % pet.	3	2%
Balsam Peru	25 % pet.	1	1%
Formaldehyde	1 % aqua	2	1%
Fragrance mix	8 % pet.	3	2%
Quaternium-15	1 % pet.	–	–
COSMETIC SERIES			
Kathon CG *	100 ppm aqua	3	2%
Oleamidopropyl dimethylamine &	0.4 % aqua	–	–
Imidazolidinyl urea (Germall 115) *	2 % pet.	–	–
2-Bromo-2-nitropropane-1,3-diol *	0.5 % pet.	–	–
Chloroacetamide *	0.2 % pet.	–	–
Triethanolamine *	2.5 % pet.	–	–
Propylene glycol *	2 % pet.	–	–
Toluenesulfonamide/formaldehyde resin *	10 % pet.	–	–
Glyceryl thioglycolate *	2.5 % aqua	–	–
Cinnamic alcohol #	2 % pet.	–	–
Hydroxycitronellal #	2 % pet.	–	–
Octyl dimethyl PABA &	5 % pet.	–	–
Benzophenone-3 #	2 % pet.	–	–
Phenyl salicylate *	1 % pet.	–	–
Butylated hydroxyanisole *	2 % pet.	–	–

Allergens obtained from:
* Hermal-Chemie (Reinbek/Hamburg, W-Germany)
# Chemotechnique Diagnostics AB (Malmö, Sweden)
& Food Inspection Service (Enschede, The Netherlands)

The diagnosis of *cosmetic* allergy was judged to be "proven" in 3 cases (2%) (all due to Kathon CG), and "possible" in 7 individuals (5%). Thus, in 10 (7%) out of 150 patients with side effects from cosmetics and/or toiletries, contact allergy to these products was considered to be the cause. The clinical characteristics of these patients are shown in Table 9. In 108 patients (the idea only arose when the study was already in progress) a (tentative) diagnosis could be made on the basis of the history, physical examination, and patch test results (Table 10).

Table 9. Characteristics of patients suspected of cosmetic allergy

Age	Localisations	Suspected cosmetic products	Allergens	Cosmetic allergy?
18	face	facial makeup	nickel sulfate wool alcohols	possible
55	face	moisturising cream	neomycin wool alcohols	possible
28	axillae, folds of elbows and knees	body lotion	thiuram mix fragrance mix PTBP form. resin	possible (worsening atopic eczema)
33	periorbital	"eye-cosmetics" (the patient used a Kathon CG-containing cream as remover)	Kathon CG	proven
36	axillae, face, "body"	deodorant moisturising cream bath foam	fragrance mix	possible
56	periorbital	moisturising cream (containing Kathon CG)	Kathon CG	proven
36	periorbital	eye shadow (the patient used a Kathon CG-containing cream; this was not suspected)	Kathon CG	proven
37	face	cream	rosin	possible
20	periorbital, neck	soap, makeup	fragrance mix formaldehyde	possible
35	face	"natural products"	balsam Peru	possible

34 patients (31%) were diagnosed as having suffered from irritant dermatitis (18 atopics, 16 non-atopics) due to cosmetic products and/or toiletries. In 18 patients (17%) seborrhoeic dermatitis had been worsened by cosmetics, in 8 (7%) acne, in 1 rosacea. Many of these still had such skin changes when investigated.

DISCUSSION

In the population investigated, 26% of the women interviewed claimed to have suffered an adverse reaction from cosmetics and/or toiletry products during the preceding 5 years. In a previous investigation (12), the percentage responders was 16% in a female population of a rural community, selected

Table 10. Clinical diagnoses of the cosmetic-related side effect in 108 patients patch tested

Diagnosis	No. of patients	%
Irritant dermatitis – atopics 18 – non-atopics 16	34	31%
Worsening of seborrhoeic dermatitis	18	17%
Worsening of acne	8	7%
Cosmetic allergy – possible – proven	4 2	4% 2%
Worsening of rosacea	1	1%
Diagnosis uncertain	41	38%

only by age (33-64 years). Although we have no data on the cosmetic usage pattern of this latter group, it may be assumed that the higher percentage of individuals who claimed adverse reactions in the present study is caused by the selection of a more heavily exposed population (clients of beauticians). Also, women with a disposition towards cosmetic-related reactions may be more likely to seek advice from a beautician, and may in this respect be more alert.

In this investigation, most reactions were attributed to skin care products (37%), followed by personal cleanliness products (30%), eye cosmetics (24%) and deodorant/antiperspirant (13%). These are also the product categories causing most reactions in the previous survey (12; Chapter 2.3). However, in that rural population, most reactions were attributed to personal cleanliness products, followed by skin care products, deodorant/antiperspirant and eye shadow. These differences probably also reflect a different cosmetic usage pattern: products for personal cleanliness and deodorants may be used similarly in both groups, but skin care products and eye cosmetics will probably be used by a greater percentage (and/or more often) in the group of clients of beauticians.

In the previous investigation (12), we speculated that an atopic diathesis (diagnosis made on the basis of (family) history of atopic diseases) predisposes to the development of cosmetic-related side effects, especially irritation. The data in the present study are confirmatory: the responders (clients who claimed adverse reactions) were overrepresented for all 6 parameters of atopy, and for 2 of these the differences were statistically significant.

The most important finding in this study is the confirmation of the previously postulated, but unproven, assumption, that contact allergy is

a relatively rare cause of cosmetic-related side effects, irritation being the most common cause.
The products may irritate normal skin, but also worsen dermatoses already present such as seborrhoeic dermatitis and acne.
Of 150 patients patch-tested, only 3 (2%) were definitely classified as suffering from cosmetic allergy (all caused by Kathon CG). Another 7 (5%) "possibly" had cosmetic allergy. It may be argued that several cases of cosmetic allergy were missed, as no patch tests were performed with the incriminated cosmetic products. However, the European standard series (Appendix 3) and the cosmetic series detect more than 80% of cosmetic allergens (35). Extrapolation of these data into the present study suggest that only 2 cases of cosmetic allergy may have gone undetected by not testing the suspected cosmetic products.

Only one previous study from the UK Consumers' Association (3) has addressed this problem.
That study concluded, that 25% of adverse reactions are due to contact allergy, and that 1-3% of the population may suffer an allergic contact dermatitis to a cosmetic or cosmetic ingredient in any year. Unfortunately, this study was very poorly performed, and no reliable conclusions can be drawn from it (Chapter 2.2).

From our data we conclude that:

1 Only a small percentage of cases of adverse reactions to cosmetics and toiletry products (less than 10%) are caused by contact allergy. The majority of reactions are due to irritation from personal cleanliness products such as soap, shampoo, bath foam and from deodorant.
2 Irritant effects of cosmetics and toiletries may worsen preexisting dermatoses such as seborrhoeic dermatitis, acne and rosacea.
3 An atopic diathesis may predispose to cosmetic-related irritant side effects.

2.5 ROUTINE TESTING WITH PRESERVATIVES AND FRAGRANCE MATERIALS IN PATIENTS WITH SUSPECTED COSMETIC-RELATED ALLERGIC CONTACT DERMATITIS (22)

SUMMARY

179 patients suspected of cosmetic allergy were patch tested with a series of 16 fragrance materials and 9 preservatives. In 67 patients (37%), 1 or more of these substances gave positive reactions. In the group of fragrance materials, the largest numbers of positive reactions were seen to isoeugenol,

oak moss, geraniol, α-amylcinnamic alcohol, and a mixture of α-amylcinnamic aldehyde and α-hexylcinnamic aldehyde. The fragrance mix in the European standard series detected nearly 80% of cases of contact allergy to fragrance materials other than its constituents. In the group of preservatives, Kathon CG and quaternium-15 scored the highest number of positive reactions. A screening series for cosmetic allergy should include Kathon CG and quaternium-15.

INTRODUCTION

Patch testing with cosmetics and toiletry products not infrequently yields false-negative results. Toiletry products such as soap, shampoo, bath/shower foam and toothpaste have to be diluted in order to avoid false-positive irritant patch test reactions. By doing so, the concentration of the possible allergen often falls below the threshhold for detection by patch testing. In cosmetics, reactions may be false-negative due to a low concentration of the allergen; well-known examples are the parabens and Kathon CG (Chapter 4). Thus testing with a "screening" series with the ingredients most commonly causing cosmetic allergy, in addition to the patients' own products, may increase the reliability of patch test results in patients with suspected cosmetic-related allergic contact dermatitis. To determine which allergens deserve a place in a cosmetic screening series, based on the frequency of allergic reactions in patients with suspected (cosmetic) allergic contact dermatitis, the following investigations were performed:

1. patients with proven contact allergy to cosmetics were tested with all ingredients of the suspected products (Chapter 3.4).
2. patients suspected of contact dermatitis were routinely tested with a tray of preservatives used in cosmetics (Chapter 2.6).
3. patients suspected of cosmetic dermatitis were routinely tested with a tray of fragrance materials and cosmetic preservatives. The results are reported here.

MATERIALS AND METHODS

Dermatological out-patients were admitted to the study when they were suspected of suffering from cosmetic-related contact dermatitis on the basis of one or more of the following criteria:

1 The patient suspected cosmetic products to cause or worsen the skin eruption.
2 The localisation of the skin eruption was suggestive of a cosmetic reaction (e.g. eyelids, lips, axillae).
3 The patient had mild generalised erythema with slight scaling and itching, after excluding other causes.

4 The patient had frequent occupational contacts with cosmetic products: hairdressers, beauticians, cosmetic salespersons, pedicures.
5 The patient was found to be allergic to indicators of fragrance sensitivity in the European standard series: rosin, wood tars, balsam Peru, and/or the fragrance mix.
6 The patient was found to be allergic to cosmetics.

These patients were tested with the European standard series (Appendix 3) and a tray consisting of 16 fragrance materials (or mixes) and 9 preservatives (Table 11). Of the 8 constituents of the fragrance mix (Appendix 3) in the European standard series, α-amylcinnamic aldehyde, isoeugenol, oak moss and geraniol were incorporated in the tray (the other 4: cinnamic alcohol, cinnamic aldehyde, eugenol and hydroxycitronellal had been investigated in a previous study from the Dutch Contact Dermatitis Group (19)). Most of the other 12 fragrances (or mixtures of fragrances) had been selected on the basis of a large annual use in perfumes, cosmetics, toiletries, or other fragranced or flavoured products.

Carvacrol and cuminaldehyde were investigated as they showed structural similarity to sensitisers present in degraded *p-tert*-butylphenolformaldehyde resin, an important sensitiser in shoes (20).
The test tray was completed with 9 preservatives, as this class of cosmetic ingredients is also a frequent cause of cosmetic allergy (21). Substances, for which an adequate patch test concentration and vehicle were not apparent from literature data, were tested at an empirically determined concentration, utilising (60) controls to exclude irritancy. These concentrations were deliberately chosen high in order to avoid missing weak sensitisations. Patch test procedures were carried out according to internationally accepted recommendation (17).

RESULTS

179 patients in whom cosmetic dermatitis was suspected were evaluated, 144 women and 34 men (in 1 the sex had not been recorded). The numbers and percentages of positive reactions to the allergens in the European standard series and in the cosmetic tray are shown in Tables 11 and 12. The largest number of positive reactions to fragrance materials was seen to isoeugenol (n=36), oak moss (n=21), geraniol (n=11), α-amylcinnamic alcohol (n=7), and the mixture of α-amylcinnamic aldehyde and α-hexylcinnamic aldehyde (n=7).
In the group of preservatives the highest number of positive patch test reactions was observed to Kathon CG (n=6), quaternium-15 (n=5), and sorbic acid (n=4).

Table 11. Patch test results: cosmetic series

	test conc. (in pet.)	positive reactions	(%)
Isoeugenol $	8%	36	20.1
Oak moss $	10%	21	11.7
Geraniol $	10%	11	6.1
α-Amylcinnamic alcohol	20%	7	3.9
α-Amylcinnamic aldehyde } $	10%		
α-Hexylcinnamic aldehyde } $	10%	7	3.9
Kathon CG	1%	6	3.4
Lilial *	20%	5	2.8
Quaternium-15	2%	5	2.8
Sorbic acid	5%	4	2.2
Cuminaldehyde	15%	3	1.7
Galoxolide *	25%	3	1.7
Carvacrol *	5%	2	1.1
Dehydroacetic acid	3%	2	1.1
Ionone (mixed isomers) } $	10%		
γ-Methylionone } $	10%	2	1.1
D-Limonene	10%	2	1.1
Nopyl acetate *	25%	2	1.1
Thimerosal	0.1%	2	1.1
Triclosan	2%	2	1.1
2-Bromo-2-nitropropane-1,3-diol	0.5%	1	0.6
Isoamyl salicylate *	50%	1	0.6
Phenylethyl alcohol	25%	1	0.6
Triclocarban	10%	1	0.6
Linalool	30%	–	–
Terpineol (mixed isomers) } $	15%		
Terpinyl acetate } $	10%	–	–
Zinc pyrithione	3%	–	–

$ ingredients of the fragrance mix

* false-positive reactions due to the excited skin syndrome not excluded in some cases

In 13 patients, positive reactions were observed to one or more of the 4 tested ingredients of the fragrance mix in the cosmetic series, whereas the fragrance mix itself was negative (7x isoeugenol, 4x oak moss, 1x geraniol, and 1 combination). A positive reaction to 1 or more of the other fragrance materials was seen in 18 patients. In this group, 4 patients (20%) did not react to the fragrance mix.

DISCUSSION

The high percentages of positive reactions to rosin, wood tars, balsam Peru and the fragrance mix are caused by the selection procedure. In the

Table 12. Patch test results: European standard series (ICDRG 1982)

	No. of positive reactions	(%)
Fragrance mix *	56	31.3
Balsam Peru *	32	17.9
Nickel sulfate	25	14.0
Wood tars *	24	13.4
Rosin *	11	6.1
Cobalt chloride	10	5.6
Potassium dichromate	8	4.5
p-Phenylenediamine dihydrochloride	6	3.4
PPD mix	6	3.4
Formaldehyde	5	2.8
Carba mix	4	2.2
Thiuram mix	4	2.2
Epoxy resin	3	1.7
Ethylenediamine dihydrochloride	3	1.7
Neomycin	3	1.7
Clioquinol	2	1.1
Mercapto mix	2	1.1
Wool alcohols	2	1.1
Parabens	1	0.6
Naphthyl mix	–	–

* indicators of fragrance sensitivity

cosmetic tray, most reactions were observed to the ingredients of the fragrance mix, as 56 patients had been selected to participate in the study on the basis of a positive patch test reaction to this mix. With the exception of α-amylcinnamic alcohol, all other fragrance materials only occasionally induced positive responses, and consequently are considered to be of little value for a cosmetic screening series. Moreover, some of the rarer allergies were seen mainly or even exclusively in patients who had many positive patch test reactions. Hence, false positive reactions due to the Excited Skin Syndrome (23) cannot be excluded with certainty (Lilial 4/5, Galoxolide 3/3, carvacrol 2/2, ionone-mix 1/2, isoamyl salicylate 1/1, and nopyl acetate 1/2). The fragrance mix, originally designed by Larsen (24), has been shown to be a valuable screening agent for perfume dermatitis (25). It is estimated that the fragrance mix detects 70-80% of all cases of fragrance sensitivity (26). In our study, 18 patients had 1 or more positive reactions to fragrance materials not included in the mix. 14 of these also reacted to the fragrance mix, which thus had detected nearly 80% (14/18) of cases of fragrance sensitivity.

When the positive reactions to the fragrance mix are subdivided according to its constituents (α-amylcinnamic aldehyde excepted, as this was part

of a mixture), the following relative percentages were found: isoeugenol 50%, geraniol 18%, and oak moss 29%.

Table 13. Allergic reactions to the fragrance mix and 3 of its constituents: comparison with Calnan's study (25)

	Calnan et al (25) No. of pos. reactions	(%)	Test Conc.	This study No. of pos. reactions	(%)	Test Conc.
Fragrance mix	172		8x2%	56		8x 2%
Isoeugenol	48	(28%)	2%	28	(50%)	8%
Geraniol	7	(4%)	2%	10	(18%)	10%
Oak moss	29	(17%)	2%	16	(29%)	10%

Table 13 clearly shows that these figures are higher than those of Calnan et al (25). The discrepancies may be explained by the differences in test concentrations, which were much higher in our study (Table 13). It is remarkable that in 13 patients positive reactions were seen in the cosmetic series to 1 or more of the ingredients of the mix, tested in the higher concentration (7x isoeugenol, 4x oak moss, 1x geraniol, 1x a combination), whereas the fragrance mix itself, tested in the lower concentration of 8x2%, showed no reaction. The interpretation is difficult: are our figures too high due to false-positive reactions, or are the numbers in Calnan's study too low due to false-negative reactions? Our results in the pilot study point to the latter possibility. The results with oak moss also seem to favour this assumption. The relative percentage of reactions in our study (29%) is higher than that of Calnan et al (25), and in 5 patients a positive reaction was seen to oak moss in the absence of a reaction to the fragrance mix. As the test concentration of oak moss 10% in petrolatum, used by us, is also considered to be non-irritating by the Research Institute for Fragrance Materials RIFM (27), these figures indicate false-negative reactions in the other study rather than false-positive reactions in our series. However, false-positive reactions to isoeugenol 8% may have occurred. The relative percentage of positive reactions in patients with a positive patch test reaction to the fragrance mix was 50%, which appears to be excessively high. In addition, RIFM (28) considers isoeugenol 8% in pet. to be potentially irritant.

On the basis of our results, oak moss, and probably also geraniol and isoeugenol should be tested in a higher concentration than the commonly used 2%, as several cases of fragrance sensitivity may otherwise be missed. The fragrance mix (8x2%) not uncommonly induces weak-"positive" irritant reactions (26), especially in cases of the Excited Skin Syndrome. Consequently, an increase in concentration of its ingredients is undesirable. On the contrary, the International Contact Dermatitis Research Group

(ICDRG) has lowered the test concentration to 8x1%. Therefore, we recommend testing geraniol, oak moss and possibly isoeugenol in concentrations higher than 2% separately whenever fragrance sensitivity is suspected. The preservatives in the test tray showed much lower numbers of positive patch test reactions, which is due to a positive selection towards fragrance allergy through the fragrance mix and the indicator allergens. Most reactions were caused by Kathon CG, quaternium-15 and sorbic acid.

From this study we conclude that:
1. Kathon CG and quaternium-15 may be important cosmetic allergens; their role in cosmetic allergy needs to be investigated further.
2. the fragrance mix in the European standard series detects at least 80% of all cases of fragrance sensitivity. The individual fragrance materials investigated in this study need not be part of a screening series for cosmetic allergy.
3. the commonly used test concentrations of 2% for oak moss, geraniol and isoeugenol are too low to detect all cases of sensitisation. We recommend that these individual fragrances be tested separately in higher concentrations when fragrance sensitivity is suspected.

2.6 ROUTINE TESTING WITH PRESERVATIVES IN PATIENTS WITH SUSPECTED ALLERGIC CONTACT DERMATITIS (31,32)

SUMMARY

To evaluate the frequency of sensitisation to cosmetic preservatives in patients with suspected contact dermatitis, and to identify allergens suitable for inclusion in a (cosmetic) screening series, 2 groups of such patients (N= resp. 627 and 501) were tested with trays of preservatives. Prevalence rates of sensitisation higher than 1% were observed only to benzoic acid 5% pet (1.3%), benzalkonium chloride 0.1% aqua (1.3%), DMDM hydantoin 3% aqua (1.2%), Kathon CG 0.67% pet (1.4%) and alkyl trimethyl ammonium chloride 0.1% aqua (2.0%). At the concentrations used, benzoic acid, benzalkonium chloride and alkyl trimethyl ammonium chloride appeared to be marginal irritants, so some reactions interpreted as allergic may have been false-positive. The reactions to DMDM hydantoin were caused by formaldehyde sensitivity (33).
It is concluded that the frequency of sensitisation to cosmetic preservatives in patients with suspected allergic contact dermatitis is low. However, Kathon CG should be added to a (cosmetic) screening series.

INTRODUCTION

As testing with cosmetics and toiletry products often yields false-negative results, testing a screening series containing the most important cosmetic sensitisers in patients with suspected cosmetic-related contact dermatitis may increase the reliability of patch test results. In a previous study (22, Chapter 2.5), 179 patients with suspected cosmetic dermatitis were tested with a tray of fragrance materials and preservatives. Of the preservatives, Kathon CG and quaternium-15 most frequently elicited positive reactions; these were considered to be suitable for inclusion in a "cosmetic screening series".
This study describes the results of patch testing with trays of cosmetic preservatives in patients seen for routine testing because of suspected allergic contact dermatitis. The aims were to determine the frequency of preservative allergy in this population, and to identify allergens suitable for incorporation in a (cosmetic) screening series.

MATERIALS AND METHODS

In the period January 1 – April 30, 1985, the first tray of 13 preservatives (Table 14) was tested in 627 consecutive patients, who were selected for routine patch testing because of suspected allergic contact dermatitis. The second tray of 12 preservatives (Table 14) was tested in such patients between September 1 – December 31, 1985. All patients were also tested with the European standard series (Appendix 3). Test procedures were carried out according to internationally accepted recommendations (17).

RESULTS

The preservatives, test concentrations, vehicles, numbers and percentages of positive reactions are shown in Table 14. Three patients (0.3%) reacted to parabens and to quaternium-15 in the European standard series. Formaldehyde allergy was diagnosed in 31 patients (2.7%).

Overall, a low prevalence rate of positive reactions was observed to the allergens in the preservative series. Only benzoic acid, benzalkonium chloride, DMDM hydantoin, Kathon CG and alkyl trimethyl ammonium chloride scored higher than 1%. No reactions were seen to benzylparaben, dehydroacetic acid, triclosan, benzyl alcohol, diazolidinyl urea, zinc pyrithione and dichlorophene. Irritant or dubious (?+) reactions were frequently seen to 2-bromo-2-nitropropane-1,3-diol in the test concentration of 1% (n=40, 6.4%), benzalkonium chloride (n=27, 4.3%), benzoic acid (n=12, 1.9%), and alkyl trimethyl ammonium chloride (n=58, 11.6%). In 3 of 4 patients reacting to 1 or more parabens, there was a discrepancy

Table 14. Results of patch testing with preservatives

Preservative	Conc.	No. pos. reactions	(%) (N=1128)
European standard series			
Parabens	5x3% pet	3	0.3
Formaldehyde	1% aqua	31	2.7
Quaternium-15	1% pet	3	0.3
Preservative	**Conc.**	**No.pos. reactions**	**(%) (N=627)**
Preservative series I *			
Methylparaben	5% pet	1	0.2
Propylparaben	5% pet	3	0.5
Butylparaben	5% pet	1	0.2
Ethylparaben	5% pet	2	0.3
Benzylparaben	10% pet	–	–
Sorbic acid	2.5% pet	2	0.3
Dehydroacetic acid	3% pet	–	–
2-Bromo-2-nitropropane-1,3-diol	0.25% pet	1	0.2
	1% pet	5	0.8
Imidazolidinyl urea	2% pet	3	0.5
Benzoic acid	5% pet	8	1.3
Benzalkonium chloride	0.1% aqua	8	1.3
Triclosan	2% pet	–	–
Chloroxylenol	1% pet	2	0.3
Preservative	**Conc.**	**No. pos. reactions**	**(%) (N=501)**
Preservative series II *			
Phenoxyethanol	5% pet	1	0.2
DMDM hydantoin	3% aqua	6	1.2
Benzyl alcohol	10% pet	–	–
Captan	0.5% pet	3	0.6
Diazolidinyl urea	2% pet	–	–
Kathon CG	0.67% pet	7	1.4
Zinc pyrithione	1% pet	–	–
Bispyrithione	1% pet	2	0.4
Chloroacetamide	0.2% pet	3	0.6
Chlorhexidine digluconate	1% aqua	4	0.8
Alkyl trimethyl ammonium chl.	0.1% aqua	10	2.0
Dichlorophene	1% pet	–	–

* Test dilutions in pet: w/w Test dilutions in aqua: w/v

between the test results of the paraben mix in the European standard series and the individual parabens in the cosmetic series: 1x paraben mix positive, individual parabens negative; 1x paraben mix negative, propyl- and butylparaben positive; 1x paraben mix negative, propylparaben positive. 5 patients had a positive patch test to 2-bromo-2-nitropropane-1,3-diol 1% pet, but only 1 also reacted to 0.25% pet. 5 of the preservatives tested are formaldehyde releasers (34): quaternium-15 (in the European standard series), 2-bromo-2-nitropropane-1,3-diol, imidazolidinyl urea, DMDM hydantoin, and diazolidinyl urea (36).
All 3 patients reacting to quaternium-15 were allergic to formaldehyde. One of the 3 patients reacting to imidazolidinyl urea, and the only patient reacting to both concentrations of 2-bromo-2-nitropropane-1,3-diol also reacted to formaldehyde. Of the 6 patients with a positive patch test reaction to DMDM hydantoin, 4 were allergic to formaldehyde.

DISCUSSION

Of the preservatives showing prevalence rates of sensitisation exceeding 1%, benzoic acid, benzalkonium chloride and alkyl trimethyl ammonium chloride appeared to be marginal irritants at the concentrations tested; consequently, some reactions interpreted as allergic may actually have been irritant. Further testing with lower concentrations is necessary. Chlorhexidine digluconate 1% aqua caused 4 reactions (0.8%), but it has recently been shown that this concentration may be marginally irritant (37,38). 5 of the 6 patients allergic to DMDM hydantoin were retested later (33). In 3 the patch test reactions were probably caused by formaldehyde sensitivity, whereas the reactions to DMDM hydantoin observed in 2 patients *not* allergic to formaldehyde were not reproducable (33). Thus, only Kathon CG allergy seemed to be frequent enough to justify its inclusion in a (cosmetic) screening series, confirming previous observations (22,39; Chapter 2.5) All other preservatives had prevalence rates of sensitisation of 0.6% or less. Contact allergy to them does not seem to occur frequently enough to warrant their inclusion in a (cosmetic) screening tray. As for the preservatives in the European standard series, formaldehyde scored 2.7%, but only 3 reactions (0.3%) were observed to parabens and quaternium-15.
2 patients showed positive reactions to propylparaben and/or butylparaben in the absence of a positive reaction to the paraben mix in the European standard series. We do not know if the test concentration of 5% pet. used in the preservative series for the individual parabens may be irritant in some patients, or whether the concentration of 5x3% used in the European standard series is too low to detect all cases of sensitisation.
The low prevalence rate of sensitisation to quaternium-15 is somewhat surprising, as the allergen has recently been found important enough to

be included in the European standard series by the members of the International Contact Dermatitis Research Group (ICDRG). Also, in a previous study (Chapter 2.5), a higher prevalence rate of sensitisation of 2.8% (5/179) was found. However, the population in that study had been carefully selected on the basis of suspected cosmetic allergy.
The findings in this study are in sharp contrast with results from the United Kingdom (40). Of 2169 women and 1575 men patch tested in London, 4.3% and 1.9% had a positive patch test, respectively. 6.8% of women with facial eczema were allergic to quaternium-15. Men were more likely to have a concomitant formaldehyde sensitivity, which was often present when a contact source with quaternium-15 could not be found. We do not know the explanation for these significant differences between London and the Netherlands; possibly quaternium-15 is used less often in cosmetic products in our country.
From this study we conclude that of the cosmetic preservatives tested, Kathon CG is the only one suitable for inclusion in a (cosmetic) screening series.

2.7 CONCLUSIONS

This chapter reports the results of a series of investigations aimed at determining the nature and frequency of cosmetic-related side effects, and the products involved. From these studies and literature data the following conclusions are drawn:

1. Adverse effects from cosmetics and toiletry products may affect approximately 10% of the adult population in a period of 1-5 years
2. Less than 10% of these reactions are caused by contact allergy. Most are due to irritation from personal cleanliness products such as soap, shampoo, bath foam and from deodorant.
3. Irritant effects of cosmetics and toiletries may worsen pre-existing dermatoses such as seborrhoeic dermatitis, acne and rosacea.
4. Product categories causing most adverse reactions in women are personal cleanliness products, deodorant/antiperspirant, skin care products, and eye cosmetics. In men most reactions are caused by personal cleanliness products, aftershave, and deodorant/antiperspirant.
5. An atopic diathesis may predispose to irritant cosmetic-related side effects.
6. Of dermatological patients patch tested for suspected allergic contact dermatitis, 3-5% are allergic to cosmetic products.
7. Skin care products, nail cosmetics, hair cosmetics and fragrance products cause most cases of allergic cosmetic dermatitis (See also Chapters 3.3. and 3.4).
8. Kathon CG should be added to a cosmetic screening series.

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Chapter 3 The allergens in cosmetics

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Chapter 3 The allergens in cosmetics

3.1 INTRODUCTION

Although there are many publications on contact allergy to cosmetics and toiletries, few studies have systematically investigated the allergens in such products. This may be explained by a general lack of information on their ingredients. Data on the constituents of the individual marketed cosmetic products are readily available only in the United States where, since 1978, regulations have required that all ingredients, other than components of flavours and fragrances be declared on cosmetic products labels. According to EEC regulations, cosmetic companies are required to provide information on the ingredients of their products to the proper authorities (under provision of secrecy) in cases of proven adverse reactions, for purposes of medical treatment (Chapter 1.5). Indeed, most companies are quite cooperative, and dermatologists pursuing the matter usually succeed in obtaining the information necessary for ingredient patch testing. Nevertheless, much time and energy often has to be spent, and this has generally discouraged dermatologists from such investigation. In addition, the identification of the causative allergen(s) has usually little practical value for the patient, as without product ingredient labelling he/she would still be unable to choose products not containing the offending substances. This chapter presents the results of 2 studies investigating the allergens in cosmetics and toiletries, and surveyes the literature on the issue. Case-reports of rare or "new" cosmetic allergens, published by the author, are summarised.

3.2 LITERATURE SURVEY

3.2.1. INTRODUCTION

Studies on the allergenic ingredients in cosmetics may be divided into 3 categories:

1 Studies in which a large number of patients suffering from cosmetic allergy has been subjected to (full) ingredient patch testing. Only the members of the North American Contact Dermatitis Group (304) have performed such an investigation.

2 Studies in which a large number of patients suffering from cosmetic allergy have been tested with (a variety of) allergens known to be present in cosmetic products, but not with the ingredients of the suspected products themselves. In these investigations it usually remained unconfirmed that the allergens identified were actually present in the suspected products. Such studies have been reported from the USA (308), France (307), Sweden (311), Italy (305), Spain (306), and Belgium (309,310).

3 Isolated case-reports of patients with cosmetic allergy tested with all or some ingredients of the suspected products, in which the allergens were identified (1-278).

These literature data are summarised here. In addition, some chemicals which are (or were) important cosmetic allergens are discussed.

3.2.2. INGREDIENTS WHICH ARE (OR WERE) IMPORTANT COSMETIC ALLERGENS

D & C red no. 31

Since the latter half of the 1950's, many cosmetic dermatitis patients with accompanying bizarre pigmentation have been observed in Japan (292). The descriptive term pigmented cosmetic dermatitis has been proposed for this disease (293). Most of these patients were found to be allergic to colour- containing cosmetic products such as rouge, lipsticks and face powders (294). Many of them proved to be hypersensitive to certain coal tar dyes used in such products, especially D & C Red no. 31 (Brilliant lake Red R) and other 1-phenylazo- 2-naphthol derivatives (294). Brilliant lake Red R was considered to be the most important causative agent of pigmented cosmetic dermatitis in Japan (297). The commercial dye was found to contain many impurities (295), of which 1-phenylazo-2-naphthol (CI 12055, Solvent Yellow 14, Sudan I) was probably the major allergenic ingredient (296). The role of fragrances and photocontact allergy proved to be far less important (294) than previously suspected (293). After 1976, cosmetic products containing D & C Red no. 31 rapidly disappeared from the Japanese market, and the incidence of pigmented cosmetic dermatitis soon decreased. In Europe and the USA, pigmented cosmetic dermatitis has only rarely been reported (92).

Eosin

Eosin (CI 45380:2, Solvent Red 43, D & C Red no. 21, tetrabromofluorescein) in lipstick used to be the most common cause of cosmetic allergy in the fifties (284). Calnan & Sarkany saw 110 cases within a period of 5 years; this represented approximately half the number of patients with contact dermatitis due to cosmetics (284). The allergen is not eosin itself, but an impurity (285-287); all patients allergic to the colour have reacted more weakly to patch tests with eosin purified by crystallisation than to the original impure dye (285-287). The exact chemical identity of the allergen has not been established. The incidence of eosin sensitivity fell rapidly after 1960 (288) because (i): paler shades of lipstick, not requiring the routine addition of eosin, became more fashionable, and (ii): much purer (and consequently less allergenic) eosin became available.

Nowadays, lipstick is a relatively infrequent cause of cosmetic allergy (304-

311), although a large number of its ingredients have been described as sensitisers (Table 8).

Halogenated salicylanilides

In the 1960s, the halogenated salicylanilides and related antibacterial and antifungal compounds caused almost an epidemic of photoallergic reactions. Tetrachlorosalicylanilide (TCSA) was responsible between 1960 and 1961 for an estimated 10,000 cases in England (298) before it was removed from general use. Subsequently, a number of related phenolic compounds were incorporated into soaps and other vehicles to combat infection, reduce body odour, act as preservatives, and destroy fungi. Photocontact reactions were induced by many of these agents, including bithionol, the brominated salicylanilides, hexachlorophene, dichlorophene, trichlorocarbanilide, Fenticlor, Multifungin (bromochlorosalicylanilide), Jadit (a mixture of buclosamide and salicylic acid: 299,300) and chloro-2-phenylphenol (301).

There has been a rapid decline in the induction of photocontact dermatitis by the halogenated salicylanilides and related compounds since 1968 (302); this probably as a result of the removal of the more potent of these photosensitisers from general use.

Although this thesis discusses photosensitivity to cosmetics only briefly (Chapter 1.4), this important episode of adverse effects to cosmetic products has been included, as often patients (also) had a "plain" contact allergy (303).

p-Phenylenediamine

An allergic reaction to hair dye is rarely missed by either patient or the physician. Most cases of sensitisation to the hair dye *p*-phenylenediamine occurred in the 1930s, when patients with severe dermatitis were reported in the literature (290). Sensitisation by *p*-phenylenediamine has, in the past, been considered so great a hazard that its use in hair dyes has been prohibited in some European countries such as Germany, France and Sweden. Currently its incorporation in cosmetic products is allowed in the EEC at a maximum concentration of 6% (as free base). The label must clearly state that the product can cause allergic reactions, and that a sensitivity test prior to usage is advised.

Other oxidation dyes such as toluene-2,5-diamine, 2-nitro-*p*-phenylenediamine and *N*-phenyl-*p*-phenylenediamine proved to have no obvious advantages over *p*-phenylenediamine (291). In recent years, the incidence of dermatitis due to hair dyes containing *p*-phenylenediamine appears to have decreased (289); this is attributed to the provision of cautionary notices on the product, awareness of the risks, patch testing, improvements in the technical quality of the cosmetic product and improvements in the technique of application of these dyes (289). The real incidence remains unknown. Although about 40% of women in the United States are said

to use a hair dye, the proportion of permanents to semipermanents (which rarely cause allergic contact dermatitis) is unclear.
Also, it must be noted that the allergy is widely known by the public and their doctors; many patients are probably diagnosed and treated by their general practitioners, without reference to a dermatologist. In the study of the North American Contact Dermatitis Group (304), 41 of 578 patients (7%) with allergic cosmetic dermatitis were hypersensitive to *p*-phenylenediamine. In other studies, between 5-11% of patients allergic to cosmetics reacted to *p*-phenylenediamine and/or hair colour products (307-311).

Toluenesulfonamide/formaldehyde resin
Resins are an essential ingredient of nail lacquers; they improve the gloss, adhesion, hardness and flow of the lacquer. By far the most commonly used compound is toluenesulfonamide/formaldehyde resin, made by reacting *p*-toluenesulfonamide with formaldehyde. Contact allergy to nail lacquer was first described in 1925 (279), and it was soon established that the resin was the antigen (280-282). Simon (280) patch tested 7 patients allergic to nail lacquers with 25 substances used in the manufacture of these cosmetics: all 7 reacted to "formaldehyde-sulfonamide resin". Keil and van Dyck (282) investigated 26 such patients: 25 reacted upon patch testing to toluenesulfonamide/formaldehyde resin. They stated that this group was only a small fraction of all patients seen with nail lacquer dermatitis. In 1958, a series of 56 patients with cosmetic allergy caused by nail lacquers was described by Calnan & Sarkany (283). At that time, nail lacquer was the second commonest cause of cosmetic dermatitis after lipstick, accounting for approximately 20% of all cases of cosmetic allergy. Of the 56 patients reported (283), "little more than half" could be investigated in detail; 28 reacted to sulfonamide/formaldehyde resin. The resin is nearly always the sensitiser in nail lacquers. Other causes have been described occasionally: drometrizole, formaldehyde, and guanine (Tables 7 and 8).
In the study of the North American Contact Dermatitis Group (304) toluenesulfonamide/formaldehyde resin was the 6th most common cause of cosmetic allergy after fragrances (unspecified), quaternium-15, *p*-phenylenediamine, glyceryl thioglycolate, and propylene glycol.
In a study from Spain (306) nail lacquers were the most common cause of cosmetic allergy in 195 patients (47 cases, 24%). In France (307), nail lacquers were the 2nd most common cause in 91 patients with cosmetic allergy (20 reactions, 22%). However, in other studies nail lacquers were infrequently implicated (308,309,311).

Zirconium
In 1956-58, American dermatologists were confronted with a unique and

highly distinctive clinical entity. The dermatosis was invariably found in the axillae, and was characterised by a chronic papular eruption. Pruritus and acute inflammation were occasionally present. Most patients were women, who were in the habit of shaving their axillae. All used deodorants containing zirconium salts, notably sodium zirconium lactate. The eruption was often chronic, persisting for months or years. No therapy was effective, and in most cases there has been gradual spontaneous involution. Histologically, a granulomatous reaction was observed in the dermis.
Six such cases were presented by Shelley and Hurley (353), who also reviewed 64 cases reported previously. It was demonstrated that the "zirconium deodorant granulomas" were allergic in nature. Patch tests were always negative, but the hypersensitivity was demonstrated by intradermal testing.

3.2.3. LARGE-SCALE STUDIES OF PATIENTS WITH COSMETIC ALLERGY

United States
During 64 months (1977 to 1983) the members of the North American Contact Dermatitis Group (NACDG) studied 713 patients with cosmetic dermatitis (304). Cosmetic allergy was observed in 578 (81%). To identify the causative ingredients, 273 patients (38%) were patch tested with the suspected cosmetics and some of their ingredients; 130 patients (18%) were tested with all ingredients. This resulted in identification of 87 ingredients or classes of ingredients that had caused allergic cosmetic dermatitis (Table 1). Fragrance and fragrance ingredients were responsible for the greatest number of reactions (n=161). In most cases (n=67) the individual fragrance component could not be determined, but when it could, the most frequent causes were cinnamic alcohol (n=17), hydroxycitronellal (n=11), musk ambrette (n=11), isoeugenol (n=10), and geraniol (n=8). Preservatives were the second most frequent causes of reactions (n=149), followed by *p*-phenylenediamine (n=41), lanolin and derivatives (n=29), and glyceryl thioglycolate and propylene glycol (25 each). The preservative ingredients causing the greatest number of reactions were quaternium-15 (n=65), imidazolidinyl urea (n=21), parabens (unspecified as to type, n=19), 2-bromo-2-nitropropane-1,3-diol (n=16) and formaldehyde (n=16).
Comment: This is the only study in the literature that has systematically investigated the allergenic ingredients in cosmetic products.

In another American study (308) 70 patients with proven cosmetic allergy were investigated. The identified allergens are shown in Table 2. Most reactions were caused by parabens (n=8), followed by dichlorophene (n=6), lanolin (n=5), mercurials (n=5) and sorbic acid (n=4).

Table 1. Causative ingredients in 578 patients with cosmetic allergy (304)

Ingredient	No. of reactions	Ingredient	No. of reactions
Acrylate, unspecified	1	Jasmine, synthetic	2
Allantoin	2	Lanolin	15
Amylcinnamic aldehyde	2	Lanolin alcohol	12
Amyl dimethyl PABA	2	Lanolin oil	2
Beeswax	1	Methacrylate monomer (unspecified)	1
Benzalkonium chloride	2	Microcrystalline wax	1
Benzocaine	2	Mineral oil	1
Benzoin	2	Musk ambrette	11
Benzophenone (unspecified)	1	Neomycin	1
Benzophenone-4	2	Nitrocellulose	1
Benzophenone-8	1	2-Nitro-*p*-phenylenediamine	1
Benzyl alcohol	3	Oak moss	3
Benzyl benzoate	1	Octyl dimethyl PABA	5
Benzyl salicylate	1	Oleamide DEA	1
BHA	3	Oleyl alcohol	1
Bismuth oxychloride	1	Oxyquinoline	1
2-Bromo-2-nitropropane-1,3-diol	16	PABA	3
Butyl acetate	1	Paraben (unspecified)	19
Captan	2	PEG-4 dilaurate	1
Cetearyl alcohol	1	Peru balsem	3
Cetyl alcohol	1	*p*-Phenylenediamine	41
Cherry oil	1	Potassium sorbate	2
Chloroxylenol	1	Propylene glycol	25
Cinnamal	6	Propyl gallate	1
Cinnamic alcohol	17	Quaternium-15	65
Clove oil	1	Resorcinol	3
Coal tar	1	Sandalwood oil	3
Costus oil	1	Shellac	1
Coumarin	4	Sodium bisulfite	1
Dibutyl phthalate	1	Sorbic acid	6
Diethylene glycol dimethacrylate	1	Stearamidoethyl diethylamine	3
Disodium mono-oleamido sulfosuccinate	1	Stearic acid	1
Ethyl methacrylate	5	TEA-stearate	1
Eugenol	4	Tetrachlorsalicylanilide	1
Formaldehyde	16	Tetrahydrofurfuryl methacrylate	1
Fragrance (unspecified)	67	Thimerosal	1
Geraniol	8	Thioglycolate (unspecified)	1
Glyceryl PABA	5	Tocopherol	2
Glyceryl thioglycolate	25	Toluenesulfonamide/	23
Hydrolyzed animal protein	1		

Table 1. (continued)

Ingredient	No. of reactions	Ingredient	No. of reactions
Hydroxycitronellal	11	formaldehyde resin	
Imidazolidinyl urea	21	Tribromsalan	1
Isoeugenol	10	Triclosan	1
Jasmine, absolute	3	Triethanolamine	3
		UV-absorber (unspecified)	1

Table 2. Allergens identified in 70 patients with cosmetic allergy (308)

Allergen	No. pos. reactions
Parabens	8
Dichlorophene	6
Lanolin	5
Mercurials	5
Sorbic acid	4
Balsam Peru	3
Cinnamal	3
Formaldehyde	3
EDTA	2
Isoeugenol	2
Laureth-4 and Steareth-2	2
Lavender oil	2
Bergamot oil	1
Clove oil	1
Eucalyptus oil	1
Eugenol	1
Hexachlorophene	1

Comment: The author emphasised that specific ingredient testing was very limited. It was stressed that the routine screening of parabens, lanolin fractions and dichlorophene represented an obvious bias.

Sweden

In a Swedish study (311) 35 patients had positive patch test reactions to their cosmetic products. Other positive reactions were seen to rosin (n=2), parabens (n=2), balsam Peru (n=2), wood tars (n=1), and *p*-phenylene-diamine (n=1). Ingredients in the products were "sometimes" tested: 3 patients allergic to an antiperspirant reacted to its ingredient propantheline bromide, and 3 to the "specific perfume" in eau de toilette or aftershave.

France

In a French study (307) 91 patients had cosmetic allergy as determined by positive patch tests to cosmetic products. Other positive reactions in these patients to allergens which may be present in cosmetics are summarised in Table 3. Most reactions were caused by chloroacetamide (n=5), followed by the fragrance mix (n=4), *p*-phenylenediamine (n=4), balsam Peru (n=3), imidazolidinyl urea (n=3), lanolin (n=3), propylene glycol (n=3) and thioglycerin (n=3).

Table 3. Positive patch test reactions to cosmetic ingredients in 91 patients with cosmetic allergy (307)

Allergen	No. pos. reactions
Chloroacetamide	5
Fragrance mix	4
p-Phenylenediamine	4
Balsam Peru	3
Imidazolidinyl urea	3
Lanolin	3
Propylene glycol	3
Thioglycerin	3
Formaldehyde	2
Jasmin oil	1
Lavender oil	1
Thimerosal	1
Triethanolamine	1
Sorbitan oleate	1
Other	4

Comment: The authors emphasised that the relevance of these reactions for the cosmetic-related contact dermatitis was not ascertained; nevertheless, they were felt to be indicative.

Spain

In a study from Spain (306) 460 patients were considered to have positive patch tests related to cosmetics. The results are shown in Table 4. Most reactions were caused by *p*-phenylenediamine (n=148), followed by the fragrance mix (n=80), balsam Peru (n=61), wool alcohols (n=55) and formaldehyde (n=43).

Comment: These data have very limited value. Only 195 of the 460 patients actually had positive patch test reactions to cosmetic products. In addition, they were not tested with the ingredients of the incriminated products.

Table 4. Positive patch tests with allergens related to cosmetics in 460 patients (306)

Allergen	No. pos. reactions	(%)
p-Phenylenediamine	148	(32%)
Fragrance mix	80	(17%)
Balsam Peru	61	(13%)
Wool alcohols	55	(12%)
Formaldehyde	43	(9%)
Parabens	37	(8%)
Turpentine	37	(8%)
Mercury	28	(6%)
Cinnamon	25	(5%)
Hexachlorophene	19	(4%)
Benzalkonium chloride	16	(3%)
Rosin	16	(3%)
Ethylenediamine	14	(3%)
Clioquinol	7	(2%)

The reactions in the 460 patients were attributed to cosmetic allergy, but the criteria for this diagosis were not specified; non-cosmetic sources of sensitisation were apparently not excluded.

Italy

A study from Italy (305) presented data on certain forms of cosmetic-induced contact dermatitis: (1) cosmetic allergy caused by hair cosmetics; (2) cosmetic allergy of the eyelids; and (3) contact cheilitis.

34 patients had suffered from contact allergy to *hair* cosmetics. 33 (97%) reacted to *p*-phenylenediamine, 15 (44%) to diaminodiphenylmethane, and 4 (12%) to benzocaine. These latter 2 reactions were interpreted as cross-reactions to the hair dye *p*-phenylenediamine. Two patients (6%) reacted to formaldehyde, and 1 (3%) to parabens and Balsam Peru, which are ingredients of other hair cosmetics including shampoos.

Allergic contact dermatitis of the *eyelids* was diagnosed in 52 patients. The allergens considered to be responsible were nickel sulfate (23 patients, 44%), cinnamal (15 patients, 29%), Balsam Peru (12 patients, 23%), parabens (4 patients, 8%) and eugenol (1 patient, 2%).

Allergic *contact cheilitis* was diagnosed in 11 patients. These patients had positive patch test reactions to guaiazulene (n=5), Balsam Peru (n=3), the fragrance mix (n=2), methyl methacrylate (n=2) and parabens (n=1). The reactions to guaiazulene were caused by sensitivity to mouth washes.

Comment: Even though in many cases additional cosmetic allergens were tested, most of the patients in this study were *not* tested with the separate

ingredients of the suspected cosmetics. Probably only in a few cases (the hair dyes excepted) was the relevance of the identified allergens ascertained. It appears highly unlikely that nickel was responsible for so many instances of allergic cosmetic dermatitis of the eyelids.

Belgium

In a Belgian study (310) 279 patients with allergic contact dermatitis caused exclusively by cosmetic products were investigated. The most common cosmetic allergens in these patients are summarised in Table 5.

Most reactions were caused by balsam Peru (n=92), followed by the fragrance mix (n=84), *p*-phenylenediamine (n=30), wood tars (n=25), cinnamal (n=19), and isoeugenol (n=19).

Table 5. Extracts from the frequency list of the most common cosmetic allergens in 279 patients with allergic cosmetic dermatitis (310)

Allergen	No. pos. reactions	(%)
Balsam Peru	92	(33%)
Fragrance mix	84	(30%)
p-Phenylenediamine	30	(11%)
Wood tars	25	(9%)
Cinnamal	19	(7%)
Isoeugenol	19	(7%)
Formaldehyde	18	(6%)
Eugenol	15	(5%)
Oak moss	14	(5%)
Cinnamic alcohol	11	(4%)
Thimerosal	11	(4%)
Hydroxycitronellal	10	(4%)
Toluenesulfonamide/formaldehyde resin	10	(4%)
Chloroacetamide	7	(3%)
Geraniol	6	(2%)
Phenyl salicylate	6	(2%)
Benzyl alcohol	5	(2%)
α-Amylcinnamic aldehyde	4	(1%)
2-Bromo-2-nitropropane-1,3-diol	4	(1%)
Benzoic acid	3	(1%)
Imidazolidinyl urea	3	(1%)
Sorbic acid	3	(1%)
Quaternium-15	2	(1%)

In another Belgian study (309) 156 patients had allergic contact dermatitis caused exclusively by cosmetic products. The specific allergens identified are shown in Table 6.

Most reactions were caused by balsam Peru (n=52), followed by the fragrance mix (n=49), isoeugenol (n=16), *p*-phenylenediamine (n=16), wood tars (n=13), and eugenol (n=11).

Table 6. Specific allergens identified in 156 patients with cosmetic allergy (309)

Allergen	No. pos. reactions	(%)
Balsam Peru	52	(33%)
Fragrance mix	49	(31%)
Isoeugenol	16	(10%)
p-Phenylenediamine	16	(10%)
Wood tars	13	(8%)
Eugenol	11	(7%)
Cinnamal	8	(5%)
Wool alcohols	8	(5%)
Oak moss	7	(4%)
Cinnamic alcohol	6	(4%)
Formaldehyde	6	(4%)
Hydroxycitronellal	6	(4%)
Thimerosal	6	(4%)
2-Nitro-*p*-phenylenediamine	5	(3%)
N-Phenyl-*p*-phenylenediamine	5	(3%)
Jasmin oil	4	(3%)
Sorbic acid	4	(3%)
p-Toluene sulfate	4	(3%)
Disperse Yellow	3	(2%)
Parabens	3	(2%)
Phenyl salicylate	3	(2%)
Amylcinnamic alcohol	2	(1%)
Benzyl alcohol	2	(1%)
2-Bromo-2-nitropropane-1,3-diol	2	(1%)
Geraniol	2	(1%)
Propylene glycol	2	(1%)
Toluene-2,5-diamine	2	(1%)

Comment: There is probably a considerable overlap between these two Belgian studies. The criteria for the diagnosis of cosmetic allergy were not specified. Ingredient patch testing was not performed; the relevance of the allergens identified was not ascertained. In the first study (310) apparently some allergens have, for reasons unknown, been deleted from the list. In the second study (309), only 50 patients (32%) had positive patch tests to their cosmetic products. Soap and shampoos caused the greatest number of reactions (64 patients, 41%); this seems to be highly unlikely, considering the short contact time of these products with the skin and the high dilution with water under normal conditions of use.

3.2.4 CASE-REPORTS OF PATIENTS WITH COSMETIC ALLERGY: TABULATION OF THE SENSITISERS

Nearly 300 case-reports of patients with cosmetic allergy, in whom the ingredients responsible for the allergic reaction were identified by (full) ingredient patch testing, have been reported in the literature (1-278).

From these references the following data were collected:

a. name of the allergenic ingredient
b. its function in the cosmetic
c. the cosmetic that caused the allergic reaction
d. the number of patients observed

An alphabetical listing of the cosmetic sensitisers with the relevant data is presented in Table 7.
Table 8 specifies the cosmetic product categories and the allergens identified in them.

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Acetarsone	antimicrobial	toothpaste	1	55
Aluminum chloride	antiperspirant	antiperspirant	1	126
		antiperspirant	1	127
		antiperspirant	1	217
Ammoniated mercury	depigmenting agent	bleaching cream	21	247
Amyl dimethyl PABA	UV-filter	lip balm	1	76
		sunscreen	1	147
Anethole	flavour	toothpaste	1	1
		toothpaste	1	19
Anise oil	flavour	toothpaste	1	20
Avocado oil	emollient	sunscreen	1	232
Azulene	counterirritant/	toothpaste	1	139
	botanical colour	lipstick	1	117
Balsam Peru	flavour	lip balm	8	32
Benzalkonium chloride	antimicrobial	deodorant	1	186
	conditioner	hair dressing	2	40
Benzethonium chloride	antimicrobial	feminine hygiene spray	2	188
Benzoin	fragrance	cream	1	90
		facial makeup (greasepaint)	2	58
		lipstick	?	260
	resin	hair lacquer	1	91

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Benzophenone- 3	UV-filter	sunscreen	1	53
		sunscreen	1	193
		sunscreen	1	226
Benzophenone- 4	UV-filter	sunscreen	1	73
		sunscreen	1	185
Benzophenone- 8	UV-filter	sunscreen	1	53
		sunscreen	1	193
Benzophenone-10	UV-filter	sunscreen	2	74
		sunscreen	1	110
		sunscreen	1	148
		sunscreen	6	243
Benzoxonium chloride	antimicrobial	moisturising cream	1	239
Benzyl alcohol	fixative/	perfume	1	35
	antimicrobial	aftershave	1	35
	preservative	sunscreen	1	171
BHA	antioxidant	sunscreen	1	119
		lipstick	3	119
		facial makeup	1	119
		eye shadow	1	119
		hair cream	1	119
		skin care product	1	46
		hand cream	1	249
BHT	antioxidant	lipstick	1	119
Bismuth oxychloride	colour	eye shadow	1	182
Bornelone	UV-filter	skin care product	2	108
Butyl alcohol *t*-		sunscreen	1	208
Butyl hydroquinone	antioxidant	eye shadow	1	11
2,5-*ditert*-		eye shadow	1	12
Butyl hydroquinone *t*-	antioxidant	lipstick	1	81
		lipstick	1	114
		lipstick	1	119
		eye shadow	1	119
		skin care product	1	140
Butyl methoxy-	UV-filter	sunscreen	1	243
dibenzoylmethane		(sunscreen)lipstick	1	235
Carmine	colour	lip salve	3	203
Carotene β-	UV-filter	sunscreen	1	70
Carvone	flavour	toothpaste	1	1
		toothpaste	4	19
Carvone L-	flavour	toothpaste	1	116

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Castor oil	emollient	skin care product	1	93
		lipstick	1	105, 106
		lipstick	1	122
		lip cream	1	105, 106
Cetrimonium bromide	conditioner	shampoo	1	257
Cetyl alcohol	emollient	hand lotion	1	200
Chlorhexidine	antimicrobial	feminine hygiene spray	1	188
Chloroacetamide	preservative	cream	2	5
		body massage cream	1	89
		hand lotion	1	101
		skin care product	1	34
		skin care product	3	160
		skin care product	1	223
		body lotion	1	5
		body lotion	1	199
		eye cream	1	7
		eye cream	1	164
		facial aerosol spray adstringent	1	169
Chloroxylenol	antimicrobial	soap	1	270
	preservative	hand lotion	2	162
Chlorphenesin	antifungal	deodorant	1	236
Chromium hydroxide	colour	soap	1	92
Cinnamal	flavour	toothpaste	3	21, 22
		toothpaste	15	23
		toothpaste	7	57
		toothpaste	1	191
		toothpaste	1	224
		(sunscreen)lipstick	1	224
Cinnamic alcohol	fragrance	aftershave	1	54
Cinnamon oil	flavour	toothpaste	1	17
		toothpaste	1	18
		toothpaste	1	153
Cinoxate	UV-filter	sunscreen	3	149
		sunscreen	1	243
Cocamide DEA	emulsifier	hand gel	1	68
	surfactant	shampoo	1	233
Cocamidopropyl betaine	surfactant	shampoo	2	128
Coco-betaine	surfactant	shampoo	2	103
D&C Orange no. 17 lake	colour	lipstick	1	255

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
D&C Red no. 17	colour	lipstick	2	42
		eye cream	1	80
		facial makeup	1	13
D&C Red no. 19	colour	lipstick	1	262
D&C Red no. 31	colour	facial makeup	3	62
		lipstick	1	62
		lipstick	2	151, 262
D&C Red no. 31 lake	colour	lipstick	2	262
D&C Red no. 36	colour	facial makeup	1	134
		facial makeup	1	255
		lipstick	1	157
		lipstick	2	255
D&C Yellow no. 11	colour	lipstick	2	42
		facial makeup	1	13
		facial makeup	1	16
		facial makeup	1	42
		eye cream	1	80
		hair cream	1	240
		soap	1	210, 349
Diazolidinyl urea	preservative	soap	1	245
		hair gel	1	168
Dibutyl phthalate	emollient	antiperspirant/ deodorant	1	9
		antiperspirant	1	38
Dichlorodifluoromethane	propellant	antiperspirant	1	41
		deodorant	1	244
Dichlorophene	preservative	hand lotion	1	183
		facial makeup	1	251
		toothpaste	7	173
		toothpaste	1	174
		toothpaste	1	177
Diethylstilbestrol	hormone/hair growth stimulant	hair lotion	1	201
Dihydroabietyl alcohol	binder/ film former	mascara	1	61
		mascara	4	146
		eyeliner	3	277
Diisopropanolamine	emulsifier	eye shadow	1	10
		facial makeup	1	153
Drometrizole	UV-filter	nail lacquer	1	95
		skin care product	4	143
Emulgol	emulsifier	hand lotion	3	200

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Eusolex 8021	UV-filter	sunscreen	1	234
		skin care product	1	86
Fenticlor	antimicrobial	hair cream	1	6
		deodorant	1	26
Formaldehyde	antimicrobial/ antiperspirant	deodorant	1	145
	antiperspirant	antiperspirant	4	197
		antiperspirant	10	196
	hardener	nail hardener	1	87
		nail hardener	6	181
		nail hardener	1	206
		nail hardener	1	264
	solvent	nail lacquer	3	154
	preservative	shampoo	5	113
		shampoo	1	265
	preservative/ antimicrobial	toothpaste	1	136
Geraniol	fragrance	lip salve	1	83
Glutaral	preservative	hair conditioner	1	267
Glycerin	emollient	hand lotion	1	200
Glyceryl-3-(glyceroxy)-anthranilate	UV-filter	sunscreen	1	47
Glyceryl isostearate	emollient	lipstick	1	238
Glyceryl PABA	UV-filter	sunscreen	4	48, 50
		sunscreen	1	51
		sunscreen	1	52
		sunscreen	1	59
		sunscreen	1	60
		sunscreen	1	170
		sunscreen	1	194
Glyceryl stearate	emulsifier	sunscreen	1	74
	emollient	deodorant	1	254
Glyceryl thioglycolate	waving agent	permanent wave	4	213
		permanent wave	17	272
Guaiazulene	counterirritant	toothpaste	5	116
Guanine	colour	nail lacquer	4	179
Hexachlorophene	antimicrobial	deodorant	1	251
Hexenyl salicylate *cis*-3-	fragrance	toilet water	1	99
Hexylresorcinol		toothpaste	2	256
Hinokitiol	hair growth promotor	hair lotion	1	104

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Homosalate	UV-filter	sunscreen	2	195
Hydroquinone	depigmenting agent	bleaching cream	1	97
		bleaching cream	1	115
Hydroxycitronellal	fragrance	eye cream	1	27, 28
		aftershave	1	54
		aftershave	1	98
		facial makeup	1	65
		skin care product	1	65
Imidazolidinyl urea	preservative	skin care product	1	25
		skin care product	1	190
		skin care product	1	241
		hand cream	1	221
		eyeliner	1	25
		eyeliner	1	190
Isoeugenol	fragrance	eye cosmetics	1	14
		aftershave	1	40
Isopropyl-dibenzoylmethane 4-	UV-filter	skin care product	1	234
		skin care product	1	243
		sunscreen	1	222
		sunscreen	3	234
		sunscreen	3	243
		(sunscreen)lipstick	5	234
Isopropyl myristate	emollient	feminine hygiene spray	1	188
Isostearyl alcohol	emollient	deodorant	1	218
		lipstick	1	238
Kathon CG	preservative	cream	3	266
		shampoo	1	225
		moisturising cream	24	225
		sunscreen	1	219
		skin care product	2	132
		skin care product	1	219
Labilin		moisturising cream	4	137
		baby oil	1	137
		body powder	1	137
Lanolin	binder	facial makeup	1	262
	emollient	skin care product	7	198
		hand lotion	1	184
		hand lotion	1	189
		lipstick	1	152
Lanolin alcohol	absorption base	lipstick	2	14
		eye cosmetics	3	14

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Lanpol 5	emollient	lipstick	1	227
Lauramide DEA	surfactant	shampoo	1	233
Laurel oil	fragrance	face mask	1	350
Laurylpyridinium chloride	conditioner	hair conditioner	1	239
Lead acetate	dye	hair dye	1	167
Lilial	fragrance	antiperspirant	1	100
Limonene d-	flavour	mouthwash	1	44
Limonene l-	flavour	mouthwash	1	44
Linalool	fragrance	sunscreen	1	234
		aftershave	1	98
Liquid petrolatum		hair lotion	1	176
Mercury	antimicrobial	soap	1	107
	depigmenting agent	bleaching cream	1	206
Methylbenzylidene)-camphor 3-(4-	UV-filter	sunscreen	1	96
		sunscreen	2	234
		sunscreen	1	269
		(sunscreen)lipstick	3	234
Methyl glucose sesquistearate	emulsifier	tanning lotion	1	118
		skin care product	1	118
Methyl heptine carbonate	fragrance	aftershave	1	54
		lipstick	3	261
		skin care product	1	258
Methylionone γ-	fragrance	facial makeup	1	94
Methylparaben	preservative	skin care product	2	155
		sunscreen	1	166
Microcrystalline wax	emollient	lipstick	2	129
Mineral oil	emollient	skin care product	3	144
Miranol MSA	emulsifier	skin care product	1	204
Monobenzone	depigmenting agent	bleaching cream	1	180
		bleaching cream	1	115
Musk ambrette	fragrance	aftershave	1	63
		aftershave	1	88
		aftershave	8	271
		preshave lotion	1	63
		shaving cream	1	211
		deodorant	1	63
Nickel	contaminant	lipstick	2	172
		eye shadow	1	85
		mascara	1	85

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Nordihydroguiaretic acid	antioxidant	cream	1	250
Oak moss	fragrance	aftershave	1	273
		skin care product	1	65
Octyl dimethyl PABA	UV-filter	skin care product	1	243
		sunscreen	1	226
		sunscreen	1	243
Oleyl alcohol	emollient	lipstick	3	202
Olive oil	emollient	cream	1	77
PABA	UV-filter	sunscreen	1	75
		sunscreen	1	97
		sunscreen	1	226
		sunscreen	1	274
Panthenyl ethyl ether	antiseborrhoeic agent	hair lotion	1	109
Parabens	preservative	shampoo	1	103
		skin care product	1	156
		skin care product	2	158
		sunscreen	1	158
		facial makeup	1	56
Parabens (butyl- and methyl-)	preservative	deodorant	1	209
Parabens (methyl- and propyl-)	preservative	eye cream	1	80
PEG-300	lubricant	soap	1	276
Peppermint oil	coolant/flavour	mouthwash	1	44
	flavour	toothpaste	2	19
Phellandrene	flavour	mouthwash	1	44
Phenyl dimethicone	emollient	sunscreen	1	214
Phenylphenol *o*-	preservative	skin care product	2	159
		hand cream	1	78
Phenyl salicylate	fragrance/flavour	mouthwash	1	82
	UV-filter/flavour	lip salve	1	72
		lip salve	19	83
		lip balm	3	32
		lipstick	11	263
Pinene α-	flavour	mouthwash	1	44
Potassium persulfate	bleaching agent	hair bleach	1	150
Potassium sorbate	preservative	facial makeup	1	207
Procaine	hair growth stimulant	hair tonic	2	229
			1	228

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Propantheline bromide	anticholinergic agent	antiperspirant	11	39
			3	67
			3	215
			1	2
			1	4
			6	30
			1	31
			1	165
Propolis	natural ingredient	toothpaste	1	102
		toothpaste	1	131
	emollient	ointment	18	45
		ointment	1	130
	emollient/ moisturiser	cream	1	131
		hand cream	1	230
		skin care product	1	102
		skin care product	1	121
		skin care product	1	141
	emollient	lipstick	1	130
		mascara	1	146
Propylene glycol	emollient	lipstick	1	275
	moisturiser	cream	4	278, 351
	solvent	antiperspirant	2	30
		antiperspirant	1	39
	emollient	skin care product	1	351
		deodorant	1	351
		hand lotion	1	351
Propyl gallate	antioxidant	lipstick	1	71
		cream	1	246
Propylparaben	preservative	skin care product	2	155
Pyridoxine 3,4-dioctanoate	antiseborrhoeic agent	hair lotion	1	104
Quaternium-15	preservative	baby lotion	1	123
		hand/body lotion	1	125
Rosin	emollient	soap	1	29
	binder	lipstick	1	227
		eye shadow	1	8
		eye shadow	2	163
		facial makeup	1	33
Selenium sulfide	antiseborrhoeic agent	shampoo	3	178
Sesame oil	emollient	lipstick	1	242

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Shellac	binder	lipstick	1	227
		mascara	1	248
Sodium laureth sulfate	surfactant	shampoo	1	103
Solvent Red 1	colour	sunscreen	1	212
Solvent Red 3	colour	skin care product	1	220
		sunscreen	1	212
Solvent Yellow 44	colour	lipstick	1	24
		lipstick	1	205
Spearmint oil	flavour	toothpaste	4	19
Stearamidoethyl diethylamine	emulsifier	skin care product	3	111
		deodorant	1	111
Sulfated castor oil	surfactant	hair conditioner	12	79
Sulfiram	antimicrobial	soap	1	66
TEA-Coco-hydrolyzed animal protein	emulsifier	skin care product	1	192
TEA-PEG-3 cocamide sulfate	surfactant	shampoo	2	128
TEA-stearate	emulsifier	sunscreen	1	166
Thimerosal	preservative	eye cream	1	135
Thioglycerin	depilatory agent	depilatory cream	1	252
Thymol		toothpaste	1	352
Tioxolone	antiseborrhoic agent	hair lotion	1	84
Tocopherol	antioxidant/ vitamin	deodorant	3	187
		skin care product	1	268
Tolusafranine	colour	facial makeup	1	259
Trichlorofluoromethane	propellant	antiperspirant	3	41
Triclocarban	antimicrobial	antiperspirant	2	30
		antiperspirant	1	31
		antiperspirant	3	39
		soap	2	3
Triclosan	antimicrobial	foot powder	1	15
		foot powder	1	36
		deodorant	1	15
		deodorant	1	36
		deodorant	1	37
		deodorant	2	43
		deodorant	2	161
		soap	1	43
		soap	1	245

Table 7. Summary of literature data on case-reports of patients with cosmetic allergy: causative ingredients

INGREDIENT	FUNCTION	COSMETIC	NO. PAT.	REF
Triethanolamine	emollient/ emulsifier	hand lotion	27	200
		hand cream	1	141
		skin care product	1	142
		shaving cream	1	175
Trilaureth-4 phosphate	emulsifier	hand/body lotion	1	125
Witisol	UV-filter	sunscreen	1	112
Yellow iron oxide	colour	mascara	1	138
Zinc pyrithione	antidandruff agent	shampoo	1	69
		shampoo	1	133
		shampoo	1	205
		shampoo	1	233
		hair dressing	1	64
		hair lotion	1	64
		hair cream	1	124
Zinc ricinoleate	emollient	deodorant	2	237
Zirconium salts	antiperspirant	antiperspirant	70	353

Table 8. The allergenic ingredients by product category (for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
SHAMPOO	Cetrimonium bromide
	Cocamide DEA
	Cocamidopropyl betaine
	Coco-betaine
	Formaldehyde
	Kathon CG
	Lauramide DEA
	Parabens
	Selenium sulfide
	Sodium laureth sulfate
	TEA-PEG-3 cocamide sulfate
	Zinc pyrithione
HAIR CONDITIONER/GEL	Benzalkonium chloride
	Diazolidinyl urea
	Glutaral
	Laurylpyridinium chloride
	Sulfated castor oil
	Zinc pyrithione
HAIR DYE/BLEACH	Lead acetate
	Potassium persulfate

Table 8. The allergenic ingredients by product category (for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
OTHER HAIR COSMETICS	Benzoin
	BHA
	D&C Yellow no. 11
	Diethylstilbestrol
	Fenticlor
	Glyceryl thioglycolate
	Hinokitiol
	Liquid petrolatum
	Panthenyl ethyl ether
	Procaine
	Pyridoxine 3,4-dioctanoate
	Tioxolone
	Zinc pyrithione
SKIN CARE PRODUCTS	BHA
	Bornelone
	Butyl hydroquinone *t*-
	Castor oil
	Chloroacetamide
	Drometrizole
	Eusolex 8021
	Hydroxycitronellal
	Imidazolidinyl urea
	Isopropyl-dibenzoylmethane 4-
	Kathon CG
	Lanolin
	Methyl glucose sesquistearate
	Methyl heptine carbonate
	Methylparaben
	Mineral oil
	Miranol MSA
	Oak moss
	Octyl dimethyl PABA
	Parabens
	Phenylphenol *o*-
	Propolis
	Propylene glycol
	Propylparaben
	Solvent Red 3
	Stearamidoethyl diethylamine
	TEA-Coco-hydrolysed animal protein
	Tocopherol
	Triethanolamine

Table 8. The allergenic ingredients by product category (for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
MAKE UP/ROUGE	Benzoin
	BHA
	D&C Red no. 17
	D&C Red no. 31
	D&C Red no. 36
	D&C Yellow no. 11
	Dichlorophene
	Diisopropanolamine
	Hydroxycitronellal
	Lanolin
	Methylionone γ-
	Parabens
	Potassium sorbate
	Rosin
	Tolusafranine
BLEACHING CREAM	Ammoniated mercury
	Hydroquinone
	Mercury
	Monobenzone
EYE COSMETICS	BHA
	Bismuth oxychloride
	Butyl hydroquinone 2,5-*ditert*-
	Butyl hydroquinone *t*-
	Dihydroabietyl alcohol
	Diisopropanolamine
	Imidazolidinyl urea
	Isoeugenol
	Lanolin alcohol
	Nickel
	Propolis
	Rosin
	Shellac
	Yellow iron oxide
EYE CREAM	Chloroacetamide
	D&C Red no. 17
	D&C Yellow no. 11
	Hydroxycitronellal
	Parabens (methyl and propyl)
	Thimerosal

Table 8. The allergenic ingredients by product category
(for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
LIPSTICK	Azulene
	Benzoin
	BHA
	BHT
	Butyl hydroquinone *t*-
	Butyl methoxydibenzoylmethane
	Castor oil
	Cinnamal
	D&C Orange no. 17 lake
	D&C Red no. 17
	D&C Red no. 19
	D&C Red no. 31
	D&C Red no. 31 lake
	D&C Red no. 36
	D&C Yellow no. 11
	Glyceryl isostearate
	Isopropyl-dibenzoylmethane 4-
	Isostearyl alcohol
	Lanolin
	Lanolin alcohol
	Lanpol 5
	Methylbenzylidene)-camphor 3-(4-
	Methyl heptine carbonate
	Microcrystalline wax
	Nickel
	Oleyl alcohol
	Phenyl salicylate
	Propolis
	Propylene glycol
	Propyl gallate
	Rosin
	Sesame oil
	Shellac
	Solvent Yellow 44
LIP SALVE/CREAM	Amyl dimethyl PABA
	Balsam Peru
	Carmine
	Castor oil
	Geraniol
	Phenyl salicylate

Table 8. The allergenic ingredients by product category (for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
TOOTHPASTE	Acetarsone
	Anethole
	Anise oil
	Azulene
	Carvone (L-)
	Cinnamal
	Cinnamon oil
	Dichlorophene
	Formaldehyde
	Guaiazulene
	Hexylresorcinol
	Peppermint oil
	Propolis
	Spearmint oil
	Thymol
MOUTHWASH	Limonene d-
	Limonene l-
	Peppermint oil
	Phellandrene
	Phenyl salicylate
	Pinene α-
SHAVING COSMETICS	Benzyl alcohol
	Cinnamic alcohol
	Hydroxycitronellal
	Isoeugenol
	Linalool
	Methyl heptine carbonate
	Musk ambrette
	Oak moss
	Triethanolamine
HAND LOTION/CREAM/GEL	BHA
	Cetyl alcohol
	Chloroacetamide
	Chloroxylenol
	Cocamide DEA
	Dichlorophene
	Emulgol
	Glycerin
	Imidazolidinyl urea
	Lanolin
	Phenylphenol *o*-
	Propolis

Table 8. The allergenic ingredients by product category (for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
	Propylene glycol
	Quaternium-15
	Triethanolamine
BODY LOTION/CREAM/GEL	Chloroacetamide
	Propylene glycol
	Trilaureth-4 phosphate
OTHER LOTIONS/CREAM/GEL	Benzoin
	Benzoxonium chloride
	Chloroacetamide
	Kathon CG
	Labilin
	Nordihydroguiaretic acid
	Olive oil
	Propolis
	Propylene glycol
	Propyl gallate
	Quaternium-15
DEODORANT/ANTIPERSPIRANT	Aluminum chloride
	Benzalkonium chloride
	Chlorphenesin
	Dibutyl phthalate
	Dichlorodifluoromethane
	Fenticlor
	Formaldehyde
	Glyceryl stearate
	Hexachlorophene
	Isostearyl alcohol
	Lilial
	Musk ambrette
	Parabens (butyl- and methyl-)
	Propantheline bromide
	Propylene glycol
	Stearamidoethyl diethylamine
	Tocopherol
	Trichlorofluoromethane
	Triclocarban
	Triclosan
	Zinc ricinoleate
	Zirconium
SOAP	Chloroxylenol
	Chromium
	D&C Yellow no. 11

Table 8. The allergenic ingredients by product category (for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
	Diazolidinyl urea
	Mercury
	PEG-300
	Rosin
	Sulfiram
	Triclocarban
	Triclosan
PERFUME / COLOGNE	Benzethonium chloride
	Benzyl alcohol
	Chlorhexidine
	Hexenyl salicylate *cis*-3-
	Isopropyl myristate
SUN COSMETICS	Amyl dimethyl PABA
	Avocado oil
	Benzophenone- 3
	Benzophenone- 4
	Benzophenone- 8
	Benzophenone-10
	Benzyl alcohol
	BHA
	Butyl alcohol *t*-
	Butyl methoxydibenzoylmethane
	Carotene β-
	Cinoxate
	Eusolex 8021
	Glyceryl-3-(glyceroxy)-anthranilate
	Glyceryl PABA
	Glyceryl stearate
	Homosalate
	Isopropyl-dibenzoylmethane 4-
	Kathon CG
	Linalool
	Methylbenzylidene)-camphor 3-(4-
	Methylparaben
	Octyl dimethyl PABA
	PABA
	Parabens
	Phenyl dimethicone
	Solvent Red 1
	Solvent Red 3
	TEA-stearate
	Witisol

Table 8. The allergenic ingredients by product category
(for detailed information see Table 7)

COSMETIC CATEGORY	INGREDIENTS REPORTED AS COSMETIC ALLERGENS
NAIL HARDENER	Formaldehyde
NAIL LACQUER	Drometrizole
	Formaldehyde
	Guanine
OTHER COSMETICS	Labilin
	Laurel oil
	Methyl glucose sesquistearate
	Thioglycerin
	Triclosan

3.3 THE ALLERGENS IN COSMETICS: A RETROSPECTIVE STUDY (313)

SUMMARY

Of 1403 patients with contact dermatitis seen during a period of 5 years (1981-1985), 49 (3.5%) suffered from allergy to cosmetic products. The facial skin was most frequently affected. In many patients the dermatitis was limited to the eyelids (20%) or the face (41%). Skin care products (moisturising and cleansing creams/lotions/milks) accounted for nearly half of the dermatitis-causing cosmetics (45%), followed by hair cosmetics (10%), shaving preparations (10%), and nail cosmetics (8%). The ingredient classes most often responsible for the cosmetic allergy were fragrances (55%), followed by preservatives (20%) and emulsifiers (8%).

INTRODUCTION

Relative to their widespread use, cosmetics and toiletries infrequently cause serious adverse effects. However, mild reactions such as itching, burning or dry skin, may be experienced by many consumers (Chapter 2.3). The most frequently *reported* side effect of cosmetics is contact allergy (320,321). The allergens in cosmetics have been studied in a systematic manner in one investigation from the North American Contact Dermatitis Group (NACDG) only (304, Chapter 3.2.3).
Therefore it was decided to investigate which are the most important cosmetic allergens in The Netherlands. A prospective study is reported in Chapter 3.4. Here the results of a retrospective study on patients with cosmetic allergy investigated between 1981-1985 are presented.

PATIENTS, MATERIALS AND METHODS

The records of all patients patch tested because of suspected contact dermatitis during the period of 1981-1985 were reviewed and screened for cases of contact allergy to cosmetics. All patients had been tested with the European standard series (Appendix 3) and, when appropriate, with supplementary series e.g. an occupational series and/or the patients' own products. During several periods, additional test trays of preservatives and fragrance materials (317,323,324) were routinely tested. In cases of cosmetic allergy, the constituents of the suspected products were obtained from the manufacturers for ingredient patch testing, and diluted to the proper test concentrations and vehicle (316) by the Food Inspection Service Enschede. When no data on the proper test concentration were available, patch tests were performed at an empirically determined concentration utilising at least 25 controls to exclude irritancy.
Most cosmetic products were tested undiluted. Shampoos and shaving soaps were diluted to 2% in water, hair colours to 5% in water. Patch test procedures were carried out according to internationally accepted criteria (314). The diagnosis of cosmetic allergy was usually based on a positive patch test to a cosmetic product, and sometimes on a positive usage test and/or repeated open application test (ROAT) (315). In all cases dermatitis was or had been present at the site of application of the cosmetic products. Upon cessation of the use of the cosmetics, the skin eruption either cleared (when the dermatitis was caused exclusively by the cosmetic product) or markedly improved (when the cosmetic had been applied to already eczematous skin). These clinical characteristics were additional criteria for the diagnosis of cosmetic allergy.

RESULTS

In the period 1981-1985, 15,522 new patients were seen. 1403 of these were patch tested for suspected allergic contact dermatitis. In this group, 49 individuals with contact allergy to cosmetics were identified, representing 0.3% of the total patient population and 3.5% of all patients with suspected allergic contact dermatitis.
The group consisted of 41 women and 8 men; their ages ranged from 10-75 years (mean 38.6). 47 cases of cosmetic allergy were identified by positive patch tests; in 2 cases patch tests were negative, but the diagnosis was established by positive use tests and/or ROAT.
32 patients had no prior history of skin disease; their dermatitis was caused exclusively by cosmetic allergy. The other 17 patients had pre-existing dermatitis (8 atopic, 3 irritant, 5 seborrhoeic, 1 non-cosmetic allergic contact dermatitis). Their skin condition improved, but was not cured by stopping the use of the incriminated cosmetics. The most frequently affected body

sites were the face and periorbital area (76%), followed by the arms (24%), axillae (16%) and trunk (16%) (Table 9). The eyelids and the face (including the eyelids) were the *only* parts affected in 20% and 41% of the patients, respectively.

Table 9. Body sites affected by cosmetic dermatitis

	No. of patients affected	% (N=49)
Scalp	4	8%
Face	26	53%
Eyelids	22	45%
Neck	5	10%
Axillae	8	16%
Arms	12	24%
Hands	7	14%
Legs	5	10%
Feet	2	4%
Trunk	8	16%
Other	4	8%

Face (including eyelids) affected : 37 (76%)
Only the face (including eyelids) affected : 20 (41%)
Only the eyelids affected : 10 (20%)

Nearly half of the cutaneous reactions caused by cosmetic allergy (45%) were associated with skin care products (creams, lotions, milks) (Table 10). Shaving preparations and hair cosmetics followed with 6 reactions each (10%). Next were nail cosmetics with 5 reactions (8%). Eye cosmetics and deodorants each caused 4 reactions (7%), and fragrance products 3 (5%). Contact allergic reactions to one or more allergens in the European standard series (Appendix 3) which may be present in cosmetics were observed in 30 patients: 19 (39%) reacted to the fragrance mix, 10 (20%) to Balsam Peru, 5 (10%) to rosin (colophony), 3 (6%) to *p*-phenylenediamine and formaldehyde, 2 (4%) to wool alcohols, and 1 (2%) to parabens.
20 of the 49 patients were tested with all ingredients of the cosmetics (n=25) to which they had reacted. In 17 of these (22 products) the causative allergens were identified. The causative allergens in the other 3 patients (3 products) were not found. The causal allergens in 22 patients (27 products), of which the ingredients were not tested separately, could be established with high probability by the results of testing the European standard series and/or additional cosmetic allergens. The majority of these patients had positive patch test reactions to perfumed products, and in addition a positive reaction to the fragrance mix and/or to the indicator allergens balsam Peru and rosin. In these cases, the causative ingredient was classified as "fragrance, unspecified".

Table 10. Product categories causing cosmetic allergy #

Hair cosmetics		**6 (10%)**	**Fragrance products**		**3 (5%)**
– shampoo	1		– perfume cream	1	
– hair colour	2		– perfume	2	
– dry shampoo	1				
– hair dressing	1		**Deodorants**		**4 (7%)**
– hair lotion	1		– lotion	3	
			– cream	1	
Skin care products		**27 (45%)**			
			Nail cosmetics		**5 (8%)**
Eye cosmetics		**4 (7%)**	– lacquer	3	
– mascara	2		– hardener	2	
– eye cream	2				
			Other products		**5 (8%)**
Shaving preparations		**6 (10%)**			
			– bath oil	2	
– aftershave	5		– powder	1	
– shaving foam	1		– lip salve	1	
			– rouge	1	

the total number of cosmetics (N=60) exceeds the number of patients, as some reacted to more than 1 cosmetic product

Thus, it was possible to identify the causative allergen with certainty or high probability in 39 of our 49 patients with cosmetic allergy. A total of 21 ingredients or classes of ingredients, responsible for 51 reactions, was identified (Table 11).

Fragrances and fragrance chemicals were reponsible for the majority of the reactions (55%). In most cases the individual fragrance components were not determined, but when they were, the most frequent causes were hydroxycitronellal and linalool. Preservatives/antimicrobials were the second most frequent causes of reactions (20%). In this category, most reactions were caused by Kathon CG. The emulsifier oleamidopropyl dimethylamine was the next most frequently identified allergen (8%).

DISCUSSION

In this investigation, 3.5% of all patients patch tested for suspected allergic contact dermatitis were hypersensitive to cosmetics. Cosmetic allergy accounted for about 12% of all contact allergens shown to be of present relevance. Most reactions were caused by skin care products. Product categories involved in cosmetic-related adverse effects and the frequency of cosmetic allergy in dermatological patients are discussed in Chapter 2.

Table 11. (Classes of) ingredients causing cosmetic allergy

		No.	% (N=51)
Fragrances, unspecified		**19**	**37%**
specified		**9**	**18%**
– Hydroxycitronellal	3		
– Linalool	2		
– Cinnamic alcohol	1		
– Citronellol	1		
– γ-Methylionone	1		
– Peppermint oil	1		
Preservatives/antimicrobials		**10**	**20%**
– Kathon CG	3		
– Quaternium-15	2		
– Benzoxonium chloride	1		
– Chloroacetamide	1		
– Formaldehyde	1		
– Imidazolidinyl urea	1		
– Parabens	1		
Emulsifiers		**4**	**8%**
– Oleamidopropyl dimethylamine	4		
Miscellaneous		**9**	**18%**
– Toluenesulfonamide/ formaldehyde resin	2		
– Lanolin derivatives	2		
– PARA hair colours	2		
– Bornelone	1		
– Drometrizole	1		
– Myristyl alcohol	1		
	51		

Outside the USA no studies have been performed in which a large number of patients with cosmetic allergy were tested with all (or some) ingredients of the cosmetics to which they were allergic. In the study of the NACDG (304) in which 130 patients were tested with all and 273 with some ingredients of the suspected cosmetics, fragrances and fragrance ingredients were responsible for the greatest number of reactions (Chapter 3.2.3.).
Preservatives were the second most frequent cause of reactions (quaternium-15, imidazolidinyl urea, parabens, 2-bromo-2-nitropropane-1,3-diol, formaldehyde), followed by *p*-phenylenediamine, lanolin and derivatives, glyceryl thioglycolate and propylene glycol (304).

In the present study, fragrances and preservatives also were the most frequent causative ingredients. In the preservative group, Kathon CG caused the greatest number of reactions, whereas in the NACDG study contact allergic reactions to Kathon CG were not encountered. Kathon CG is discussed in Chapter 4.
Quaternium-15, the most common cause of preservative allergy in the NACDG study (65 reactions out of 149) was responsible for only 2 reactions in our investigation. Contact allergic reactions to quaternium-15 appear to be infrequent in The Netherlands (323,324) and in Belgium (310), contrasting sharply with the USA and the United Kingdom (328).
This study confirms our previous observation (120) that the cationic emulsifier oleamidopropyl dimethylamine is an important cause of cosmetic-related contact dermatitis in The Netherlands. This allergen is discussed in Chapter 5.
From this study we conclude that fragrances and preservatives are the major causes of cosmetic allergy in The Netherlands up to 1985.

3.4 THE ALLERGENS IN COSMETICS: A PROSPECTIVE STUDY (348)

SUMMARY

The ingredients responsible for allergy to cosmetics were determined in 119 patients suffering from cosmetic-related contact dermatitis. Most reactions (56%) were caused by skin care products, followed by nail cosmetics (13%), perfumes (8%) and hair cosmetics (6%). Preservatives were most frequently implicated (32%), followed by fragrances (27%) and emulsifiers (14%). The most important cosmetic allergen was Kathon CG, reacting in 33 patients (28%). Other frequent causes of cosmetic-related contact allergic reactions were toluenesulfonamide/formaldehyde resin in nail hardener and/or nail lacquer (15 patients, 13%), and oleamidopropyl dimethylamine (13 patients, 11%).

INTRODUCTION

Although there have been many studies of cosmetic allergy, only two investigations from the USA (304) and from The Netherlands (313, Chapter 3.3) have studied the specific allergens more systematically. The study from The Netherlands was retrospective and relatively small. Therefore, it was decided to initiate a new study of cosmetic allergy. The main aim of the investigation was to determine the causative ingredients in cases of proven cosmetic allergy.

PATIENTS, MATERIALS AND METHODS

The multicenter study into the causative allergens in cosmetic products was initiated March 1, 1986, and ended July 31, 1987.*Patients diagnosed in the 17 month period as suffering from cosmetic allergy were investigated further. The diagnosis was based on one or more of the following criteria:

1. a positive patch test to a cosmetic product (n=92).
2. negative patch tests with cosmetics, but positive use tests with one or more suspected cosmetic products (n=5).
3. negative patch tests with cosmetics, but positive repeated open application tests (n=7).
4. stopping the use of suspected cosmetic products, negative on patch testing, but known to contain one or more allergens in the European standard series or additional test series to which the patient reacted, resulted in a cure or marked improvement of the patient's dermatitis (n=15).

An additional criterion for inclusion in the study in all cases was that dermatitis was or had been present at the site of application of the cosmetic product.

The patch test procedures have been specified in Chapter 3.3. (under "Patients, Materials and Methods").

The following data were recorded for each patient on a preprinted form:

- sex, age and occupation
- duration of complaints
- duration of usage of the incriminated products
- did the patient suspect cosmetic allergy
- had the product been applied to healthy or damaged skin
- did the dermatitis improve or disappear after discontinuation of the suspected cosmetics
- were the complaints caused exclusively by cosmetic allergy, or were other factors involved (if yes, which)
- localisations of the dermatitis
- other data the patient or investigator felt to be important
- patch test results: European standard series, personal products, additional series of allergens, cosmetic ingredients

The patients were tested with the ingredients of the products that had

* Participants in this study were:
Dr. D.P. Bruynzeel (Free University, Amsterdam)
Dr. J.D. Bos (University of Amsterdam)
Prof. Dr. Th. van Joost (University of Rotterdam)
Dr. H.L.M. van der Meeren (formerly University of Nijmegen)
Dr. B.A. Jagtman (formerly University of Maastricht)
Dr. J.W. Weyland, Ph.D. (Food Inspection Service, Enschede)

caused cosmetic dermatitis on average 8-10 weeks after the initial diagnosis of cosmetic allergy.

RESULTS

In the 17-month period, the allergens in cosmetics responsible for contact allergic dermatitis were established in 119 patients. 102 patients (86%) were women, 17 (14%) men. Their ages ranged from 12-78 years, with an average of 36 years. 81 patients (68%) were tested with all ingredients of the suspected cosmetic products, 38 (32%) with 1 or more allergens known to be present in cosmetics used.
47 patients (39%) had suspected that their dermatitis was caused/worsened by the use of cosmetics; the other 72 (61%) had not, and many were quite surprised to be informed of their cosmetic allergy.
In 48 patients (40%) the cosmetics had been applied to previously healthy skin. In 33 (28%), cosmetics had been used on damaged skin. Application to both normal and abnormal skin had occurred in 23 patients (19%), and in the other 15 (13%) the products had not been applied to the skin but to the nails (nail hardeners and/or lacquers).
The localisations of the dermatitis in the 119 patients were as follows: the most frequently affected area was the face, including the eyelids and the lips (63%), followed by neck (26%), hands (26%) and the arms (26%). The dermatitis was limited to the face in 25 patients (21%). More than half of all reactions (Table 12) were caused by skin care products (n=67, 56%). Next were nail cosmetics (n=16, 13%), followed by perfumes (n=10, 8%), hair cosmetics (n=7, 6%), deodorants (n=6, 5%) and lip cosmetics (n=5, 4%).
In 53 patients (45%) the dermatitis was the result of cosmetic allergy only. In 61 (51%) other factors were also involved: non-cosmetic contact allergy (n=17), irritant dermatitis (especially the hands) (n=17), atopic dermatitis (especially the hands, arms and legs) (n=17). Less often implicated were herpes labialis, unclassified dermatitis, seborrhoeic dermatitis and photoallergy.

The results of patch testing were as follows: in the European standard series, most reactions were observed to the fragrance mix (n=31, 26%). Next was nickel sulfate (n=17, 14%), followed by Balsam Peru (n=12, 10%), formaldehyde (n=10, 8%), wool alcohols (n=6, 5%), quaternium-15 (n=5, 4%) and colophony (n=5, 4%). Ingredient patch testing revealed a total of 53 cosmetic allergens (Table 13). The most frequent contact allergen was Kathon CG, reacting in 33 patients (28%).
Second was toluenesulfonamide/formaldehyde resin, causing cosmetic allergy in 15 patients (13%), followed by oleamidopropyl dimethylamine (13 patients, 11%). 15 reactions (13%) were caused by "fragrance, unspecified". 4 patients reacted to eugenol and hydroxycitronellal; 3 reacted

Table 12. Product categories causing cosmetic allergy in 119 patients*

	NUMBER OF PRODUCTS		(%)
Skin care products		**67**	**(56%)**
Nail cosmetics		**16**	**(13%)**
– hardener/lacquer	16		
Perfumes		**10**	**(8%)**
Hair cosmetics		**7**	**(6%)**
– shampoo	2		
– dry shampoo	1		
– cream	2		
– conditioner	2		
Deodorants		**6**	**(5%)**
– roller	2		
– spray	2		
– cream	1		
– stick	1		
Lip cosmetics		**5**	**(4%)**
– lip cream	1		
– stick with UV-filter	4		
Eye cosmetics		**3**	**(3%)**
– mascara	2		
– eye shadow	1		
Shaving preparations		**3**	**(3%)**
– aftershave	2		
– shaving foam	1		
Personal cleanliness products		**2**	**(2%)**
– bath foam	1		
– soap	1		
Other products		**12**	**(10%)**
– veterinary cream #	6		
– sunscreen cream	2		
– herbal cosmetics	2		
– facial makeup	1		
– bleaching cream	1		

* The number of cosmetics exceeds the number of patients, as some reacted to more than 1 product
# Used as moisturiser

to diazolidinyl urea, quaternium-15 and cocamidopropyl betaine. Reactions to the following allergens were observed in 2 patients each: imidazolidinyl urea, propylparaben, cinnamic alcohol, citronellol, geraniol, isoeugenol, cocamide DEA, 4-isopropyl-dibenzoylmethane, 3-(4-methylbenzylidene)-camphor and myristyl alcohol. To the other 34 allergens only 1 positive patch test reaction was observed.

The classes of cosmetic allergens are shown in Table 13. Due to the large number of patients reacting to Kathon CG, preservatives were the most important category implicated with 47 reactions (32%). Fragrances followed with 39 reactions (27%), and emulsifiers (mostly oleamidopropyl dimethylamine) with 21 reactions (14%).

Table 13. Causative (classes of) ingredients (N=147) in 119 patients with cosmetic allergy

			No. pat.
Preservatives			**47 (32%)**
Kathon CG	33	Benzoxonium chloride	1
Diazolidinyl urea	3	Bronopol	1
Quaternium-15	3	Chloroacetamide	1
Imidazolidinyl urea	2	Formaldehyde	1
Propylparaben	2		
Fragrances			**39 (27%)**
UNSPECIFIED	15		
SPECIFIED	24		
Eugenol	4	Coumarin	1
Hydroxycitronellal	4	Hexylcinnamic aldehyde	1
Cinnamic alcohol	2	Linalool	1
Citronellol	2	Linalyl acetate	1
Geraniol	2	Lyral	1
Isoeugenol	2	γ-Methylionone	1
α-Amylcinnamic aldehyde	1	Pelargol	1
Emulsifiers			**21 (14%)**
Oleamidopropyl dimethylamine	13		
Cocamide DEA	2		
Cocamidopropyl betaine	3		
Lauramide DEA	1		
PEG-32 stearate	1		
Stearic acid	1		
Toluenesulfonamide/formaldehyde resin			**15 (10%)**

Table 13. (continued)

			No. pat.
Lanolin (derivatives)			**4 (3%)**
Acetylated lanolin	1		
Eucerit	1		
Lanolin	1		
Lanolin oil	1		
Miscellaneous			**21 (14%)**
4-Isopropyl-dibenzoylmethane	2	Cyclomethicone	1
3-(4-Methylbenzylidene)-camphor	2	Laurylpyridinium chloride	1
Myristyl alcohol	2	Mineral oil	1
Arnica extract	1	Octyl gallate	1
Avocado oil	1	Propolis	1
t-Butyl hydroquinone	1	PVP-hexadecene copolymer	1
Butyl methoxy-dibenzoylmethane	1	Selenium sulfide	1
Calendula extract	1	Sodium PCA	1
Colophony (Rosin)	1	Zinc pyrithione	1

The cosmetic products in which the various allergens were present are specified in Table 14.
Discontinuation of the suspected products resulted in a cure of the dermatitis in 69 patients (58.0%). In 39 (32.8%), a marked improvement was observed, and in 3 patients ceasing the use of the cosmetics led to no improvement. 8 patients (6.7%) did not return for follow-up.

DISCUSSION

In the present study, skin care products (creams, milks, lotions, tonics) were responsible for more than half of all cases of cosmetic allergy. Nail cosmetics were second, followed by perfumes, hair cosmetics and deodorants. The various studies on cosmetic product categories causing contact allergic reactions reported have been reviewed in Chapter 2.
This study confirms (317-319), that Kathon CG is an important cause of cosmetic allergy. This allergen is discussed in Chapter 4.
Our study also confirms the role of the cationic emulsifier oleamidopropyl dimethylamine as cosmetic allergen in The Netherlands (120,313). This allergen is discussed in Chapter 5. As in the comparable study of the NACDG (Chapter 3.2.3), fragrances, both in perfumes and other scented cosmetic products, were important cosmetic allergens. The spectrum of individual fragrances responsible was similar to the USA results, most reactions being caused by the chemicals present in the fragrance mix.

Table 14. The allergens: numbers of positive reactions in 119 patients with cosmetic allergy, and presence in cosmetic products

ALLERGEN	nos. pos.	COSMETICS (for codes see below) A B C D E F G H I J K L M N O P Q R S T U
Acetylated lanolin	1	1
α-Amylcinnamic aldehyde	1	1
Arnica extract	1	1
Avocado oil	1	1
Benzoxonium chloride	1	1
Bronopol	1	1
t-Butyl hydroquinone	1	1
Butyl methoxy-dibenzoylmethane	1	1
Calendula extract	1	1
Chloroacetamide	1	1
Cinnamic alcohol	2	1 1
Citronellol	2	1 1
Cocamide DEA	2	1 1
Cocamidopropyl betaine	3	3
Colophony (Rosin)	1	1
Coumarin	1	1
Cyclomethicone	1	1
Diazolidinyl urea	3	3
Eucerit	1	1
Eugenol	4	1 2 1
Formaldehyde	1	1
Fragrances, specified (see individual fragrances)	24	
Fragrances, unspecified	15 *	10 1 2 8 1 1
Geraniol	2	1 1
Hexylcinnamic aldehyde	1	1
Hydroxycitronellal	4	2 1 1
Imidazolidinyl urea	2	2
Isoeugenol	2	1 1
4-Isopropyl-dibenzoylmethane	2	2
Kathon CG	33 *	29 1 1 3 1 1
Lanolin	1	1
Lanolin oil	1	1
Lauramide DEA	1	1
Laurylpyridinium chloride	1	1
Linalool	1	1
Linalyl acetate	1	1

Table 14. (continued)

ALLERGEN	nos. pos.	COSMETICS (for codes see below) A B C D E F G H I J K L M N O P Q R S T U
Lyral	1	J: 1
3-(4-Methylbenzylidene)-camphor	2	C: 2
γ-Methylionone	1	B: 1
Mineral oil	1	S: 1
Myristyl alcohol	2	B: 2
Octyl gallate	1	R: 1
Oleamidopropyl dimethylamine	13	B: 13
PEG-32 stearate	1	B: 1
Pelargol	1	B: 1
Propolis	1	B: 1
Propylparaben	2	J: 1; L: 1
PVP-hexadecene copolymer	1	B: 1
Quaternium-15	3	B: 3
Selenium sulfide	1	D: 1
Sodium PCA	1	B: 1
Stearic acid	1 *	B: 1; F: 1
Toluenesulfonamide/ formaldehyde resin	15	H: 15
Zinc pyrithione	1	D: 1

CODES FOR COSMETICS

A skin care products	H nail hardener/lacquer	O perfumes
B shampoo	I dry shampoo	P hair cream
C hair conditioner	J deodorant	Q lip cream
D lipstick with UV-filter	K mascara	R eye shadow
E aftershave	L shaving foam	S bath foam
F soap	M veterinary cream #	T sunscreen cream
G herbal cosmetics	N facial makeup	U bleaching cream

* This particular ingredient was present in more than 1 cosmetic product in 1 or more patients
# Used as moisturiser

Nail cosmetics were an important product category implicated in cosmetic-related adverse effects. Of our 16 patients reacting to nail hardener and/ or nail lacquer, 15 were allergic to toluenesulfonamide/formaldehyde resin. One reacted to formaldehyde, present in a nail hardener.
10 patients used both a hardener and 1 or more nail lacquers. It was striking that most of the 10 patients allergic to nail hardener had used nail lacquers for many years without ill- effects, but developed symptoms

of sensitisation within weeks to months after first using the nail hardener (all of the same brand). Possibly the presence of formaldehyde in this product increases the risk of sensitisation to toluenesulfonamide/formaldehyde resin, present in the nail hardener and virtually all nail lacquers (330).
An interesting finding was the occurrence of contact sensitisation to diazolidinyl urea (Germall II) in 3 patients. All were sensitised to this preservative in one particular brand of "hypoallergenic" stay-on cosmetics, which was introduced only in March 1986. Relatively few patients have been exposed to diazolidinyl urea in this brand or other products. It has been suggested (331) that the sensitising potential of this preservative is greater than that of the related antimicrobial imidazolidinyl urea (Germall 115).
p-Phenylenediamine, glyceryl thioglycolate and propylene glycol, in the American study causing more reactions than toluenesulfonamide/formaldehyde resin (Chapter 3.2.3, Table 1), appear to play no role of importance in Dutch consumers. Possibly this may be caused by more widespread use of hair colours (*p*-phenylenediamine) and permanent wave (glyceryl thioglycolate) in the USA.
On the other hand, some reactions to propylene glycol and glyceryl thioglycolate interpreted as allergic may actually have been irritant.

Our study indicates that preservatives, fragrances, and emulsifiers are the main classes of ingredients responsible for cosmetic allergy in The Netherlands.
The most important contact allergen in cosmetic products is Kathon CG, followed by toluenesulfonamide/formaldehyde resin and oleamidopropyl dimethylamine.

3.5 RARE COSMETIC ALLERGENS: A SUMMARY OF PUBLISHED CASES

SUMMARY

14 articles on (at the time of writing) rare or previously unreported cosmetic allergens, published by the author between 1983-1988, are summarised. "New" allergens included the UV-filter bornelone, the emulsifiers oleamidopropyl dimethylamine and lauramide DEA, the quaternary ammonium compounds benzoxonium chloride and laurylpyridinium chloride, and the emollient avocado oil.

INTRODUCTION

Since 1978, USA regulations require that all ingredients of cosmetics and toiletry products, except components of flavours and fragrances, be declared on product labels. Such ingredient labelling greatly facilitates the dermatologists' search for the offending allergen(s) in patients suffering from hypersensitivity reactions to cosmetic products. In addition, patients can purchase cosmetics that do not contain "their" allergens (and preferably also possibly cross-reacting substances) by checking the labels. In most other countries however, ingredient labelling is not compulsory, and therefore seldom done. This also applies to the European Economic Community (EEC). Thus, the lack of information on the composition of the products hampers attempts to identify the causative ingredient(s) in cases of cosmetic allergy. Sometimes the nature of the offending allergen is suggested by positive reactions to cosmetic allergens which are routinely tested in the European standard series (*p*-phenylenediamine dihydrochloride, rosin, parabens, wool alcohols, balsam Peru, formaldehyde, fragrance mix, quaternium-15), or in an additionally tested "cosmetic series". A telephone call to the manufacturer or importing company may in such cases provide sufficient information to establish a final diagnosis.

However, in a number of cases the causative allergens are not apparent from the results of the first patch test session. Further investigation is usually possible and fruitful (either by writing to the manufacturer or by contacting the government agency responsible for the quality control of cosmetics), but usually takes much time and energy. Even when the offending substances can be identified, this is often of little help to the patient, who still cannot choose other cosmetics not containing the responsible allergens, since the composition is not disclosed.

Consequently, patients suffering from cosmetic allergy are rarely patch tested with all ingredients of the responsible products. Therefore, the dermatologist who performs full ingredient patch testing in patients suffering from cosmetic allergy, is often "rewarded" with the finding of "new" causes of cosmetic allergy, or allergens which have (at that time) rarely been reported as allergens (in cosmetics).

In the period 1983-1988, the author has published 14 case-reports on this subject (95,98,108,120,132,223,232,233,234,235,239,241,331,347). This chapter summarises the results of these studies.

PATIENTS, MATERIALS AND METHODS

All patients reported had consulted the dermatologist* for dermatitis. The criteria for the diagnosis of cosmetic allergy, and patch test procedures have been documented in Chapter 3.3 (under "Patients, Materials and Methods").

RESULTS

Six ingredients found to be responsible for cosmetic-related allergic contact dermatitis had not previously been described as allergens (refs. 108,120,232,233,239,347). The other cases either refer to (at the time of writing) rarely documented allergens (refs. 95,98,132,233,234,235,331) and/or were reported because of certain unusual features (refs. 98,223,241). The cosmetics implicated, causative ingredients and other relevant data are summarised in Table 15.

DISCUSSION

Linalool (98)

The fragrances linalool and hydroxycitronellal were found to be the sensitisers in an aftershave. Linalool has 3 forms: the l-form (licareol), the d-form (coriandrol), and the synthetic dl-form, which is accepted as "linalool" by the perfumer today. Linalool occurs naturally in more than 200 oils from herbs, leaves, flowers, and wood. It is widely used in the cosmetic industry (Appendix 2), and also as a flavour ingredient in the food industry. Maximisation tests on 25 volunteers with linalool 8% in pet. (333) and linalool 20% in pet., also on 25 subjects (334), produced no sensitisation reactions. Fregert & Hjorth (335) patch tested 792 patients suffering from eczema with linalool 10% ; 2 patients reacted, but details were not provided. Cosmetic allergy to linalool in a dry-shampoo has been documented recently (313,336).

Drometrizole (Tinuvin P) (95)

The UV-filter drometrizole (Tinuvin P) was found to be the sensitiser in nail lacquer. Cosmetic allergy from nail lacquer is nearly always caused by toluenesulfonamide/formaldehyde resin. Rare causes have included formaldehyde, glyceryl phthalate resin, rosin and guanine. Drometrizole has previously been described as the allergen in face creams (337), but

* Most patients were seen by the author. Some were studied by other investigators: Dr. D.P. Bruynzeel (Amsterdam), Dr. J.D. Bos (Amsterdam), Dr. H.L.M. van der Meeren (Eindhoven), Dr. B.A. Jagtman (Venlo), Dr. H.B. van der Walle (Arnhem), Dr. G. Smeenk (Deventer), Dr. J.H.H. Veeger (Enschede), Dr. P.M. Burger (Hardinxveld-Giessendam), and Prof.Dr. J.P. Nater (Groningen).

not in nail lacquer. Besides its application in cosmetic formulations, drometrizole (2-(2'-hydroxy-5'-methylphenyl)-benzotriazole) is used for stabilising plastics and other organic materials against discoloration and deterioration.

Bornelone (Prosolal S 9) (108)
The UV-filter bornelone (5(3,3-dimethyl-2-norbornylidene)-3- penten-2-one, Prosolal S 9) was found to be the sensitiser in a face cream in 2 patients. It is an UVC and UVB absorber with peak absorption at 298 nm. Bornelone is an alicyclic dienon, and is chemically different from the main classes of UV-absorbers. Contact allergy to it has not previously been reported.

Oleamidopropyl dimethylamine (Tegamine 0-13, Lexamine O-13) (120)
The emulsifier oleamidopropyl dimethylamine was found to be the sensitiser in baby body lotion in 3 patients. Contact allergy to it has not previously been reported. Later it was establised to be a very important cause of cosmetic allergy in The Netherlands (Chapter 3.4). Oleamidopropyl dimethylamine is discussed in Chapter 5.

Benzoxonium chloride (Bradophen) (239,347)
The quaternary ammonium compound benzoxonium chloride (Bradophen, Absonal, dodecylbenzyldihydroxyethylammonium chloride) was found to be the sensitiser in an ointment used as moisturiser in 2 patients. The product, containing 0.5% benzoxonium chloride, is primarily intended for veterinary use, but it is very widely used in the rural population for the treatment of various skin disorders such as dry hands and rhagades in humans. Benzoxonium chloride has been shown to posess high in vitro antibacterial, antiviral and antimycotic activity; it has been used for the inhibition of dental plaque formation, as topical therapy for burns, and for disinfection of surgical instruments. One patient possibly cross-reacted to the quaternary ammonium compounds domiphen bromide and benzalkonium chloride. Our 2 cases are the only instances of (well-)documented contact allergy to benzoxonium chloride.

Kathon CG (Methyl(chloro)isothiazolinone) (132)
The preservative Kathon CG was found to be the sensitiser in all-purpose cosmetic cream in 2 patients. A third patient, who was allergic to the emulsifier Eucerit and the fragrance in this cream, was sensitised by being patch-tested with Kathon CG 150 ppm pet. Kathon CG is discussed in Chapter 4.

Chloroacetamide (223)
The preservative chloroacetamide was found to be the sensitiser in an

"anti-wrinkle serum". It is a well known cause of cosmetic allergy in Europe. It was found to be the allergen in cases of cosmetic allergy from baby body lotion, cleansing lotion, eye cream, massage cream, face cream and hand lotion. In the United States, chloroacetamide is not used in cosmetic products, and cases of cosmetic allergy to it are rare, and due to imported products (338). Our patient had a positive patch test reaction to non-human placental protein, an allergen apparently not previously reported. However, thin-layer chromatography demonstrated the presence of chloroacetamide in this product.

Avocado oil (232)
The emollient avocado oil was found to be the sensitiser in a "herbal" sunscreen cream. Avocado oil is the oil obtained by pressing the dehydrated sliced flesh of the avocado pear Persea americana. It consists principally of the glycerides of fatty acids. Avocado oil was present in 257 of approximately 19,000 cosmetic formulations on file with FDA in 1976 (339). Possibly the number of products containing the oil may increase in response to the growing popularity of "natural" cosmetics. This report provides the only documented case of contact allergy to avocado oil.

Cocamide DEA and Lauramide DEA (233)
The surfactants cocamide DEA and lauramide DEA were found to be the sensitisers in shampoos. The patient became sensitised by using a shampoo containing cocamide DEA. The first time he used another shampoo, dermatitis reappeared. The sensitiser in this shampoo proved to be lauramide DEA. Thus, the reaction to lauramide DEA probably represented a (pseudo)-cross-sensitisation to cocamide DEA.
Cocamide DEA and lauramide DEA are non-ionic surfactants which have good foam-producing and stabilising properties. They are widely used in shampoos, hand gels and hand-washing liquids. Cocamide DEA has been reported as a sensitiser in hand gel (340) and in a hydraulic mining oil (341), but not as a cause of allergy to shampoos. Lauramide DEA is a mixture of ethanolamides of lauric acid. The CTFA cosmetic ingredient dictionary (3rd Edition, 1982) lists more than 100 synonyms. This report provides the only documented case of contact allergy to lauramide DEA.

4-Isopropyl-Dibenzoylmethane and 3-(4-Methylbenzylidene)-Camphor (234)
The sunscreen Eusolex 8021 was found to be the sensitiser in 10 cases of cosmetic allergy. Five patients were sensitised to a lipstick, 4 to a sunscreen cream, and 1 reacted to several cosmetic creams. Of 9 patients tested with the 2 ingredients of Eusolex 8021, 5 proved to be allergic to both (chemically unrelated) constituents: 4-isopropyl- dibenzoylmethane and 3-(4-methylbenzylidene)-camphor; 4 were allergic to 4-isopropyl-dibenzoylmethane only. The dibenzoylmethanes (including 4-isopropyl-

dibenzoylmethane and butyl methoxydibenzoylmethane) are a relatively new class of chemicals which are becoming popular very rapidly because of their broad absorption spectra with maximal absorption in the UVA-range. The dibenzoylmethanes are usually combined with other sunscreens, e.g. 2-ethylhexyl-4-methoxycinnamate and 3-(4-methylbenzylidene)-camphor. Several cases of (photo)contact allergy to 4-isopropyl-dibenzoylmethane have previously been reported (342). Allergy to 3-(4-methylbenzylidene)-camphor had been reported only once (343) despite its widespread use. Therefore it was surprising that at least 5 of our 10 patients were allergic to it. It was hypothesised that 4-isopropyl-dibenzoylmethane is a strong allergen, promoting concomitant sensitisation to the weak allergen 3-(4-methylbenzylidene)-camphor (344). Several data indicate that allergy to Eusolex 8021 may not be rare.

Butyl Methoxydibenzoylmethane (235)
The UV-absorber butyl methoxydibenzoylmethane (Parsol 1789) was found to be the sensitiser in a lipstick. It is a broadspectrum sunscreen with a maximum absorption at 358 nm.
In a previous study (342) 2 patients allergic to the related 4-isopropyl-dibenzoylmethane had a positive patch test reaction to butyl methoxy-dibenzoylmethane, but their clinical relevance was not discussed. Our patient was also allergic to 4-isopropyl-dibenzoylmethane. The patch test reaction to this chemical was far stronger, which may suggest that the patient had primarily become sensitised to 4-isopropyl-dibenzoylmethane, and that the allergy to butyl methoxydibenzoylmethane was due to cross-sensitisation.

Laurylpyridinium chloride (239)
The quaternary ammonium compound laurylpyridinium chloride (Dehyquart C, 1-dodecylpyridinium chloride) was found to be the sensitiser in a hair conditioner. Not the woman using it, but her husband became sensitised (connubial dermatitis). As cationic surface active agents, quaternary ammonium compounds improve the properties of fabrics like wool, cotton and some synthetic fibres. In hair conditioners, they make the hair feel soft and manageable after shampooing. This report provides the only documented case of allergy to laurylpyridinium chloride.

Formaldehyde in Imidazolidinyl urea (241)
Formaldehyde in the preservative imidazolidinyl urea (Germall 115) was found to be the sensitiser in a face cream. Allergy to this chemical is not infrequent, and the case was reported because of its unusual features. The patient did not react to the cosmetic upon patch testing, but a Repeated Open Application Test (ROAT) was strongly positive. The ingredients were obtained from the manufacturer, but negative results were again observed.

The patient was then instructed to perform a ROAT with all constituents, and she had a positive reaction on 2 occasions to imidazolidinyl urea 2% in water. Although this preservative is said to release only small amounts of formaldehyde, and a patch test to it in the standard series had been negative, the possibility of the reaction being caused by a very weak allergy to formaldehyde was considered. A ROAT with formaldehyde 1% aqua was indeed positive, as were patch tests with higher concentrations of 3% and 7.5% in water. It was surprising that in this patient, who had only a very weak allergy to formaldehyde, the small amount of formaldehyde contained in imidazolidinyl urea in the cream could provoke clinically manifest dermatitis, even though it was located on (and limited to) one of the most sensitive areas, the eyelids.

Diazolidinyl urea (Germall II) (331)
The preservative diazolidinyl urea (Germall II) was found to be the sensitiser in day and night cream of a "hypoallergenic" brand, containing 0.3% of the chemical, in 4 patients. Diazolidinyl urea belongs to the same family of antimicrobial preservatives as imidazolidinyl urea (Germall 115). The latter is a known formaldehyde-releaser, and it may cause allergic reactions in patients allergic to formaldehyde (241). It has been assumed that diazolidinyl urea may also release formaldehyde (168,345). Indeed, 2 patients already sensitive to formaldehyde had (exacerbations of) dermatitis due to the diazolidinyl urea-containing creams. The 2 other patients became sensitised to the preservative by the use of the cosmetics containing it; they were not allergic to formaldehyde. Primary sensitisation to diazolidinyl urea not due to formaldehyde allergy has been reported once (168). The sensitising potential of diazolidinyl urea had already been established by means of maximisation tests in guinea pigs (345) and humans (346).
The following tentative conclusions were drawn from our study and literature data:

1. Contact allergy to diazolidinyl urea may or may not be due to formaldehyde sensitivity.
2. Patients allergic to formaldehyde may suffer from contact allergic reactions by the use of cosmetic products containing diazolidinyl urea.
3. Patients sensitised to diazolidinyl urea may cross-react to imidazolidinyl urea and vice-versa.
4. The sensitising potential of diazolidinyl urea may be greater than that of imidazolidinyl urea.

Table 15. Summary of published case-reports

Ref.	Cosmetic	Allergen(s)	No.pat.	Comments
98	Aftershave	Linalool and Hydroxycitronellal	1	The patient developed facial psoriasis as a Koebner fenomenon to the allergic contact dermatitis from after-shave.
95	Nail lacquer	Drometrizole (Tinuvin P) in the colour "Synthetic Pearl I and II"	1	First report of contact allergy to drometrizole in nail lacquer.
108	Face cream	Bornelone (Prosolal S 9)	2	First report of contact allergy.
120	Baby body lotion	Oleamidopropyl dimethylamine (Lexamine O-13)	3	First report of contact allergy. See Chapter 5.
239 & 347	Veterinary ointment used as moisturiser	Benzoxonium chloride (Bradophen)	2	First report of contact allergy (347). Cross-reaction to domiphen bromide and benzalkonium chloride in 1 patient (347).
132	All-purpose moisturising cream	Kathon CG (methyl(chloro)-isothiazolinone)	3	One patient was sensitised by patch testing Kathon CG 150 ppm pet. This isothiazolinone preservative was soon found to be the most important cosmetic sensitiser in Europe. See Chapter 4.
223	Anti-wrinkle serum	Chloroacetamide	1	The preservative was "hidden" in the ingredient non-human placental protein.
232	Sunscreen cream	Avocado oil	1	First report of contact allergy.
233	Shampoo	Cocamide DEA and Lauramide DEA	1	First report of contact allergy to lauramide DEA (probably cross-reaction to primary sensitisation from cocamide DEA).
234	Sunscreen lipstick	IDM * and MBC *	3	The commercial sunscreen Eusolex 8021 contains IDM * and MBC *
	Sunscreen lipstick	IDM *	2	
	Sunscreen cream/ lotion	Eusolex 8021 and/ or IDM * and/or MBC*	4	

Table 15. (continued)

Ref.	Cosmetic	Allergen(s)	No.pat.	Comments
	Various cosmetics	IDM *	1	
235	Lipstick	Butyl methoxy-dibenzoylmethane	1	Possibly cross-reaction from 4-isopropyl-dibenzoylmethane.
239	(Wife's) hair conditioner	Laurylpyridinium chloride	1	No cross-reactions to other quaternary ammonium compounds. First report of contact allergy.
241	Face cream	Formaldehyde in imidazolidinyl urea (Germall 115)	1	The patient had a very weak allergy to formaldehyde, but the cosmetic allergy was caused nevertheless by the formaldehyde donor imidazolidinyl urea.
331	Face cream	Diazolidinyl urea (Germall II)	4	Diazolidinyl urea is a formaldehyde donor. Two patients were presensitised to formaldehyde, the other 2 were sensitised by diazolidinyl urea. One also reacted to imidazolidinyl urea.

* IDM = 4-Isopropyl-dibenzoylmethane
MBC = 3-(4-Methylbenzylidene)-camphor

3.6 CONCLUSIONS

1. Studies of the allergens in cosmetics and toiletry products are seriously hampered by the lack of information on their ingredients. For scientific and practical purposes the dermatological community should urge politicians and medical authorities to enforce (EEC) regulations requiring that all ingredients be declared on cosmetic product labels.

2. Which are the most important sensitisers in cosmetics varies in time. The cosmetic industry tends to avoid ingredients known to have caused many instances of cosmetic- related side effects, if possible. Certain coal tar dyes, (impure) eosin and halogenated salicylanilides have largely been replaced with safer alternatives. On the other hand, the nail lacquer resin toluenesulfonamide/formaldehyde resin (TSFR) and the hair colour *p*-phenylenediamine are still widely used, although they have caused many cases of cosmetic allergy. In the case of TSFR, no alternatives with the same qualities are available. As for *p*-phenylenediamine, no other hair dyes with the same technical and cosmetic properties are known which have proved to be safer than *p*-phenylenediamine itself.

3. There are geographical differences in which are the most important sensitisers. These are due to differences in (i) cosmetic usage patterns, (ii) ingredients used in cosmetic products, and (iii) regulations concerning cosmetic products.

The following examples illustrate this item:

(i) the widespread use of bleaching creams containing ammoniated mercury has caused many instances of allergic cosmetic dermatitis in Taiwan (247). Even if such products were allowed in The Netherlands, mercury would not become an important cosmetic allergen there.

(ii) oleamidopropyl dimethylamine is an important cosmetic allergen in The Netherlands, due to its presence in a very widely used baby body lotion. From no other country has contact allergy to this emulsifier been reported. Pigmented cosmetic dermatitis due to coal tar dyes (Chapter 3.2.2.) has been reported only from Japan. Allergy to chloroacetamide has been well-documented in Europe (223), but it is not used in cosmetics in the USA, and consequently cosmetic allergy to it is very rare (169).

(iii) ammoniated mercury in bleaching creams has caused many instances of cosmetic dermatitis in Taiwan (247), but in the EEC its use in cosmetic products has been banned.

4. Preservatives and fragrances probably are the most important categories of cosmetics sensitisers universally.
5. For a cosmetic screening series (which should be adapted according to local circumstances) the following allergens are suggested:

2-Bromo-2-nitropropane-1,3-diol	0.25% pet.
Chloroacetamide	0.2% pet.
Diazolidinyl urea	2% aqua or pet.
Glyceryl thioglycolate	2.5% pet.
Imidazolidinyl urea	2% pet.
4-Isopropyl-dibenzoylmethane	2% pet.
Kathon CG	100 ppm aqua
Oleamidopropyl dimethylamine	0.4% aqua
Phenyl salicylate	1% pet.
Propolis	10% pet.
Propylene glycol	5% aqua
Toluenesulfonamide/formaldehyde resin	10% pet.

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This chapter is based on the following publications:

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Chapter 4 Kathon CG

The preservative system methylchloroisothiazolinone + methylisothiazolinone is sold under various brand names. The commercial product most widely used is Kathon CG (Rohm and Haas, Philadelphia, USA).
In nearly all studies on the preservative, this trade name is used for the isothiazolinone mixture. Therefore (and also for practical purposes), we decided to use the name Kathon CG throughout this chapter, instead of "the mixture of methylchloroisothiazolinone and methylisothiazolinone".

SUMMARY

Kathon CG, containing as active ingredients 2-methyl-4-isothiazolin-3-one and its 5-chloro analogue, is a preservative widely used in cosmetics and toiletries.
Several studies have indicated that Kathon CG is a frequent cause of cosmetic allergy in The Netherlands, if not the most important one. The results of these studies are presented, and a review of the literature on the isothiazolinone mixture is provided.

4.1 INTRODUCTION

Biocidal chemicals have long been used to preserve a variety of products that come into frequent contact with the skin, such as cosmetics and toiletries. Preservatives prevent the growth of both pathogenic and non-pathogenic micro-organisms that may enter the formulation during their manufacture or post-sale use. In addition to the potential adverse effects of the pathogens on humans, microbial contamination may cause discoloration, unpleasant odours, and physical and chemical degradation of products.
Preservatives are an important cause of cosmetic allergy (1). While preparing the protocol for a study on allergy to fragrances and preservatives in cosmetic products (2), Dr. D.H. Liem (formerly Food Inspection Service, Enschede, The Netherlands) suggested the inclusion of Kathon CG (then virtually unknown to dermatologists) in the series of allergens to be tested, as the use of this preservative was rapidly increasing in The Netherlands, due to its growing popularity in the cosmetic industry.
This was the first of a series of investigations that showed that Kathon CG is a frequent cause of cosmetic allergy in The Netherlands, if not the most important one.

4.2 WHAT IS "KATHON" ?

"Kathon" is the proprietary name for a family of microbiocides and

preservatives containing as active ingredients a mixture of 5-chloro-2-methyl-4-isothiazolin-3- one and 2-methyl-4-isothiazolin-3-one in an approximate ratio of 3:1. The CTFA adopted names are methylchloroisothiazolinone and methylisothiazolinone. These CTFA names will be used throughout this chapter. MgCl2 (±9%) and Mg(NO3)2 (±16%), and/or cupric salts are present as stabilisers. Several formulations are sold (Table 2) as Kathon WT, Kathon 886 MW, Kathon CG, Kathon CG/ICP (USA only), Kathon DP (Europe only), and Kathon LX (Rohm and Haas, Philadelphia, USA). Other companies also market isothiazolinones under their own brand names (Table 1).

Table 1. Some brand names for the mixture of methyl (chloro) isothiazolinone (3)

Acticide	Mitco CC 32 L
Algucid CH 50	Mx 323
Amerstat 250	Parmetol A 23
Euxyl K 100	Parmetol DF 12
Fennosan IT 21	Parmetol DF 18
GR 856 Izolin	Parmetol DF 35
Grotan TK 2	Parmetol K 40
Kathon WT/886 MW/CG/DP/LX	Parmetol K 50
Mergal K 7	Piror P 109
Metatin GT	P 3 Multan D
Mitco CC 31 L	

These biocides are effective preservatives for toiletries, cosmetics, and household cleaning products. They are also used as a biocide for swimming-pool water, and in a variety of industrial applications (4) such as cooling-tower water, metal working fluids (5), latex emulsions, and for controlling slime in paper mills (Table 2).

One of the Kathon formulations, Kathon CG (CG = Cosmetic Grade) is now widely used in many cosmetics and toiletries. The structural formulae of the active ingredients are shown in Table 3, together with detailed product information. Kathon CG contains 1.5% active ingredients: methylchloroisothiazolinone 1.125% and methylisothiazolinone 0.375%.

This preservative is effective at very low concentrations in controlling growth of a wide range of bacteria, yeasts and fungi. The manufacturer recommends levels of between 0.02% to 0.1% by weight (3-15 ppm as active ingredients) in products such as shampoos and hair conditioners, hair and body gels, bubble baths, skin creams and lotions (6).
At present Kathon CG is not permitted in the EEC in any pharmaceutical or dermatological application, nor as a food additive, nor for internal

use by humans. However, Kathon CG in a maximum concentration of 30 ppm active ingredients (a.i.) has in 1986 been approved for use as a cosmetic and toiletry preservative in the EEC (Council Directive 86/199/EEC). In the USA, Kathon CG is on file at the FDA.

Table 2. Applications of the Kathons

Kathon WT (14% and 1.5% active ingredients)
bactericide and slimicide in:
- closed water cooling systems
- oil field
- air washers
- papermill
- wood treatment
- cooling towers

Kathon 886 MW (14% and 1.5% active ingredients)
bactericide for:
- metalworking fluids
- hydrolic fluids

Kathon CG (1.5% active ingredients)
cosmetic and toiletry preservative

Kathon CG/ICP (1.5% active ingredients, USA only)
industrial, household and consumer products
(surfactants, detergents, fabric softeners)

Kathon DP (1% active ingredients, Europe only)
same applications as Kathon CG/ICP

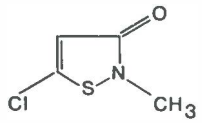
Kathon LX (14% and 1.5% active ingredients)
- protection of polymers
- in container preservative for paints
- adhesives
- commercial photoprocessing

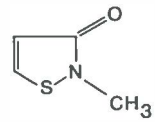
4.3 TOXICOLOGICAL STUDIES

IRRITATION STUDIES

Kathon CG as supplied is a strong irritant (Draize eye irritation index: corrosive; skin primary irritation index: severe irritant). In a Lanman-Maibach test conducted in human subjects to determine irritation threshold, the highest non-irritating concentration was 100 ppm of Kathon CG in

Table 3. Kathon CG: structural formulas and product information





Structural formulas of the active ingredients of Kathon CG:
5-chloro-2-methyl-4-isothiazolin-3-one
2-methyl-4-isothiazolin-3-one

CTFA adopted names:

methylchloroisothiazolinone	(CAS number: 26172-55-4)
methylisothiazolinone	(CAS number: 2682-20-4)

Composition of Kathon CG as supplied:

methylchloroisothiazolinone	1.125%
methylisothiazolinone	0.375%
magnesium salts	23.0 %
water	75.5 %

Appearance	:	Clear liquid
Colour	:	Light amber
Specific gravity at 20£C	:	1.19
pH (as supplied)	:	3.5
Activity spectrum	:	Bacteria, yeast, fungi
Use concentration	:	0.02% – 0.1% (as supplied); 3-15 ppm active ingredients
Suggested applications	:	shampoos and hair conditioners, hair and body gels, bubble baths, skin creams and lotions, cosmetic surfactants
Solubility	:	miscible with water, lower alcohols, glycols
Optimum pH	:	1 to approximately 9, higher pH in conjunction with some ingredients may inactivate
Stability	:	At least 1 year at RT; at least 6 months at 50°C; good freeze-thaw stability
Compatibility/Inactivation	:	May be inactivated by amines, sulfites and mercaptans. Not inactivated by anionics or cationics. Compatible with surfactants and emulsifiers of all ionic types
Regulatory status	:	Approved in the EEC (Council Directive 86/199/EEC), max. conc. 30 ppm a.i. On file at the FDA

water. Slight to moderate irritation was observed at 200 ppm active ingredients in aqueous solution (6). All concentrations expressed in this chapter in ppm refer to active ingredients (methyl(chloro)isothiazolinone). Using 21-day cumulative irritancy assays Maibach (7) confirmed that concentrations of Kathon CG up to 100 ppm, either in water or in petrolatum (containing 2.5% polysorbate 85 to assist solubility) do not induce significant skin irritation. Of 12 subjects tested with 100, 200 and 300 ppm aqua, 4 had cumulative scores at 200 ppm and 300 ppm indicative of irritation; however, at least one of them was sensitised by the irritancy assay. It was concluded that "there is evidence that 200 ppm may produce irritation".

Closed epicutaneous tests performed for the manufacturer by Schulz in Hamburg (6) with dilutions of Kathon CG on human subjects gave the following results: in none of 100 subjects tested with 0.1% , 0.33% and 1% Kathon CG (15, 50 and 150 ppm resp.) was irritation observed. However, 6 of 10 subjects tested with 3.3% (500 ppm) and 7 of 10 subjects tested with 10% (1500 ppm) had signs of irritation. It was concluded that the threshold for cutaneous irritation is between 1% and 3.3% of Kathon CG (150 and 500 ppm).

In Sweden, a test concentration of 300 ppm aqua was used for single diagnostic patch tests (3). 976 patients were patch tested, and 43 reacted (4.4%). These reactions were all considered to be due to contact allergy, and the test concentration was thought to be non-irritant, based on clinical appearence of the reactions, histological examination and open tests. However, in another Swedish study (8) 3/534 patients tested at 150 ppm, 3/526 tested at 200 ppm and 15/645 tested at 300 ppm had irritant patch test reactions. Taken together all these observations indicate that the highest non-irritant concentration is around 200 ppm for most patients.

EXPERIMENTAL SENSITISATION STUDIES

Studies both in guinea pigs (6,9-11) and humans (6,7) have shown that Kathon CG can induce contact hypersensitivity.

ANIMAL STUDIES

Magnusson-Kligman maximisation tests with Kathon CG were performed for the manufacturer by Schulz (6). A 1% solution was injected intracutaneously, together with full Freunds adjuvant. Epicutaneous application was performed 1 week later with a 30% solution. The animals were challenged after 2 weeks with solutions of Kathon CG 0.3%, 1%, 3%, 10% and 30%. All 18 animals showed reactions, of varying degrees, to challenge concentrations of 3% or more. At the challenge concentration of 1%, 9 out of 18 animals reacted, but none showed a positive reaction to a 0.3% solution (6).

The manufacturer of Kathon CG has also evaluated its potential to produce

contact sensitisation in guinea pigs using a modified Buehler's occluded epicutaneous patch technique (9). For the induction phase, 0.4 ml doses of the diluted product were used, induction concentrations ranging from 25 to 2000 ppm. Three, 6-hour applications were made per week over three consecutive weeks. Twelve to 15 days later, the animals were challenged with 0.4 ml of the diluted product, concentrations ranging from 20-2000 ppm. The incidence of delayed contact dermatitis was dependent on the induction concentration. At a challenge concentration of 2000 ppm, 20/20, 10/10, 9/15, 2/15 and 1/20 guinea pigs responded when induced with 2000, 500, 100, 50, and 25 ppm, respectively. The incidence of delayed contact dermatitis was also dependent on the challenge concentration.
At an induction concentration of 1000 ppm, 4/5, 3/5, 3/15, and 0/20 guinea pigs responded when challenged with 1000, 500, 200 and 50 ppm, respectively. The investigators suggested that the data indicated a "no response concentration zone". This zone corresponded to induction (I) and challenge (C) active ingredient concentrations of: 2000 (I) and 20 (C) ppm; 1000 (I) and 50 (C) ppm; 500 (I) and 100 (C) ppm; 50 (I) and 100 (C) ppm; and 25 (I) and 200 (C) ppm. It was concluded that: (i) the potential of the biocide to cause contact sensitisation was dependent on both the induction and challenge concentrations; (ii) the number of induction doses may be an important factor in demonstrating the sensitising potential and (iii) there is a "no response concentration" at which the product can be used without concern for clinically significant allergic contact dermatitis (9).
No incidence of allergic contact dermatitis was observed when Kathon CG was applied to the skin of guinea pigs at induction and challenge concentrations of 1500 ppm. The induction phase consisted of one application per week for 3 weeks (cited in ref.9). In a separate study, allergic contact dermatitis was induced in guinea pigs treated with 16,000 ppm methylisothiazolinone; however, no response was noted when methylisothiazolinone was challenged at 1600 ppm (cited in ref.9).
No skin sensitisation was observed in a Magnusson-Kligman test when guinea pigs were exposed to Kathon CG at 56 ppm (12).
Bruze et al (10) studied the sensitising potential of both active ingredients of Kathon CG, and investigated the cross- reaction patterns using a modification of the Magnusson- Kligman guinea pig maximisation test. For intradermal sensitisation 0,1 ml of methylisothiazolinone 0.076% w/v and 0.1 ml of methylchloroisothiazolinone 0.1% w/v in propylene glycol were used, both alone and in combination with Freunds complete adjuvans. For topical sensitisation 200 μL of the suspected sensitisers in ethanol 99.5% were used at concentrations of 0.05% w/v (methylchloroisothiazolinone) and 0.038% (methylisothiazolinone) after pretreatment with 200 μL sodium lauryl sulfate 10% w/v in dimethylacetamide/ acetone/ethanol 99.5% 4/3/3/ v/v/v. Two weeks after the second stage of sensitisation

a 24-hour occluded patch test (challenge) was performed with 30 μL of the test solution (0.02% methylchloroisothiazolinone in ethanol 99.5% w/v ; 0.015% methylisothiazolinone in ethanol 99.5% w/v).
One week after the challenge, rechallenge was performed. 0.1 ml of the isothiazolinones (same test substances as with intradermal sensitisation) were injected intradermally 2 days after the first challenge application. Five days later the animals were rechallenged with the sensitiser and 4 chemically-related substances (all in ethanol 99.5% w/v): methylchloroisothiazolinone 0.20%, methylisothiazolinone 0.015%, 4,5-dichloro-2-methyl-4-isothiazolin-3-one 0.025%, 2-n-octyl-4-isothiazolin-3-one 0.029%, and 1,2-benzisothiazolin-3-one 0.020%.
Of 24 animals, 19 were sensitised by the procedure to methylchloroisothiazolinone, compared to 1 out of 12 in a control group. 4 resp. 11 animals were sensitised to methylisothiazolinone in 2 series of 24 animals, with no controls reacting. Possible cross-reactivity was indicated to 4,5-dichloro-2-methyl-4-isothiazolin-3-one with methylchloroisothiazolinone as the sensitiser, and to methylchloroisothiazolinone with methylisothiazolinone as the sensitiser.
It was concluded that methylchloroisothiazolinone is a strong sensitiser, and methylisothiazolinone a weak sensitiser. In another study from the same authors (11) 4,5-dichloro-2-methyl-4-isothiazolin-3-one, which is present as a contaminant in Kathon CG at a concentration of approximately 0.025% (11), was shown to be a strong sensitiser; all animals reacting to it also reacted to methylchloroisothiazolinone when rechallenged.

HUMAN STUDIES

In a repeated insult patch test performed by the manufacturer (occluded 3 times/week for 5 weeks, 2 weeks rest, 24 hour challenge) conducted with an aqueous solution containing 25 ppm of Kathon CG, 1 of 18 subjects exhibited a reaction indicative of sensitisation. When concentrations of 56 ppm were tested in vehicles such as nonionic creams or anionic lotions, sensitisation was observed in some individuals (2/10 and 4/50 respectively) (6).
Maibach (7) used modified Draize skin sensitisation studies to determine the sensitising potential of Kathon CG. In each study, 0.2 ml of the appropriate test material (50 ppm in water, 100 ppm in water, 100 ppm in petrolatum with 2.5% polysorbate 85 to increase solubility) was applied to the upper arm or back of the subject. The patch remained in place for 48-72 hours. This procedure was repeated 3 times a week for 3 consecutive weeks, utilising the same site for patch application. Of the 96 participants who were exposed to 50 ppm test material, none showed evidence of sensitisation during the induction or challenge phases. When 52 of these subjects were rechallenged with 100 ppm, 1 subject had an

equivocal response. However, 2 of 104 participants tested with 100 ppm a.i., manifested a positive skin response when induced and subsequently challenged at this dosage. None of 80 subjects tested with 100 ppm pet. had a positive elicitation (7).
Single diagnostic patch tests with concentrations of 250 ppm or 300 ppm may cause sensitisation to Kathon CG (3).
Of 976 patients tested with 300 ppm 8 (0.8%) became allergic from the patch test. Of 170 patients patch tested with 250 ppm 2 (1.2%) were sensitised by the test.
A series of prophetic repeat insult patch tests involving Kathon CG were performed on 1450 subjects (13). Kathon CG was tested in aqueous solution, in vehicles consisting of aqueous dilutions of prototype rinse-off products, and in a prototype body lotion; the concentrations ranged from 5-20 ppm. No signs of induction and elicitation of allergic contact dermatitis resulted from testing at levels below 12.5 ppm. 1 subject tested with 12.5 ppm of Kathon CG in a 0.1% aqueous shampoo vehicle, and 2 (of 45) tested with 20 ppm in water were sensitised (13).

4.4 EXPOSURE OF THE POPULATION TO KATHON CG

There is virtually no information on the extent to which the population in various countries is exposed to Kathon CG. This preservative is used not only for preserving cosmetics and toiletries, but contact with it may occur from many sources, both occupational and non-occupational (Table 2). In recent years the use of the preservative in cosmetics and toiletries has increased considerably. The manufacturers have estimated that in 1980 Kathon CG was used in 55,000 tons of cosmetic products in Europe, and 20,000 tons in the USA (14). Kathon CG first appeared in the USA in 1980 with 38 uses in approximately 18,850 cosmetic products on file at the Food & Drug Administration (41); 7 years later, this preservative system had reached a level of 512 uses, and already ranked 8 in the list of most frequently employed preservatives.
In Sweden (15), 123 commercial products, brought in by patients allergic to Kathon CG, were investigated for the presence of the preservative using High Performance Liquid Chromatography (HPLC). Of 56 "leave-on" products, 16 (29%) contained the preservative, and of 67 "rinse-off" products, 22 (33%) contained it. The concentrations calculated ranged from 1-15 ppm (15).
The results of a Dutch study investigating the presence of Kathon CG in cosmetics and toiletries by means of HPLC are summarized in Table 4. The aims of that study (16) were (i) to provide the dermatologist with a practical list of cosmetics which could be consulted when advising patients allergic to Kathon CG on the use of cosmetics, and (ii) to determine the

extent of the use of Kathon CG in water-containing cosmetics. Therefore, samples of cosmetics and toiletry products were collected from various sources, including patients seen for routine testing, the authors and their families, their secretaries, and 2 helpful drugstores. In order not to bias the results, the cosmetics brought in by patients allergic to Kathon CG were NOT included in the study.

Of 253 products investigated, 59 (23%) were found to contain the preservative system. In the rinse-off category (shampoo, bath/shower foam, toothpaste), 15 of 42 products (36%) contained Kathon CG. The other products had a positive score in 21%. The categories that had the highest percentages of positive results were bath/shower foam (64%), all-purpose cream/lotion (43%), body lotion/milk (30%), shampoo and face scrub/peeling/mask (27%) and facial cream (24%).

Table 4. Number of cosmetics and toiletries containing Kathon CG in The Netherlands (16)

Product category	Number of products investigated	containing Kathon CG	(%)
Shampoo	22	6	(27%)
Setting gel & conditioner	14	2	(14%)
Other hair products	2	–	–
Eye makeup remover	3	–	–
Toothpaste	6	–	–
Lip cream	2	–	–
Face: cream	46	11	(24%)
Face: lotion/tonic/milk	14	3	(21%)
Face: cleansing	13	2	(15%)
Face: makeup	14	–	–
Face: scrub/mask/peeling	11	3	(27%)
Aftershave cream/balm	4	–	–
Depilatory cream	3	–	–
Sunscreens	14	2	(14%)
Self tanning creams	14	2	(14%)
Bath/shower foam	14	9	(64%)
Bath cream	2	–	–
Body lotion/milk	23	7	(30%)
Hand cream	9	2	(22%)
All-purpose cream/lotion	23	10	(43%)
Total	253	59	(23%)

4.5 CONCENTRATION AND VEHICLE FOR PATCH TESTING

Kathon CG is insoluble in petrolatum, and consequently an emulsifier such as soya lecithin (2,17) or polysorbate 85 (7) has to be used when petrolatum is chosen as the vehicle for testing. As this may have some practical and theoretical draw-backs most authors prefer water as the vehicle for patch testing Kathon CG. The most frequently used test concentration is now 100 ppm a.i. (approximately 0.67% Kathon CG as supplied).
A lower test concentration (18, 19, 20) is inadequate as many reactions will then be lost (3,21-23). The results of serial dilution tests are shown in Table 5. Of 17 patients reacting to Kathon CG 100 ppm aqua, 8 also reacted to 30 ppm, and only 2 to 10 ppm (3). In a Finnish study (21), of 18 patients reacting to Kathon CG 100 ppm, 10 still reacted to 50 ppm, but only 4 of these also reacted to 25 ppm aqua, and to 10 ppm only 1 reaction was observed. In an American study (22) of 9 patients allergic to Kathon CG as indicated by a positive patch test to 100 ppm aqua, 6 reacted to 50 ppm, only 1 to 25 ppm and none to 10 ppm aqua. In Germany (23), 6 patients allergic to Kathon CG were tested with concentrations of 50, 30 and 10 ppm. Only 2 reacted at 50 ppm, and 1 had a ?+ reaction at 30 ppm.

Table 5. Results of serial dilution testing with Kathon CG

	NUMBER OF REACTORS			
TEST CONCENTRATION (active ingredients)	(3)	(21)	(22)	(23)
250-300 ppm	34	–	–	–
100 ppm	17	18	9	6
50 ppm	–	10	6	2
30 ppm	8	–	–	1
25 ppm	–	4	1	–
10 ppm	2	1	0	0

– indicates: this concentration was not tested

Thus, test concentrations lower than 100 ppm will leave many cases of sensitisation to Kathon CG undetected. Also, a lower test concentration is unnecessary, as no cases of patch test sensitisation from testing Kathon CG 100 ppm aqua have neither been documented nor suspected.
Shuster and Spiro (24) retested 45 patients, who did not react to Kathon CG at the first test session, with the preservative at 100 ppm aqua after 4 weeks, in order to assess the risk of patch test-induced sensitisation; all remained negative (24).
Possibly however, the test concentration should be increased. The con-

centration of 100 ppm is used by most investigators as few irritant responses were produced in tests using 21-day cumulative irritancy assays (7), and experiments by the manufacturer had previously suggested higher concentrations to be irritant (6). Farm and Wahlberg (8) found 3 irritant reactions among 534 patients tested with Kathon CG at 150 ppm, another 3 among 526 patients tested with the preservative at 200 ppm, and even 15 irritant patch test reactions in a group of 645 tested with 300 ppm. Björkner et al (3) also used concentrations of 100 ppm, 250 ppm and 300 ppm (water) for patch testing. However, they concluded from their results that testing with Kathon CG 300 ppm aqua does not produce irritant responses.

Moreover, of 34 patients reacting to Kathon CG 300 ppm aqua, judged to be allergic to the preservative, only 17 also had a positive patch test reaction to the lower test concentration of 100 ppm (Table 5). Consequently, the authors believed that up to 50% of patients allergic to Kathon CG may be missed, when the currently employed test concentration of 100 ppm is used (3). Nevertheless, these authors also use lower concentrations for patch testing, because of an unacceptably high risk (±1%) of patch test sensitisation, when patients are exposed to patch tests with 250 or 300 ppm Kathon CG in water. The finding of Hannuksela (21) that some patients who reacted to open tests with cosmetics containing only 7 ppm Kathon CG had negative patch tests to 100 ppm aqua also indicates that some if not many cases of sensitisation to Kathon CG are missed with the currently employed test concentration.

Further studies using higher concentrations of Kathon CG for patch testing should be performed. A careful approach to the problem is indicated, as patch test sensitisation to Kathon CG 150 ppm (in pet.) has been documented (17), although only once.

4.6 CLINICAL STUDIES

STUDIES PERFORMED IN THE NETHERLANDS

179 patients with suspected cosmetic-related contact dermatitis were tested with a series of 16 fragrance materials and 9 preservatives, including Kathon CG 1% (150 ppm) in petrolatum (2, Chapter 2.5). Six patients (3.4%) had a positive patch test reaction to Kathon CG. The relevance of 4 reactions was not established, but the 2 other patients have been described in detail (17). One woman had intermittent swelling of the eyelids. Patch tests with the European standard series (Appendix 3), the series of fragrances and preservatives, and her personal cosmetics, showed her to react to benzocaine, the fragrance mix, and Kathon CG. She did not react to a moisturising cream, which she suspected to be the cause. However, a

provocation test was positive. The cream proved to contain Kathon CG at a concentration of 12 ppm. The second patient had an itchy dermatitis on the face and around the eyes. She was patch tested with the European standard series, her personal cosmetics and the series of fragrances and preservatives. A positive reaction was noted to Kathon CG 1% pet, but she did not react to the cosmetic she suspected, the same moisturising cream as used by the first patient, which we now knew to contain Kathon CG. The patient switched to another product, but this worsened her eruption; the manufacturer of this cosmetic informed us that it contained 23 ppm Kathon CG!
In a subsequent study (25, Chapter 2.6), 501 patients with suspected allergic contact dermatitis were routinely tested with a tray of cosmetic preservatives, including Kathon CG 100 ppm aqua. Seven patients (1.4%) reacted. Another study investigated the allergens in patients with proven cosmetic-related allergic contact dermatitis (26 , Chapter 3.4). Kathon CG was the most important allergenic ingredient, reacting in 33 patients (28%).

In 1986 the members of the Dutch Contact Dermatitis Group added Kathon CG 100 ppm aqua to the European standard series, in order to assess its prevalence rate of sensitisation. The results are summarised in Table 6. 3114 patients routinely tested for suspected allergic contact dermatitis were investigated. 155 (5.0%) reacted to Kathon CG, and in 109 (3.5%) the investigators judged the reactions to be relevant for the patients' dermatitis. Two very widely used cosmetic products in the Netherlands, a moisturising cream and a baby body lotion, containing Kathon CG as a preservative, accounted for approx. half of all cases of sensitisation observed. The manufacturers of both products have subsequently decided to omit Kathon CG from all their products.

STUDIES PERFORMED IN OTHER COUNTRIES

Foussereau et al (27) were the first to document cases of cosmetic allergy due to Kathon CG. In their study 2 patients allergic to a cleansing milk and a sunscreen cream respectively, reacted to the ingredient Kathon CG 1% (150 ppm) and 0.1%-0.2% pet. Cross-reactions to other isothiazolinones were observed. Both patients reacted to 1,2-benzisothiazolin-3-one (0.1% – 1% pet), and 1 patient had a positive patch test reaction to *n*-octyl-4-isothiazolin-3-one (0.1% pet) also.
After these case reports and those from The Netherlands (17), many studies performing routine testing with Kathon CG have been documented (3,8,18-21,23,24,28-33). The relevant data are summarised in Table 7.
Prevalence rates of sensitisation to Kathon CG 100 ppm aqua, in patients seen for routine patch testing because of suspected contact dermatitis, were

Table 6. Routine testing with Kathon CG 100 ppm aqua by the members of the Dutch contact dermatitis group (unpublished)

Clinic	Period	No. pat. tested	No. pat pos. (%)	No. reactions relevant (%)
Amsterdam (AMC)	1-9-1986 1-9-1987	366	15 (4.1%)	13 (3.6%)
Amsterdam (VU)	1-10-1986 1-10-1987	461	38 (8.2%)	29 (6.3%)
Deventer	1-6-1986 7-9-1987	214	18 (8.4%)	6 (2.8%)
Groningen	5-1-1987 23-10-87	325	16 (4.9%)	12 (3.7%)
's-Hertogenbosch	9-6-1986 20-08-87	413	16 (3.9%)	13 (3.1%)
Leiden	1-4-1986 1-9-1987	380	12 (3.2%)	7 (1.8%)
Rotterdam	1-9-1986 1-9-1987	310	11 (3.5%)	5 (1.6%)
Utrecht	1-6-1986 1-7-1987	645	29 (4.5%)	24 (3.7%)
		3114	155 (5.0%)	109 (3.5%) *

* 70% of all reactions to Kathon CG were of present relevance

0.9% in Denmark (28); 0.8% (29) and 0.9% (24) in England; 2.9% in Finland (21), 5.7% (30), 3.4% (23) and 3.3% (19) in Germany; 0.5% in an (unpublished) ICDRG study (31); 1.3% in Italy (33); and 1.9% – 5.9% in Sweden (3), depending on the test concentration.

In Germany (20), 5 of 49 women (10%) suspected of cosmetic allergy reacted to Kathon CG 50 ppm aqua. In Italy, 98 patients with facial dermatitis were patch tested with Kathon CG 100 ppm aqua: 6 (6%) had a positive patch test reaction (32). The prevalence rate of sensitisation to Kathon CG in patients suspected of allergy to preservatives was only 1.2% in Finland in 1984 (21), but soon afterwards a sharp increase in the percentage of positive reactions was noted: 4.9% in the first 3 months of 1986 in patients seen for routine testing. In Hungary (18) 300 patients suspected of contact dermatitis were tested with Kathon CG in an obviously far too low concentration of 15 ppm; no positive reactions were observed (18).

Patients with suspected work-related skin diseases were tested in Sweden with Kathon 100 ppm, 150 ppm, 200 ppm and 300 ppm (8). Prevalence rates ranged from 0.6-0.9% .

Probably, the differences in rates merely reflect the degree of exposure of the population to Kathon CG or methyl(chloro)isothiazolinone from other sources.

Table 7. Clinical studies of contact allergy to Kathon CG

COUNTRY	PERIOD OF INVESTIGATION	TEST CONC. & VEHICLE	NO. PAT.	POSITIVE REACTIONS: No.	%	COMMENTS / RELEVANCE	REF
Denmark	1983-1984	100 ppm a.i. aq.	1511	13	0.9%	Relevance of the pos. reactions unknown	28
England	1982 – ??	100 ppm a.i. aq.	1185	9	0.8%	The reactions were relevant in 4 patients	29
England	march 1985-febr. 1987	100 ppm a.i. aq.	1309	12	0.9%	Repeated patch testing in 45 negative patients after 4 weeks again negative	24
Finland	1984	100 ppm a.i. aq.	260	3	1.2%	Patients were suspected of preservative allergy	21
Finland	jan. 1985-march 1986	100 ppm a.i. aq.	1034	30	2.9%	Most reactions were judged to be relevant. Sharp increase in % pos. reactions in 1985-1986	21
Germany		150 ppm veh. ?	1894	108	5.7%	No details provided	30
Germany	febr. 1986-nov. 1986	100 ppm a.i. aq.	671	23	3.4%	The reactions were relevant in 12 patients (1.8%)	23
Germany	1985	50 ppm a.i. aq.	515	17	3.3%	Only women included in the series	19
Germany		50 ppm a.i. aq.	49	5	10%	The patients were suspected of cosmetic allergy	20
Hungary	1983-1985	15 ppm a.i. aq.	300	–	–	Test conc. was obviously too low	18
ICDRG		100 ppm a.i. aq.	7866	40	0.5%		31
Italy		100 ppm a.i. aq.	98	6	6%	The patients had facial contact dermatitis	32
Italy	sept. 1983-dec. 1986	100 ppm a.i. aq.	3744	50	1.3%	The prevalence rose from 0.5% in 1983 to 2.3% in 1986. In 42/50 patients the reactions were relevant	33

Table 7. (continued)

COUNTRY	PERIOD OF INVESTIGATION	TEST CONC. & VEHICLE	NO. PAT.	POSITIVE REACTIONS: No.	%	COMMENTS / RELEVANCE	REF
Sweden	febr. 1982-dec. 1984	300 ppm a.i. aq.	976	43	4.4%	8 patients (0.8%) were sensitised by patch testing	3
	1985	250 ppm a.i. aq.	170	10	5.9%	2 patients (1.2%) were sensitised by patch testing	
	1985	100 ppm a.i. aq.	210	4	1.9%		
	febr. 1982-may 1984	7 ppm a.i. aq.	2006	–	–	The test conc. was by mistake too low	
Sweden	1985	100 ppm a.i. aq.	124	–	–		8
	1984-1985	150 ppm a.i. aq.	534	4	0.7%	Relevance of the reactions uncertain	

4.7 PROFILE OF THE PATIENTS SENSITISED TO KATHON CG

Details of the patients found to react to Kathon CG upon routine testing have been provided in a few studies (21,23, 28,33,34); the relevant data are summarised in Table 8. Women far outnumber men: of 202 patients only 27 (13%) were men. The average age of the patients approximates 40 years in all studies. The face and the hands are the most frequently affected body sites. In 3 studies, comprising 117 patients allergic to Kathon CG, the localisations have been specified (23,28,34). In 59 patients (50%) the hands were affected, in 49 (42%) the face, in 21 (18%) the arms, and in 34 (29%) other localisations. Patients may both become sensitised by products applied to already damaged skin and to normal skin. There are few specific data on this point (21,34). Meneghini et al (33) mentioned that "Kathon CG allergy is frequently an aggravating factor of a preceding dermatitis". Of the 35 patients investigated by Hannuksela (21), only 4 (11%) had been sensitised by cosmetic products used on normal skin. In the other 31, patients had preexisting dermatoses: atopic dermatitis (n=11), irritant or infectious dermatitis (n=9), stasis dermatitis (n=6), nummular dermatitis (n=3), and "other" (n=2). In the series of 81 patients of de Groot et al (34), however, 37 (46%) had no previous dermatitis. In the other 44 (54%), 13 previously suffered from irritant dermatitis, 12 from atopic dermatitis, 6 from allergic contact dermatitis, 6 from dermatitis of unknown origin, and 7 from "other" dermatoses or combinations.

Most reactions to Kathon CG have been caused by stay-on products, especially moisturising creams; contact dermatitis caused by a shampoo containing 5 ppm of Kathon CG has been recorded (21), but rinse-off products are rarely implicated. In a German study (23), dish washing liquids were implicated (together with stay-on products) in 4 patients.

Table 8. Profile of patients sensitised to Kathon CG (34)

NO. PAT.	f:m	AGES	LOCALISATION	PRE-EXISTING DERMATITIS?	COMMENTS	REF
50	46:4	?	"mainly the face and/or the hands"	"frequently aggravation of preceding dermatitis	Most reactions caused by moisturising creams	33
23	20:3	22-83 (44)	hands (9) face (9) other (7)	?		23
35	30:5	16-85 (41)	?	atopic : 11 irritant : 9 stasis : 6 nummular : 3 other : 2	22/35 reactions caused by moisturising cream	21
13	9:4	21-73 (45)	hands (7) leg (1) other (5)	?	Causative cosmetics not found	28
81	70:11	11-82 (39)	face (40) hands (43) arms (21) other (21)	irritant : 13 atopic : 12 allergic : 6 e.c.i. : 6 combinat.: 5 other : 2	Nearly all reactions were caused by moisturising creams	34

4.8 USE TESTS IN PATIENTS ALLERGIC TO KATHON CG

In an American study (22) 18 subjects who had developed allergic contact hypersensitivity to Kathon CG through exaggerated, repeated occlusive exposure, were asked to use some prototype products preserved with Kathon CG: a synthetic liquid soap (5 ppm), shampoo (4 ppm), a hair conditioner (5 ppm), a liquid fabric softener (6 ppm), and a bath foam and shower foam (5 ppm).

One subject used only the liquid soap for 6 weeks. 3 Subjects concurrently used the liquid soap, shampoo and hair conditioner, and one used the liquid soap, shampoo, hair conditioner and liquid fabric softener for 3-6 weeks. Subsequent to completing the use of the liquid soap, shampoo, hair conditioner and liquid fabric softener, 10 additional subjects used a bath foam or shower foam product for their personal whole-body bathing for 3 weeks.

The 3 remaining subjects from the group of 18 used both the bath foam and shower foam for 3 weeks. No allergic reactions resulted (22). These results indicate that in their typical use these products pose at most a small risk of eliciting clinical dermatoses even among consumers who are allergic to

the preservative mixture. However, it should be realised that these experiments were conducted on individuals with healthy skin. People with damaged skin may be at greater risk of developing allergic contact dermatitis.
Also, at least one case of facial eczema caused by the use of shampoo containing only 5 ppm of the isothiazolinone mixture has been documented (21). Testing of stay-on products under use conditions is discussed in the section "Relevance of positive patch test reactions to Kathon CG" (Chapter 4.9).

4.9 RELEVANCE OF POSITIVE PATCH TEST REACTIONS TO KATHON CG

The concentration of Kathon CG in cosmetics and toiletries is rarely more than 15 ppm. Patch testing with dilutions of the preservative system has indicated that only a minority of hypersensitive individuals still show a positive patch test reaction to Kathon CG at 25 ppm (Table 5). A lower test concentration rarely elicits a reaction in a closed patch test. Consequently, cosmetics which contain Kathon CG usually give negative patch tests, even in patients allergic to it. This implies that sensitivity to Kathon CG will be missed unless it is routinely tested in the appropriate concentration in all patients suspected of allergic contact dermatitis (35).
The relevance of observed positive patch test reactions to Kathon CG can be assessed only when information is available on the presence or absence of the preservative in the products used by the patient. Since 1978 United States regulations have required that all ingredients of cosmetics and toiletries, except components of flavours and fragrances, be declared on cosmetic product labels.
In EEC countries ingredient labelling is not compulsory. However, the finding that one or more of the products used contain Kathon CG does not prove the relevance of the observed contact allergy for the patient's complaints, nor does it necessarily imply that the patient should stop using the implicated products.
The use of "rinse-off" products containing Kathon CG such as soap, shampoos and shower foams may, with some exceptions (21), be safe (13) even in hypersensitive individuals (see section "Use tests in patients allergic to Kathon CG"). This may conveniently be explained by the high dilution of the allergen with water under normal use conditions and a short contact-time with the skin.
The use of stay-on products in patients allergic to Kathon CG however, may frequently cause or contribute to the development and/or persistence of dermatitis, even when the amount of the isothiazolinones is as low as 7 ppm (21). Various authors have confirmed this by means of provocative use testing or open tests. In this test the product is applied to the antecubital fossa twice daily for a week (36). The results of various investigations have

been summarised in Table 9. With 2 exceptions (23,28) open tests with creams containing 7-19 ppm Kathon CG provoked dermatitis in 50% or more of the patients tested. A negative open test does not prove that the Kathon CG-containing product is not relevant for the patient's skin problems, as these tests were performed on healthy skin, and many patients used the products on damaged skin.

Table 9. Results of open tests

Product	Concentration of Kathon CG (ppm a.i.)	No. pat. tested	Positive		Ref.
			No.	%	
cream	12 ppm	5	3	60%	40
cream	7 ppm	10	5	50%	21
cream	15 ppm	2	1	50%	21
cream	15-19 ppm	12	6	50%	36
cream	15 ppm	13	7	54%	3
lotion	7.7-8.6 ppm	11	–	–	28
lotion	15 ppm	1	1	100%	28
lotion	15 ppm	7	4	57%	23
cream	9 ppm	7	3	43%	23

In the earlier reports (2,3,28), it was stated that the relevance of the observed patch test reactions to Kathon CG was frequently unknown, because virtually no information was available on the presence or absence of the preservative in various products used by the patients.

As experience grew, and it became known which products contained the preservative mixture (16,21,23,33,37,38), many positive patch test reactions to Kathon CG were judged to be of present relevance, based on use testing, open tests, or the observation that ceasing the use of the incriminated cosmetic(s) improves or even cures the patient's skin disorder. The relevant data are summarised in Tables 6 and 7. In England (29) the reactions in 4/9 patients (44%) were considered to be relevant. In the study of Hannuksela, (21) in 26/35 (74%) patients was the source of Kathon CG sensitivity found. In the German study (23), 70% of the reactions were (probably) relevant. In the Italian study (33), 42 of 50 reactions to Kathon CG (84%) were relevant for the dermatitis of the patients. Of 155 patients allergic to Kathon CG investigated in The Netherlands (Table 6), 109 reactions (70%) were of present relevance (past relevance not included). Thus, a low rate of relevant reactions is likely to reflect inadequate knowledge on which products contain the preservative.

In The Netherlands it became clear that approximately 50% of all reactions were caused by a moisturising cream containing 12 ppm of Kathon CG, and a baby body lotion. In Finland, some 60% of all cases of contact allergy

were caused by a cream containing 19 ppm at first, and later 7 ppm of the isothiazolinone mixture (21).

4.10 THE SENSITISER IN KATHON CG

In all studies reported, patch tests have been performed with the commercial product Kathon CG, containing methylisothiazolinone and methylchloroisothiazolinone. Bruze et al (39) have demonstrated that most reactions are caused by the chlorinated isothiazolinone by patch testing patients allergic to Kathon CG with the various constituents of the commercial product.
The results were later supported by animal experiments (10): methylchloroisothiazolinone was found to be a strong, and methylisothiazolinone a weak sensitiser (see the section on Animal Studies).

4.11 CONCLUSIONS

Kathon CG is an important cosmetic allergen in The Netherlands and some other European countries such as Sweden, Finland, Germany and Italy. The presence of Kathon CG in stay-on cosmetics in concentrations as low as 7 ppm may constitute a risk for the induction and elicitation of contact allergic reactions, especially when products such as moisturising creams are applied to damaged skin. There is a need to investigate whether lowering the concentrations in such products will significantly decrease the risk of sensitisation. The risk of both induction and elicitation of contact allergic reactions by rinse-off products containing Kathon CG 5 ppm or less under normal use conditions appears to be small. Kathon CG should be routinely tested in patients suspected of allergic contact dermatitis (35). Its optimal test concentration, which detects most contact allergies but does not produce irritation and has no substantial potential for inducing patch test sensitisation, still has to be determined. For the practising dermatologist a test concentration of 100 ppm a.i. in water is currently considered to be adequate. Use testing or open tests with the patients' products containing Kathon CG should follow the observation of a positive patch test reaction to the preservative, in order to determine the relevance of the established hypersensitivity.

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Chapter 5 Oleamidopropyl dimethylamine

This chapter is based on the following publications:

1. de Groot AC, Liem DH. Contact allergy to oleamidopropyl dimethylamine. Contact Dermatitis 1984; 11: 298-301
2. de Groot AC, Jagtman BA, van der Meeren HLM, Bruynzeel DP, Bos JD, den Hengst C, Weyland JW. Cross-reaction pattern of oleamidopropyl dimethylamine. Accepted for publication in Contact Dermatitis.
3. de Groot AC, Bruynzeel DP, Bos JD, van der Meeren HLM, van Joost Th, Jagtman BA, Weyland JW. The allergens in cosmetics. Accepted for publication in the Archives of Dermatology.
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Chapter 5 Oleamidopropyl dimethylamine

SUMMARY

The cationic emulsifier oleamidopropyl dimethylamine has been responsible for many cases of cosmetic sensitisation in The Netherlands. Of 119 patients with proven cosmetic-related allergic contact dermatitis, 13 (11%) were allergic to oleamidopropyl dimethylamine (Chapter 3.4).
The clinical data of 12 patients, all sensitised by one particular baby body lotion containing 0.3% of the emulsifier, are presented.
The cross-reaction pattern of oleamidopropyl dimethylamine was investigated by patch testing 13 patients allergic to the emulsifier with a series of related amide-amine type emulsifiers. Most cross-reactions were observed to ricinoleamidopropyl dimethylamine lactate and tallowamidopropyl dimethylamine (11 patients, 85%). 9 patients (of 12 tested: 75%) reacted to lauramidopropyl dimethylamine and 6 (46%) to myristamidopropyl dimethylamine.
It is concluded that the presence of oleamidopropyl dimethylamine in a concentration of 0.3% in stay-on cosmetics, especially when applied to damaged skin and/or the periorbital area, bears a definite risk of the induction and elicitation of contact allergic reactions.

5.1 INTRODUCTION

Oleamidopropyl dimethylamine is an amide-amine type cationic cosmetic surfactant. Contact allergy to this compound was first described in 1984 (1): 3 patients had become sensitised to oleamidopropyl dimethylamine present in a baby body lotion. Since then, many new cases of sensitisation to the emulsifier have been observed. Indeed, oleamidopropyl dimethylamine proved to be one of the most frequent causes of contact allergy to cosmetics in The Netherlands (2). This chapter describes the clinical aspects of sensitisation to this cosmetic ingredient and provides additional (technical) data. Also, the results of a study into the cross-reaction pattern of oleamidopropyl dimethylamine are presented.

5.2 PRODUCT DESCRIPTION

Oleamidopropyl dimethylamine belongs to the group of amide- amine type cationic surfactants; some of the more important representatives of this category are shown in Table 3. This group is composed of various carboxylic acid amido alkyldimethylamines having the chemical structure:

$RCONHCH_2CH_2CH_2N(CH_3)_2$.

R represents the alkoyl group of fatty acids: oleic acid, ricinoleic acid,

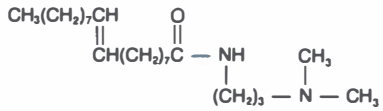
stearic acid, behenic acid, isostearic acid, tallow acid, lauric acid, myristic acid, coconut fatty acids, mink oil fatty acids, and palmitic acid.
These fatty amidopropyl dimethylamine bases offer the cosmetic formulator great flexibility in preparing cationic emulsions. The large selection of lipophilic ends provides a wide range of attainable physical properties. The tertiary amine functional group affords the additional opportunity of modifying endproduct characteristics through neutralisation. Most of the substances as such are not soluble in water, but become soluble when neutralised with a water-soluble acid such as phosphoric, citric, lactic, acetic or gluconic acid to form a cationic amine salt. Their principal uses are cationic emulsions, including creams, lotions and hair rinse preparations. As conditioners in shampoos and hair rinses, they have the advantage over quaternary ammonium compounds of being compatible with anionic surfactants.
In The Netherlands, oleamidopropyl dimethylamine has been incorporated in a baby body lotion, because this particular emulsifier makes the skin "feel soft to the touch". We know of no other cosmetic product in our country containing oleamidopropyl dimethylamine. In the United States, the amide-amine type cationic surfactants also have limited application. In 1986, oleamidopropyl dimethylamine was present in 23 of approximately 19,000 cosmetic formulas on file with the Food and Drug Administration (9). Stearamidopropyl dimethylamine (lactate) was present in 26, lauramidopropyl dimethylamine in 13, and behenamidopropyl and minkamidopropyl dimethylamine each in 7 products on file. The other tertiary amines are used in only 1 or 2 products, or not at all.
Detailed (technical) information on oleamidopropyl dimethylamine is provided in Table 1.

5.3 CLINICAL ASPECTS OF CONTACT ALLERGY TO OLEAMIDOPROPYL DIMETHYLAMINE

In a period of 5 years (1983-1987), 15 patients allergic to one particular brand of baby body lotion, the most widely used in The Netherlands, were investigated. This includes the 3 patients from our previous publication, the first and only report of contact allergy to oleamidopropyl dimethylamine (1). They were tested with all ingredients of the product, obtained from the manufacturer. Three reacted to the preservative Kathon CG. The other 12 reacted to oleamidopropyl dimethylamine (test concentration 0.4%-0.5% in water), present in the lotion at a concentration of 0.3%. This group consisted of female patients only (Table 2). Their ages ranged from 18-52 years, mean age 32 years.

Table 1. Oleamidopropyl dimethylamine: structural formula and technical data

Structural formula of Oleamidopropyl dimethylamine



Cas number:	109-28-4
Empirical formula:	$C_{23}H_{46}N_2O$
Synonyms:	*N*-(3-Dimethylamino)propyl)-9-octadecenamide Dimethylaminopropyl oleamide
Trade names:	Lexamine O-13 (Inolex) Mazeen OA (Mazer) Schercodine O (Scher)
Properties *	
Appearance	Dark amber liquid
Odour	Ammoniacal
Molecular weight (average)	366
Ionic nature	Cationic
Activity, %	100
Acid value, mg KOH/gram	4.0 max.
Alkali value, mg KOH/gram	150-160
Uncondensed ("free") oleic acid (avg.mol.wt.282), %	2.0 max.
Congealing point (typical), °C	5.0
Flash point, open cup	over 160 °C

* Schercodine O

Most had used the baby body lotion for many years, both as a moisturiser, but also for cleansing purposes, i.e. for the removal of facial and eye makeup. In 10 patients (83%), the dermatitis was localised on the face, especially in the periorbital area (N=7, 58%). Some women had dermatitis around the eyes only, even though the lotion had also been applied to the face. Six patients (50%) had no other skin diseases, and in them the dermatitis was cured upon removal of the offending product. Four patients had atopic dermatitis, and two had used the baby body lotion for the treatment of dry skin/irritant dermatitis. In 5 patients other contact allergens were identified: 2 reacted to nickel sulfate, and 1 reaction was observed to the quinoline mix, benzocaine, toluenesulfonamide/formaldehyde resin, balsam Peru, metipranolol (3), *p-tert*-butylphenolformaldehyde resin, and quaternium-15.

The reactions to toluenesulfonamide/formaldehyde resin (in nail lacquer and hardener), to quaternium-15 (in another moisturiser), and to meti-

pranolol (in eye drops) were also relevant to the patients' actual dermatitis. After removal of the offending products and adequate instructions, none of the patients have had recurrences of allergic cosmetic dermatitis.

Table 2. Clinical characteristics of patients allergic to oleamidopropyl dimethylamine

	Sex	Age	Localisation of dermatitis	Other patch test results	Pre/Co-existing dermatitis
1	f	49	Periorbital		
2	f	30	Upper eyelids	Nickel sulfate Quinoline mix	Atopic dermatitis
3	f	18	Face, Arms		Atopic dermatitis
4	f	27	Arms, Neck, Trunk, Legs		Irritant dermatitis
5	f	29	Arms, Trunk	Benzocaine, Nail lacquer and hardener, toluenesulfonamide/ formaldehyde resin	Atopic dermatitis
6	f	26	Periorbital	Balsam Peru	Atopic dermatitis
7	f	23	Hands, Arms, Face, Neck		Irritant dermatitis
8	f	24	Periorbital, Neck		
9	f	52	Periorbital, Face, Neck		
10	f	52	Periorbital	Metipranolol, Nickel sulfate, *p-tert*-Butyl-phenolformalde-hyde resin	
11	f	21	Periorbital	Quaternium-15	
12	f	32	Face, Arms, Trunk		

5.4 FREQUENCY OF SENSITISATION

Several data suggest that contact allergy to oleamidopropyl dimethylamine is far from rare:

1. The 12 patients described above were seen by the author in a period of 5 years. The catchment population of the practice approximates 140,000. The Netherlands has approximately 16 million inhabitants. Extrapolation of the data would indicate that in The Netherlands 275 patients become sensitised to oleamidopropyl dimethylamine per year.

This does not include patients who identify the offending product, and do not seek medical advice or are not referred to the dermatologist. If this number is estimated to equal the number of patients seen in dermatological clinics, some 550 patients may become allergic to the emulsifier in any year. The manufacturer has informed us that annually 600,000 units of the baby body lotion are sold in The Netherlands. This implies that 1 in every 1090 (600,000: 550) consumers using the product are sensitised per year. If 1/2 of the consumers use 2 units per year, the sensitisation index rises to 1 in every 727 individuals.

2. In a prospective study to identify the allergens in cosmetic products (2), 119 patients with proven cosmetic-related allergic contact dermatitis were investigated (Chapter 3.4). In 13 patients (11%), the allergy was caused by oleamidopropyl dimethylamine. This ingredient was the 3rd most common cause of cosmetic sensitisation after Kathon CG (28%) and toluenesulfonamide/formaldehyde resin (13%).

3. Between 1976 and 1981 the Cosmetic Department of the Food Inspection Service Enschede (4) received 35 complaints of (presumed) skin reactions to the baby body lotion. Patch tests with the ingredients have been performed in 11 patients. Two of these reacted to quaternium-15 (the preservative in the product which was later substituted with Kathon CG), 3 had no positive patch test reactions, and 6 reacted to oleamidopropyl dimethylamine. However, it should be appreciated that 5 of the 6 latter patients were tested with the emulsifier at a concentration of 1% and 2% in water: these concentrations may give rise to irritant reactions.

5.5 CROSS-REACTION PATTERN

In order to investigate the cross-reaction pattern of oleamidopropyl dimethylamine, 13 patients allergic to it were patch tested with a series of related amide-amine type cationic surfactants.

MATERIALS AND METHODS

Patients found to be allergic to the baby body lotion containing 0.3% oleamidopropyl dimethylamine were tested with a series of 11 amide-amine type cationic surfactants, including oleamidopropyl dimethylamine. Table 3 lists their CTFA names, trade names (and the companies providing the materials), CAS numbers and structural formulas. The test solutions were prepared as follows: water was added to the raw material. When insoluble, phosphoric acid was added until a clear solution developed. Solutions that had a pH of 4 or lower were neutralised with NaOH to obtain a pH

as near to neutral as possible, without precipitation taking place. Solutions that became opalescent were checked by microscope for particles.
First, all surfactants were tested at 0.5% w/v. However, this concentration proved to be irritant for most substances. The concentrations were reduced in steps of 0.025-0.1% ; the test concentrations used (Table 4) were the highest concentrations that did not cause irritation in at least 35 control subjects. The concentrations were chosen to be high on purpose, as previous experience had indicated that for oleamidopropyl dimethylamine the concentration which would detect sensitisation was very near its irritation threshold (1). Test procedures were carried out according to internationally accepted criteria (5).

RESULTS

Thirteen female patients (ages ranging from 18-51 years, mean age 35 years), reacting upon patch testing to the baby body lotion were investigated. The results are shown in Table 4. All 13 reacted to oleamidopropyl dimethylamine. One patient did not react to any of the other substances, but the other 12 had at least 4 reactions to the related surfactants. Most reactions were observed to ricinoleamidopropyl dimethylamine lactate and tallowamidopropyl dimethylamine (11 patients, 85%); next was lauramidopropyl dimethylamine with 9 reactions (in 12 patients tested: 75%), followed by myristamidopropyl dimethylamine (6 reactions, 46%). Five patients (38%) reacted to isostearamidopropyl dimethylamine, and minkamidopropyl dimethylamine. Cocamidopropyl dimethylamine scored 5 reactions in 12 patients tested (42%). To the other test substances, only 2 or 1 reaction(s) were observed.

DISCUSSION

With the exception of oleamidopropyl dimethylamine (1,2), none of the surfactants investigated in our study have been reported to be the cause of cosmetic allergy. This may be related to the limited use of these cationic surfactants in cosmetic preparations (9).
In the present study, 13 patients allergic to oleamidopropyl dimethylamine were tested with 10 related compounds. A wide variation in the number of positive reactions was observed. Nearly all patients (11/13) reacted to ricinoleamidopropyl dimethylamine lactate and tallowamidopropyl dimethylamine, whereas only occasional reactions were observed to stearamidopropyl dimethylamine lactate, behenamidopropyl dimethylamine and palmitamidopropyl dimethylamine. We have tried to find an explanation for this by looking at the following parameters:

1. The chain length of the fatty acid. This does not appear to be of paramount importance, as illustrated by Figure 1. Ricinoleamidopropyl

Table 3. Amide-amine type cationic surfactants

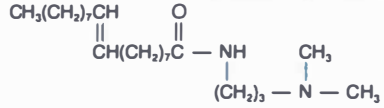
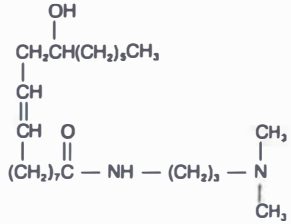
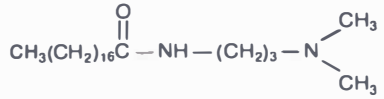
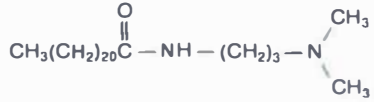
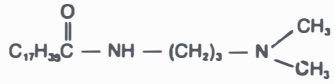
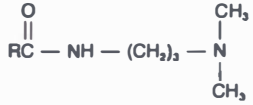
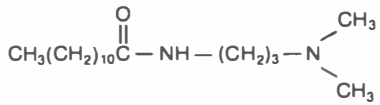
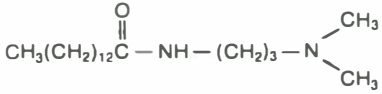
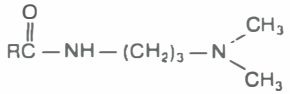
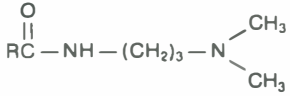
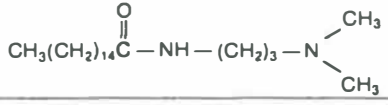
CTFA NAME	CAS-NUMBER	TRADE NAME	STRUCTURAL FORMULA
Oleamidopropyl dimethylamine	109-28-4	Schercodine O (Scher)	
Ricinoleamidopropyl dimethylamine lactate	20457-75-4	Mackalene 216 (McIntyre)	$ 
Stearamidopropyl dimethylamine lactate	55819-53-9	Mackalene 316 (McIntyre)	$ 
Behenamidopropyl dimethylamine	977063-18-5	Lexamine B-13 (Inolex)	
Isostearamidopropyl dimethylamine	67799-04-6	Schercodine I-LC (Scher)	
Tallowamidopropyl dimethylamine	68425-50-3	Schercodine T (Scher)	* 

Table 3. (continued)

CTFA NAME	CAS-NUMBER	TRADE NAME	STRUCTURAL FORMULA
Lauramidopropyl dimethylamine	3179-80-4	Schercodine L (Scher)	
Myristamidopropyl dimethylamine	45267-19-4	Schercodine M (Scher)	
Cocamidopropyl dimethylamine	68140-01-2	Mazeen CA (Mazer)	# 
Minkamidopropyl dimethylamine	68953-11-7	Foamole B (van Dyk)	@ 
Palmitamidopropyl dimethylamine	39669-97-1	Lexamine P-13 (Inolex)	

$ the structural formula shown is without lactic acid
* RCO- represents the tallow acid radical
# RCO- represents the coconut acid radical
@ RCO- represents the fatty groups derived from mink oil

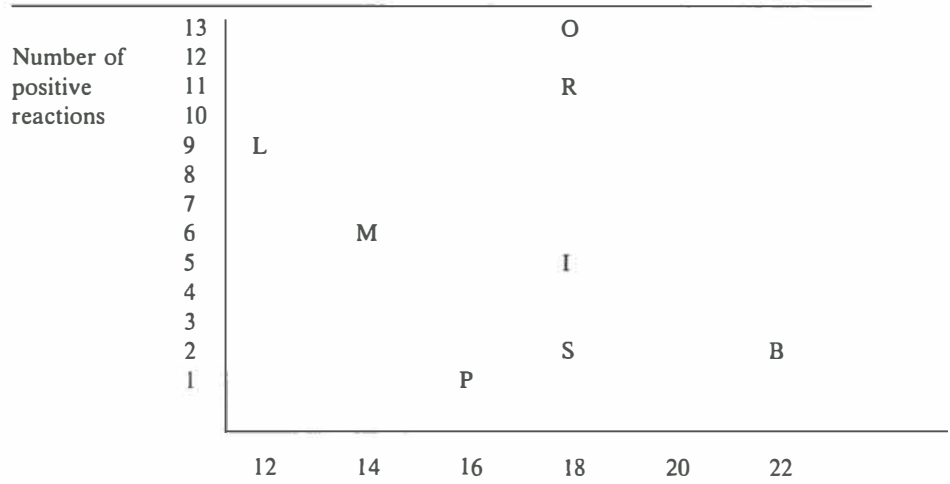
Table 4. Results of patch testing

Test substance	Test conc. (w/v aqua)	Patient													TOTAL POSITIVE (%)
		1	2	3	4	5	6	7	8	9	10	11	12	13	
Oleamidopropyl dimethylamine	0.4%	+	+	+	+	+	+	+	+	+	+	+	+	+	13 (100)
Ricinoleamidopropyl dimethylamine lactate	0.5%	+	+	+	+	+	+	+	+	+		+	+		11 (85)
Stearamidopropyl dimethylamine lactate	0.5%	+											+		2 (15)
Behenamidopropyl dimethylamine	0.5%	+											+		2 (15)
Isostearamidopropyl dimethylamine	0.3%	+			+	+			+					+	5 (38)
Tallowamidopropyl dimethylamine	0.3%	+		+	+	+	+	+	+	+		+	+	+	11 (85)
Lauramidopropyl dimethylamine	0.2%			+	+	+	+	+	+	+		+	N	+	9 (75)*
Myristamidopropyl dimethylamine	0.05%			+			+			+		+	+	+	6 (46)
Cocamidopropyl dimethylamine	0.1%			+		+	+			+			N	+	5 (42)*
Minkamidopropyl dimethylamine	0.1%	+				+	+					+		+	5 (38)
Palmitamidopropyl dimethylamine	0.025%						+								1 (8)

N means: not tested

* 12 patients tested

Figure 1. Relationship between fatty radical chain lenght and number of positive reactions



B = Behenamidopropyl dimethylamine
I = Isostearamidopropyl dimethylamine
L = Lauramidopropyl dimethylamine
M = Myristamidopropyl dimethylamine
O = Oleamidopropyl dimethylamine
P = Palmitamidopropyl dimethylamine
R = Ricinoleamidopropyl dimethylamine
S = Stearamidopropyl dimethylamine

dimethylamine lactate, having the same carbon chain length as oleamidopropyl dimethylamine, indeed has a high score (11/13), but only 2 patients reacted to stearamidopropyl dimethylamine, also with an 18 carbon chain.

2. Possible contamination of test substances with oleamidopropyl dimethylamine or oleic acid. The fatty acid radical tallow acid comes from tallow, the fat derived from the fatty tissues of sheep or cattle. Tallow oil may contain up to 43% oleic acid (6), which could be an explanation for the high rate of positive reactions (85%) to tallowamidopropyldimethylamine. The coconut fatty acid radical is derived from coconut oil, which contains only 5-7% oleic acid (7). However, it also contains up to 50% lauric acid, which may explain (at least 9 patients reacted to lauramidopropyl dimethylamine) that 5 patients reacted to cocamidopropyl dimethylamine. Minkamidopropyl dimethylamine has the fatty groups of mink oil as the fatty radical. Mink oil contains up to 45%

oleic acid (8), which may explain 5 patients reacting to this emulsifier similarly. The other materials probably are not pure, and will also contain fatty acids with other chain lenghts, the amounts depending on the purification processes. However, there are insufficient data to draw conclusions.

3. The presence or absence of double bonds.
   Both oleamidopropyl dimethylamine and ricinoleamidopropyl dimethylamine have 1 double bond, and so have (some of the molecules in) tallowamidopropyl dimethylamine and minkamidopropyl dimethylamine by virtue of the presence of oleic acid. However, lauramidopropyl dimethylamine (9 reactions) and myristamidopropyl dimethylamine (6 reactions) have no double bonds.

Some of the reactions observed may have been irritant, as most patients reacted to 4 or more test substances. Nevertheless, it appears that a certain pattern of (pseudo)cross-reactivity can be recognised.

In summary:

1 Most patients allergic to oleamidopropyl dimethylamine cross-react to ricinoleamidopropyl dimethylamine, tallowamidopropyl dimethylamine (possibly because of its high content of oleamidopropyl dimethylamine) and lauramidopropyl dimethylamine.
2 About 40-50% of the patients cross-react to isostearamidodopropyl dimethylamine, myristamidopropyl dimethylamine, cocamidopropyl dimethylamine (possibly caused by a high content of lauramidopropyl dimethylamine) and minkamidopropyl dimethylamine (possibly caused by a high content of oleamidopropyl dimethylamine).
3 Few or no cross-reactions occur to stearamidopropyl dimethylamine, behenamidopropyl dimethylamine and palmitamidopropyl dimethylamine.

5.6 CONCLUSIONS

The cationic emulsifier oleamidopropyl dimethylamine is an important cause of cosmetic sensitisation in The Netherlands. Its presence in a concentration of 0.3% in stay-on products that may be applied to damaged skin and/or around the eyes bears a definite risk of the induction and elicitation of contact allergic reactions. An estimated 1 in every 700-1000 consumers may become sensitised to oleamidopropyl dimethylamine in any year from using a particular baby body lotion containing the emulsifier. Cross-reactions to related amide-amine type cationic surfactants occur frequently, especially with ricinoleamidopropyl dimethylamine, tallowamidopropyl dimethylamine and lauramidopropyl dimethylamine.

5.7 REFERENCES

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Chapter 6 Summary, conclusions, recommendations

SUMMARY AND CONCLUSIONS

This thesis presents and discusses the results of a series of investigations aimed at determining (i) the frequency of adverse reactions from cosmetics and toiletries; (ii) the (quantitative) role of contact allergy in the spectrum of cosmetic-related side effects; and (iii) the nature of the allergens in cosmetic products.

Chapter 1 provides a general introduction into the field of "cosmetology". Data are presented on the extent of the use of these products by consumers; on the ingredients used most frequently in cosmetics and toiletries; on the spectrum of reported side effects; and on some important EEC regulations.

Chapter 2 provides the results of 2 epidemiological studies into the frequency and the nature of cosmetic-related side effects. In 2 additional investigations, selected groups of dermatological patients were patch tested with preservatives and fragrance materials in order to determine the frequency of sensitisation to these cosmetic ingredients, and to identify allergens suitable for inclusion in a "cosmetic screening series".

A (Chapter 2.3). A group of 1609 individuals selected only on age (33-64 year) were interviewed on the occurrence of side effects from cosmetics and toiletries. 196 (12.2%) claimed to have suffered from cosmetic-related adverse reactions in the preceding 5 years. Women ascribed most reactions to soap, facial cream, deodorant, shampoo and eye shadow. In the group of men soap also ranked first, followed by aftershave, deodorant and bath foam. Most reactions were localised on the face, the hands, and in the axillae. The majority of patients (63%) solved the problem by stopping the use of the suspected products and using a different brand instead. The conclusions from this investigation and a review of published data are:

- Side effects of cosmetics and toiletries are not rare; up to 10% of the adult population may be affected in a period of 1-5 years.

- Most reactions are mild; nevertheless, 30% of the patients still consulted their physician.
- Product categories causing most reactions in women are: soap, deodorant, (facial) creams, shampoo, eye cosmetics and shower foam. In men most reactions are caused by soap, aftershave, deodorant and shower foam.
- Women report side effects nearly twice as frequently as men; this difference is largely due to products applied to the face.
- The majority of adverse reactions are caused by irritation.
- Atopic individuals may be at greater risk of developing side effects from cosmetics and toiletry products caused by irritation.

B (Chapter 2.4). A group of 982 regular clients of beauticians were interviewed on the occurrence of side effects from cosmetics and toiletries. 245 (26%) claimed to have suffered from one or more cosmetic-related adverse reactions in the preceding 5 years. Most reactions were caused by skin care products, followed by personal cleanliness products, eye cosmetics, deodorant/antiperspirant and facial makeup products. In order to determine the (quantitative) role of contact allergy, 150 women claiming cosmetic-related adverse reactions were patch tested with the European standard series and an additional series of 15 cosmetic allergens. In the European standard series, only a few positive reactions were seen to allergens which may be present in cosmetics: fragrance mix (3), wool alcohols (3), formaldehyde (2), balsam Peru (1), and rosin (1). In the cosmetic series only Kathon CG elicited positive responses, in 3 patients. Cosmetic allergy was considered to be "proven" in 3 patients (2%), and "possible" in 7 (5%). The conclusions from this study are:

- Only a small percentage of cases of adverse reactions to cosmetics and toiletry products (less than 10%) are caused by contact allergy. The majority of reactions are due to irritation from personal cleanliness products such as soap, shampoo, bath foam and from deodorant.
- Irritant effects of cosmetics and toiletries may worsen preexisting dermatoses such as seborrhoeic dermatitis, acne and rosacea.
- An atopic diathesis may predispose to cosmetic-related irritant side effects.

C (Chapter 2.5). A group of 179 patients suspected of cosmetic allergy were patch tested with a series of 16 fragrance materials and 9 cosmetic preservatives. In 67 patients (37%), one or more of these allergens gave positive reactions. In the group of fragrance materials, the largest number of reactions were seen to isoeugenol, oak moss, geraniol, α-amylcinnamic alcohol, and a mixture of α-amylcinnamic aldehyde and α-hexylcinnamic aldehyde. The fragrance mix in the European standard series detected nearly

80% of cases of contact allergy to fragrance materials other than its constituents. In the group of preservatives, Kathon CG and quaternium-15 scored the highest number of positive reactions. The conclusions from this study are:

- Kathon CG and quaternium-15 may be important cosmetic allergens. Their role should be investigated further.
- The fragrance mix in the European standard series detects 80% or more of all cases of fragrance sensitivity.
- The commonly used test concentrations of 2% for oak moss, geraniol and isoeugenol are too low to detect all cases of sensitisation. They should be tested in higher concentrations separately when fragrance sensitivity is suspected.

D (Chapter 2.6). Two groups of 627 and 501 patients suspected of contact allergy were tested with trays of cosmetic preservatives. Prevalence rates of sensitisation higher than 1% were observed to benzoic acid, benzalkonium chloride, DMDM hydantoin, Kathon CG, and alkyl trimethyl ammonium chloride. At the concentrations used, benzoic acid, benzalkonium chloride and alkyl trimethyl ammonium chloride appeared to be marginal irritants, so some reactions interpreted as allergic may actually have been irritant. The reactions to DMDM hydantoin were caused by formaldehyde sensitivity. From this study it is concluded that Kathon CG should be included in a "cosmetic screening series".

Chapter 3 describes the results of a retrospective and a prospective study aimed at determining the allergens in cosmetics. A review of published data is provided (Chapter 3.2). Cases of cosmetic allergy caused by previously unreported or rare allergens, published by the author, are summarised (Chapter 3.5).

A Retrospective study (Chapter 3.3) In a period of 5 years (1981-1985) 49 patients suffering from contact allergy to cosmetics were investigated. This number represented 0.3% of the total patient population and 3.5% of all patients patch tested for suspected allergic contact dermatitis. The facial skin was most frequently affected. Skin care products (moisturising and cleansing creams/lotions/milks) accounted for nearly half of the dermatitis-causing cosmetics (45%), followed by hair cosmetics (10%), shaving preparations (10%), and nail cosmetics (8%). Twenty of the patients were tested with all ingredients of the suspected cosmetic products. In 22 other patients, the causative allergens could be established with high probability from the results of the European standard series and/or testing additional cosmetic allergens.
A total of 21 ingredients or classes of ingredients were identified. Fragrances and fragrance chemicals were responsible for the majority of the reactions

(55%). Preservatives/antimicrobials were the second most frequent cause of reactions (20%). In this category, most reactions were caused by Kathon CG. The emulsifier oleamidopropyl dimethylamine was the next most frequently identified allergen (8%). From this study it is concluded that fragrances and preservatives are the major causes of cosmetic allergy in The Netherlands up to 1985.

B Prospective study (Chapter 3.4). In a period of 17 months (1986-1987), 119 patients suffering from cosmetic allergy were investigated in a multicenter study. The facial skin, including the eyelids, was most frequently affected. More than half of all reactions (56%) were caused by skin care products. Next were nail cosmetics (13%), followed by perfumes (8%), hair cosmetics (6%), deodorants (5%) and lip cosmetics (4%). 81 patients were tested with all ingredients of the suspected cosmetic products, and 38 with 1 or more allergens known to be present in the cosmetics used. A total of 53 cosmetic allergens were identified. The most important contact allergen was Kathon CG with 33 reactions (28%). Second was toluenesulfonamide/formaldehyde resin with 15 reactions (13%), followed by oleamidopropyl dimethylamine (13 patients, 11%); 15 reactions (13%) were caused by "fragrance, unspecified". It is concluded that preservatives, fragrances and emulsifiers are the main classes of ingredients responsible for cosmetic allergy in The Netherlands. The most important allergens are Kathon CG, toluenesulfonamide/formaldehyde resin and oleamidopropyl dimethylamine.

Chapter 4 demonstrates the importance of Kathon CG in cosmetic allergy. In 1986, Kathon CG 100 ppm aqua was added to the routine patch test series by the members of the Dutch Contact Dermatitis Group, in order to assess the prevalence rate of sensitisation to this preservative. 3114 patients routinely tested for suspected allergic contact dermatitis were investigated. 155 (5.0%) reacted to Kathon CG, and in 109 (3.5%) the investigators judged the reactions to be relevant for the patients' dermatitis. Of 253 cosmetic products investigated for the presence of Kathon CG, 59 (23%) were found to contain the isothiazolinone mixture. From the studies reported in this chapter it is concluded that the presence of Kathon CG in stay-on cosmetics in concentrations as low as 7 ppm constitutes a risk for the induction and elicitation of contact allergic reactions. It is advised to add Kathon CG to the European standard series.

Chapter 5 shows that oleamidopropyl dimethylamine is an important cause of cosmetic allergy in The Netherlands. All cases of sensitisation to this cationic emulsifier were caused by one particular baby body lotion containing 0.3% of oleamidopropyl dimethylamine. The clinical aspects of 12 women sensitised to the emulsifier are presented. Most of the patients

had used the baby body lotion for many years, both as a moisturiser, but also for cleansing purposes, i.e. for the removal of facial and eye makeup. In 10 patients (83%) the dermatitis was localised on the face, especially around the eyes. It was calculated that in any year 1 in every 700-1000 consumers may be sensitised to oleamidopropyl dimethylamine by using the baby body lotion. In an additional study, 13 patients allergic to the emulsifier were patch tested with a series of related amide-amine type cationic surfactants. One patient did not react to any of these substances, but the other 12 had at least 4 reactions to the related allergens. Most reactions were seen to ricinoleamidopropyl dimethylamine lactate and tallowamidopropyl dimethylamine (11 patients, 85%); next was lauramidopropyl dimethylamine with 9 reactions in 12 patients tested (75%), followed by myristamidopropyl dimethylamine (6 reactions, 46%).

RECOMMENDATIONS

The results of the studies presented in this thesis have some practical implications both for the cosmetic manufacturer, and for the dermatologist:

1. The majority of adverse reactions from cosmetics and toiletries are caused by irritation. Therefore, investigation of the irritant potential of cosmetic ingredients and wholesale products deserves more attention than it has had hitherto. Atopic subjects are especially susceptible to developing irritant effects from cosmetics and toiletries; a pre-marketing test panel of consumers should preferably include many such individuals.
2. Kathon CG should not be used in stay-on products at a level of 7 ppm (active ingredients) or more. Further investigations aimed at determining its antimicrobial efficacy at lower concentrations, and the implications of lowering the concentration on the risk of induction and elicitation of contact allergic reactions should be performed. Combinations of low concentrations of the isothiazolinone mixture and other preservatives should be studied. The present practice of preserving rinse-off products with low concentrations of Kathon CG (<5 ppm) does not carry a significant risk for contact allergy and consequently can be continued.
3. Oleamidopropyl dimethylamine should not be used in concentrations of 0.3% or more in stay-on products which may be applied to damaged skin or around the eyes. The sensitising potential of related amide-amine type cationic surfactants should be critically evaluated, before using them in cosmetics of the stay-on variety.
4. Although the risk-*index* may be quite low, the nail lacquer resin toluenesulfonamide/formaldehyde resin is an important cause of cosmetic sensitisation. Research in this field should be directed at developing

resins of the same technical quality, but with a lower sensitising potential. The presence of formaldehyde in nail hardeners containing toluenesulfonamide/formaldehyde resin may increase the risk of sensitisation to the resin.

5. Kathon CG 100 ppm aqua should be added to the routine series which is tested in all patients in whom contact allergy is suspected.
6. For a cosmetic screening series (which should be adapted to local circumstances) the following allergens are suggested:

2-Bromo-2-nitropropane-1,3-diol (preservative)	0.25% pet.
Chloroacetamide (preservative)	0.2% pet.
Diazolidinyl urea (preservative)	2% aqua
Eugenol (fragrance)	5% pet.
Glyceryl thioglycolate (waving agent) *	2.5% pet.
Hydroxycitronellal (fragrance)	4% pet.
Imidazolidinyl urea (preservative)	2% pet.
4-Isopropyl-dibenzoylmethane (UV-filter)	2% pet.
Kathon CG (preservative)	100 ppm aqua
Oleamidopropyl dimethylamine (emulsifier) *	0.4% aqua
Phenyl salicylate (UV-filter, flavour)	1% pet.
Propolis (moisturiser)	10% pet.
Propylene glycol (moisturiser) *	5% aqua
Toluenesulfonamide/formaldehyde resin (resin)	10% pet.

* irritant reactions may occur

Appendices

Appendix 1 Cosmetic usage pattern in the 212 responders*

COSMETIC CATEGORY	FREQUENCY OF USE (SEE BELOW)								
	0 %	1 %	2 %	3 %	4 %	5 %	6 %	7 %	8 %
toothpaste	1	–	–	–	–	1	8	80	9
mouth freshener	75	4	7	3	2	5	3	1	–
deodorant/antiper.	14	1	3	1	2	5	60	13	<1
shampoo	1	1	–	2	30	61	6	–	–
colour shampoo	74	5	17	3	2	–	–	–	–
hair lacquer	50	1	4	8	11	11	14	<1	–
hair dye/bleach	71	5	25	–	–	–	–	–	–
hair conditioner	45	1	5	6	17	2	5	–	–
dry shampoo	91	2	3	1	1	<1	–	–	–
cream rinse	34	2	13	12	13	25	1	–	–
permanent (home)	95	3	2	–	–	–	–	–	–
permanent (hairdr.)	51	14	35	–	–	–	–	–	–
mascara	17	1	4	5	5	11	54	2	–
eye shadow	11	1	4	4	8	15	54	2	–
eyeliner	84	1	2	1	<1	2	8	<1	–
eye cream	75	–	2	2	4	3	11	2	–
eye pencil	39	–	2	3	4	10	40	2	–
brow pencil	73	1	–	2	1	2	20	<1	–
eye cosm. remover	38	1	2	1	4	7	45	1	–
facial cream/lotion	7	–	<1	2	1	2	59	29	–
facial powder	73	1	6	2	2	6	9	<1	–
rouge	24	1	3	3	4	18	44	3	–
facial tonic/milk	18	1	2	2	1	7	52	17	–
liquid makeup	46	1	7	6	3	11	25	1	–
facial mask	19	2	38	25	11	5	<1	–	–
camouflage stick	75	1	7	2	3	2	7	3	–
makeup remover	43	1	1	2	2	4	42	6	–

Appendix 1 (continued)

COSMETIC CATEGORY	FREQUENCY OF USE (SEE BELOW)								
lipstick	11	–	4	2	5	14	29	26	9
soap	12	–	3	1	1	5	42	19	17
body powder	88	1	2	1	2	1	4	–	–
bath/shower foam	35	1	6	4	8	19	25	1	–
bath oil	58	2	7	8	10	11	4	–	–
bath salt	81	2	4	6	4	2	1	–	–
body lotion	11	<1	6	9	8	32	32	1	–
hand lotion/cream	25	–	5	8	4	13	27	13	6
perfume	7	–	5	4	4	24	49	8	–
depilatory cream	68	4	18	8	1	–	–	–	–
nail lacquer	22	1	27	17	17	12	3	–	–
nail lacquer remover	23	2	27	17	17	12	2	–	–
nail hardener	81	1	3	4	3	6	1	<1	–
artificial nail	96	3	<1	–	–	–	–	–	–
foot powder	85	1	2	4	1	2	5	<1	–

0 means: this product is not used
1 means: this product has been used once
2 means: this product is used once/month or less
3 means: this product is used once/week to once/month
4 means: this product is used about once a week
5 means: this product is used several times per week
6 means: this product is used once daily
7 means: this product is used 2-3 times daily
8 means: this product is used more than 3 times daily

* responders are women who claimed to have experienced cosmetic-related adverse reactions

Appendix 1 Cosmetic usage pattern in the 599 non-responders*

COSMETIC CATEGORY	FREQUENCY OF USE (SEE BELOW)								
	0 %	1 %	2 %	3 %	4 %	5 %	6 %	7 %	8 %
toothpaste	5	–	–	–	<1	1	12	76	7
mouth freshener	79	2	3	3	2	5	4	2	<1
deodorant/antiper.	19	1	3	2	3	6	55	11	<1
shampoo	2	–	1	5	36	53	3	–	–
colour shampoo	77	4	15	2	2	<1	–	–	–
hair lacquer	49	1	7	7	13	12	11	1	–
hair dye/bleach	70	6	23	1	<1	–	–	–	–
hair conditioner	45	<1	6	8	25	13	2	–	–
dry shampoo	93	1	3	1	1	<1	–	–	–
cream rinse	41	2	15	10	16	16	<1	–	–
permanent (home)	94	1	4	–	–	–	–	–	–
permanent (hairdr.)	45	9	46	<1	–	–	–	–	–
mascara	29	1	5	5	5	14	37	3	–
eye shadow	20	<1	5	7	8	19	37	4	–
eyeliner	80	<1	3	1	2	4	9	1	–
eye cream	76	<1	2	2	2	6	11	1	–
eye pencil	52	<1	4	<1	4	8	29	2	–
brow pencil	67	<1	2	3	2	6	20	1	–
eye cosm. remover	57	<1	2	2	3	8	28	1	–
facial cream/lotion	7	<1	1	1	1	3	61	25	–
facial powder	75	1	3	3	2	5	10	1	–
rouge	34	1	6	5	5	13	34	2	–
facial tonic/milk	24	<1	1	2	2	7	53	12	–
liquid makeup	47	<1	6	7	7	9	23	1	–
facial mask	22	2	44	18	10	4	<1	–	–
camouflage stick	83	1	4	4	2	2	5	1	<1
makeup remover	49	<1	1	2	3	5	37	3	–
lipstick	14	<1	4	3	5	14	33	21	5
soap	13	<1	<1	1	2	7	44	23	9
body powder	85	<1	4	2	2	4	3	–	–
bath/shower foam	26	–	2	4	11	35	21	2	–
bath oil	63	1	7	7	9	11	3	–	–
bath salt	84	2	4	3	4	3	1	–	–
body lotion	21	<1	7	7	12	25	26	2	<1
hand lotion/cream	27	1	6	4	4	15	26	13	6
perfume	9	<1	4	4	7	21	47	8	<1

Appendix 1 (continued)

COSMETIC CATEGORY	FREQUENCY OF USE (SEE BELOW)								
depilatory cream	67	2	21	8	2	–	–	–	–
nail lacquer	32	1	20	16	16	12	2	–	–
nail lacquer remover	33	1	20	16	16	13	1	–	–
nail hardener	86	2	3	3	2	3	<1	<1	–
artificial nail	96	3	<1	<1	–	<1	–	–	–
foot powder	89	1	2	2	2	4	1	<1	–

0 means: this product is not used
1 means: this product has been used once
2 means: this product is used once/month or less
3 means: this product is used once/week to once/month
4 means: this product is used about once a week
5 means: this product is used several times per week
6 means: this product is used once daily
7 means: this product is used 2-3 times daily
8 means: this product is used more than 3 times daily

* non-responders are women who did NOT claim cosmetic-related adverse reactions

Appendix 2 Results of patch testing 81 cosmetic-allergic patients with all ingredients of suspected cosmetic products.
Allergens; Patch test concentrations & vehicles; Number of patients tested; Number of positive reactions (Chapter 3.4)

Ingredient/allergen	Test Vehicle *	Test Conc.	Number Tested	Number Positive
Acetone	undil.		9	
Acetylated lanolin	undil.		1	1
Acetyl cedrene	pet	5	16	
Acetyl hexamethyl tetralin	pet	4	6	
Acronal	pet	1	9	
AETT (Versalide)	pet	4	1	
Alanine	aqua	2	1	
Alcohol	undil.		5	
Aldehyde C-10	pet	10	2	
Aldehyde C-12 lauric	pet	5	1	
Aldioxa	pet	1	12	
Allantoin	pet	5	8	
Aloe extract	aqua	10	1	
Alumina (CI 77002)	pet	2	2	
Aluminum stearate	pet	5	2	
Aluminum tristearate	pet	5	1	
Amandel oil	undil.		1	
Aminoethyl propanediol oleate	aqua	5	1	
Aminoethyl propanediol stearate	aqua	5	1	
Amyl cinnamate	pet	8	1	
Amylcinnamic aldehyde α-	pet	5	22	1
Amyl salicylate	pet	2	3	
Anethole	pet	5	3	
Anisic aldehyde	pet	5	15	
Arginine	pet	2	1	
Arnica extract	alc	10 & undil.	1	1
Ascorbyl palmitate	pet	10	1	
Avocado oil	undil.		2	1 $
Balm mint extract	aqua	10	1	
Beeswax	pet	30	2	
Bentonite	aqua	5	1	
Benzaldehyde	pet	5	2	
Benzophenone-1	pet	1	1	
Benzophenone-3	pet	2	1	

Appendix 2 (continued)

Ingredient/allergen		Test Vehicle *	Test Conc.		Number Tested	Number Positive
Benzophenone-6		pet	2		1	
Benzophenone-11		pet	2		1	
Benzoxonium chloride		aqua	0.02		1	1 $
Benzyl acetate		pet	5		28	
Benzyl alcohol		pet	5		13	
Benzyl benzoate		pet	5		15	
Benzyl cinnamate		pet	5		2	
Benzylformal		aqua	3		1	
Benzyl salicylate		pet	2		16	
Bergamot oil		pet	2		1	
BHA (Butylated hydroxyanisole)		pet	5		5	
BHT (Butylated hydroxytoluene)		pet	2		4	
Bisabolol		pet	5		2	
Bismuth oxychloride		undil.			2	
Bromo-2-nitropropane-1,3-diol 2-		pet	0.5		4	1
Butyl acetate		pet	5		2	
Butyl alcohol		alc	10	&		
			undil.		9	
Butylene glycol		aqua	10		2	
Butyl hydroquinone *t*-		pet	1		2	1
Butyl methoxydibenzoylmethane		pet	2		2	1 $
Butylparaben		pet	5		9	
Calcium carbonate		pet	2		2	
Calcium pantothenate		aqua	5		1	
Calendula extract		alc	10		1	1
Camphene		pet	4		3	
Camphor		pet	10		12	
Candelilla wax		mo	40		1	
Caprylic/capric triglyceride		undil.			4	
Captan		pet	0.1		1	
Carbomer 934		undil.			2	
Carbomer 940		undil.			4	
Carbomer 941		undil.			1	
Carnauba wax		mo	50		1	
Carob oil		pet	20		1	
Caryophyllene		pet	5		14	
Castor oil	#	undil.			3	
Cedryl acetate		pet	5		9	

Appendix 2 (continued)

Ingredient/allergen	Test Vehicle *	Test Conc.	Number Tested	Number Positive
Celestolide	pet	4	5	
Ceresin	pet	30	1	
Ceteareth-5 phosphate	pet	5	1	
Ceteareth-10	pet	5	1	
Ceteareth-12	pet	20	2	
Ceteareth-20	pet	20	5	
Ceteareth-30	pet	20	1	
Cetearyl alcohol	pet	20	6	
Cetearyl octanoate	pet	20	3	
Cetrimonium bromide	aqua	0.05	1	
Cetyl alcohol	pet	30	21	
Cetyl palmitate	pet	5	5	
Cetyl phosphate	aqua	1	1	
Chlorhexidine diacetate	aqua	1	1	
Chlorhexidine dihydrochloride	aqua	1	1	
Cholesterol	pet	10	1	
CI 11920 (Solvent Orange 1)	pet	2	2	
CI 12480 (Pigment Brown 1)	pet	2	1	
CI 12490 (Pigment Red 5)	pet	2	1	
CI 14720 (Acid Red 14)	pet	2	2	
CI 15525 (Pigment Red 68)	pet	2	1	
CI 15865 (Pigment Red 48)	pet	2	1	
CI 15984	aqua	1	1	
CI 16185 (Amaranth)	aqua	2	1	
CI 16290 (Ponceau Red R 6)	pet	2	1	
CI 28440 (Food Black 1)	pet	2	1	
CI 42045 (Food Blue 3)	pet	2	1	
CI 42051 (Acid Blue 3)	pet	2	2	
CI 45190	pet	2	1	
CI 77005	pet	2	2	
Cinnamal	pet	1	2	
Cinnamic alcohol	pet	5	8	2
Citral	pet	2	8	
Citric acid	aqua	1	6	
Citronellol	pet	2	42	2
Citronellyl acetate	pet	4	3	
Cocamide DEA	aqua	0.5	2	2 $

Appendix 2 (continued)

Ingredient/allergen		Test Vehicle *	Test Conc.	Number Tested	Number Positive
Cocamidopropyl betaine		aqua	0.1	3	
	#	aqua	1	4	3
Coconut oil		undil.		1	
Cornflower extract		aqua	20	3	
Corn oil		pet	30	1	
Coumarin		pet	5	12	1
Cucumber extract		aqua	10	2	
Cuminaldehyde		pet	4	1	
Cyclamen aldehyde		pet	2	4	
Cyclomethicone		undil.	2	1 $	
Cymene *p*-		pet	4	2	
D&C Green no.6 (CI 61565)		pet	2	1	
D&C Red no.21 (CI 45480:2)		pet	2	1	
D&C Red no.34 (CI 15880:1)		pet	2	2	
D&C Yellow no.11 (CI 47000)		mo	0.016	1	
DEA-cetyl phosphate		aqua	2	2	
Decyl oleate		pet	10	4	
Dextrin		aqua	10	2	
Diazolidinyl urea		pet	2	3	3 $
Dibutyl phthalate		pet	5	2	
Diethyl phthalate		pet	5	29	
Dimethicone		pet	10	22	
Dimethyl phthalate		pet	5	1	
Disodium phosphate		aqua	1	1	
DMDM hydantoin		pet	1	1	
EDTA		pet	1	5	
Epigran		aqua	5	1	
Escin		pet	1	2	
Ethoxydiglycol		pet	10	5	
Ethoxylated castor oil		pet	10	1	
Ethyl acetate		pet	10	10	
Ethyl anthranilate		pet	4	1	
Ethyl carbonate		alc	2	1	
Ethylene brassylate		pet	5	1	
Ethylparaben		pet	5	4	
Ethyl vanillin		pet	2	3	
Eucalyptol		pet	5	7	
Eugenol		pet	5	13	4

Appendix 2 (continued)

Ingredient/allergen	Test Vehicle *	Test Conc.	Number Tested	Number Positive
FD&C Blue no.1 (CI 42090)	pet	2	5	
FD&C Red no.3 (CI 45430)	pet	2	1	
FD&C Yellow no.5 (CI 19140)	pet	2	3	
FD&C Yellow no.6 (CI 15985)	pet	2	2	
Formaldehyde	aqua	1	12	1
Fructose	aqua	10	1	
Galoxolide	pet	10	11	
Geranial	pet	1	1	
Geraniol	pet	5	23	2
Geranyl acetate	pet	4	9	
Glucose	aqua	10	1	
Glutamic acid	aqua	5	2	
Glycerin	aqua	10	12	
Glyceryl isostearate	pet	30	1	
Glyceryl oleate	pet	30	1	
Glyceryl ricinoleate	pet	30	1	
Glyceryl stearate	pet	20	23	
Glyceryl stearate + PEG-100	pet	20	1	
Glyceryl tribehenate	pet	30	1	
Glycol distearate	mo	50	1	
Heliotropin	pet	4	26	
Hexenyl salicylate *cis*-3-	pet	3	5	
Hexylcinnamic aldehyde	pet	5	19	1
Hexyl salicylate	pet	3	3	
Hybrid safflower oil	pet	30	1	
Hydrochlorofluorocarbon 113	undil.		2	
Hydrogenated coconut oil	pet	30	1	
Hydrogenated lanolin	pet	30	1	
Hydrogenated tallow glyceride citrate	pet	30	1	
Hydrogenated vegetable oil	pet	30	1	
Hydrolyzed animal protein	aqua	50	2	
Hydrolyzed elastine	undil.		1	
Hydroxycitronellal	pet	2	24	4
Hydroxycitronellol	pet	10	1	
Hydroxyethylcellulose	aqua	10	1	
Hydroxypropyl guar	pet	20	12	
Hydroxypropyl methylcellulose	aqua	5	1	
Imidazolidinyl urea	aqua	2	6	2

Appendix 2 (continued)

Ingredient/allergen		Test Vehicle *	Test Conc.	Number Tested	Number Positive
Ionone		pet	5	4	
Iron oxides		pet	2	4	
Isoamyl acetate		pet	10	9	
Isoamyl salicylate		pet	2	4	
Isobornyl acetate		pet	5	3	
Isocetyl alcohol		pet	10	1	
Isoeugenol		pet	3	9	2
Isopropyl alcohol		aqua	10	3	
Isopropyl-dibenzoylmethane 4-		pet	5	2	2 $
Isopropyl isostearate		pet	5	1	
Isopropyl lanolate		pet	20	3	
Isopropyl myristate		pet	10	5	
Isopropyl palmitate		pet	5	4	
Isostearoyl hydrolyzed animal protein		pet	10	2	
Jojoba oil		pet	20	1	
Kaolin		pet	5	1	
Lactic acid		aqua	3	1	
Lanolin		undil.		5	1
Lanolin alcohol		pet	30	7	
Lanolin oil		pet	30	2	1
Lauramide DEA		pet	1	1	1 $
Lauric acid		pet	5	1	
Lauroamphoglycinate		aqua	1	1	
Lauryl betaine	#	aqua	1	1	
Lauryl octanoate		pet	30	1	
Laurylpyridinium chloride		aqua	0.1	1	1
Lilial		pet	1	15	
Limonene		pet	2	31	
Linalool		pet	10	34	1
Linalyl acetate		pet	3	25	1
Linden extract		alc	20	1	
Lyral		pet	2	24	1
Magnesium aluminum silicate		aqua	5	1	
Magnesium stearate		undil.		1	
Magnesium sulfate		aqua	1	1	
Malic acid		aqua	1	1	
MEA-lauryl sulfate	#	aqua	0.5	1	
Menthol		pet	5	3	

Appendix 2 (continued)

Ingredient/allergen	Test Vehicle *	Test Conc.	Number Tested	Number Positive
Methyl anthranilate	pet	5	3	
Methyl benzoate	pet	3	1	
Methylbenzylidene)-camphor 3-(4-	pet	2	2	2 $
Methyl(chloro)isothiazolinone	aqua	100 ppm	22	10
Methyl cinnamate	pet	10	1	
Methyl eugenol	pet	5	2	
Methyl heptine carbonate	pet	0.5	1	
Methylionone γ-	pet	5	28	1
Methylolchloroacetamide *N*-	pet	0.2	1	
Methylparaben	pet	5	14	
Mica	pet	5	3	
Mineral oil	undil.		33	1
Mink oil	pet	30	1	
Musk ambrette	pet	5	8	
Musk ketone	pet	5	13	
Myristalkonium chloride	aqua	0.05	1	
Myristyl alcohol	pet	5	2	2
Neral	pet	1	1	
Nerolidol	pet	4	3	
Nitrocellulose	aqua	10	10	
Nopyl acetate	pet	5	4	
Octyldodecanol	pet	20	4	
Octyl gallate	pet	0.1	2	1
Octyl methoxycinnamate	pet	2	4	
Octyl stearate	pet	20	1	
Oleamidopropyl dimethylamine	aqua	0.4	12	11 $
Olive oil	undil.		1	
Orange extract	alc	10	1	
Ozokerite	undil.		4	
Palm kernel oil	pet	30	1	
Panthenol	pet	30	1	
Paraffin	undil.		11	
PEG-6	pet	20	2	
PEG-8	aqua	10	4	
PEG-32	undil.		1	
PEG-40 hydrogenated castor oil	pet	30	2	
PEG-60 hydrogenated castor oil	pet	30	1	
PEG-2 laurate	pet	30	1	

Appendix 2 (continued)

Ingredient/allergen	Test Vehicle *	Test Conc.	Number Tested	Number Positive
PEG-2 stearate	pet	20	3	
PEG-9 stearate	pet	20	1	
PEG-32 stearate	pet	20	9	1 $
PEG-40 stearate	aqua	20	1	
PEG-100 stearate	aqua	10	1	
Pelargol	pet	5	4	1
Pentaerythritol monooleate	pet	5	1	
Petrolatum	undil.		10	
Phantolide	pet	4	1	
Phenoxyethanol	pet	5	6	
Phenoxyethyl isobutyrate	pet	4	1	
Phenoxyethylparaben	pet	5	1	
Phenylacetaldehyde	pet	2	1	
Phenylbenzimidazole 5-sulfonic acid 2-	pet	2	1	
Phenylethyl acetate	pet	5	6	
Phenylethyl alcohol	pet	5	43	
Phenyl trimethicone	pet	10	1	
Phosphoric acid	aqua	0.5	13	
Pinene α-	pet	5	12	
Pinene β-	pet	5	21	
Pine oil	pet	5	1	
Plankton extract	mo	10	1	
Polyglyceryl-3 stearate	pet	20	1	
Polyquaternium-10	aqua	0.05	1	
Polysorbate 60	aqua	5	1	
Polysorbate 80	aqua	5	3	
Potassium sorbate	aqua	2	2	
Potato starch	undil.		1	
Propolis	alc	20	1	1
Propylene carbonate #	aqua	10	3	
Propylene glycol	aqua	1-10	20	
Propyl gallate	pet	5	1	
Propylparaben	pet	5	13	1
PVP	undil.		4	
PVP/Hexadecene copolymer	undil.		1	1 $
PVP/VA copolymer	undil.		1	
Quaternium-15	pet	1	4	2
Quaternium-18 hectorite	undil.		1	

Appendix 2 (continued)

Ingredient/allergen		Test Vehicle *	Test Conc.	Number Tested	Number Positive
Retinyl palmitate		undil.		2	
Rice starch		undil.		1	
Rosemary extract		alc	10	1	
Rose water		undil.		1	
Rosin (Colophony)		alc	20	1	1
Selenium sulfide		pet	2	1	1
Senecioic acid ester		ao	3	1	
Shea butter		mo	30	2	
Silica		undil.		1	
Simethicone		pet	5	2	
Sodium cetearyl sulfate		aqua	0.2	1	
	#	aqua	1	1	
Sodium chloride		aqua	0.9	5	
Sodium citrate		aqua	1	2	
Sodium dehydroacetate		aqua	3	4	
Sodium laureth sulfate		aqua	0.1-1	3	
Sodium lauryl sulfate	#	aqua	0.1	2	
Sodium PCA		aqua	2	2	1 $
Sodium phosphate		aqua	2	1	
Sodium saccharin		aqua	10	1	
Sodium stearate		aqua	1	1	
Soluble collagen		aqua	10	1	
Sorbitan sesquioleate		oo	5	2	
Sorbitan stearate		pet	5	4	
Sorbitol		aqua	10	5	
Soybean oil		undil.		1	
Soy sterol		pet	20	1	
Squalane		pet	20	12	
Stearalkonium chloride		aqua	0.05	2	
Stearalkonium hectorite		aqua	1	1	
Stearamide MEA		pet	1	1	
Stearic acid		pet	5	14	1
Steartrimonium hydrolyzed animal protein		aqua	0.05	1	
Stearyl acid phosphate		pet	1	1	
Stearyl alcohol		pet	30	2	
Stearyl heptanoate		pet	20	1	
Sucrose		aqua	10	1	

Appendix 2 (continued)

Ingredient/allergen	Test Vehicle *	Test Conc.	Number Tested	Number Positive
Sulfur	pet	1	1	
Synthetic beeswax	pet	30	3	
Synthetic wax	mo	50	1	
Talc	undil.		1	
Tartaric acid	aqua	1	1	
TEA-lauryl sulfate	aqua	0.1	1	
Terpineol	pet	5	28	
Terpinyl acetate	pet	5	8	
Tetrasodium EDTA	pet	1	4	
Titanium dioxide	undil.		4	
Tocopherol	pet	10	2	
Tocopheryl acetate	pet	10	1	
Toluene	pet	50	1	
Toluenesulfonamide/formaldehyde resin	pet	10	10	9
Traseolide	pet	5	2	
Triclosan	pet	1	4	
Triethanolamine	pet	3	16	
Trilaurin	pet	30	4	
Tyrosine	pet	2	1	
Ultramarine blue	pet	2	4	
Undecylenoyl PEG-5 paraben	pet	5	1	
Urea	aqua	10	4	
Vanillin	pet	10	5	
Vertenex	pet	4	5	
Wheat germ oil	pet	20	1	
Witch hazel extract	aqua	20	1	
Yeast extract	aqua	10	1	
Zinc pyrithione	pet	2	1	1

* pet = petrolatum oo = olive oil
alc = ethyl alcohol 70% ao = almond oil
mo = mineral oil undil. = undiluted

\# test concentration may be slightly irritant
$ 20 controls were negative

Appendix 3 The European standard series

Compound		Conc. % w/w	Vehicle
Potassium dichromate		0.5	pet
p-Phenylenediamine dihydrochloride		0.5	pet
Thiuram mix		1	pet
-tetramethylthiuram monosulfide	(TMTM)	0.25	pet
-tetramethylthiuram disulfide	(TMTD)	0.25	pet
-tetraethylthiuram disulfide	(TETD)	0.25	pet
-dipentamethylenethiuram disulfide	(PTD)	0.25	pet
Neomycin sulfate		20	pet
Cobalt chloride		1	pet
Benzocaine		5	pet
Nickel sulfate		5	pet
Quinoline mix		6	pet
-clioquinol		3	pet
-chlorquinaldol		3	pet
Colophony (Rosin)		60	pet
Parabens		15	pet
-methylparaben		3	pet
-ethylparaben		3	pet
-propylparaben		3	pet
-butylparaben		3	pet
-benzylparaben		3	pet
Black rubber mix		0.6	pet
-*N*-isopropyl-*N*-phenyl-*p*-phenylenediamine		0.1	pet
-*N*-cyclohexyl-*N*-phenyl-*p*-phenylenediamine		0.25	pet
-*N*',*N*-diphenyl-*p*-phenylenediamine		0.25	pet
Wool alcohols		30	pet
Mercapto mix		2	pet
-*N*-cyclohexylbenzothiazylsulfenamide	(CBS)	0.5	pet
-mercaptobenzothiazole	(MBT)	0.5	pet
-dibenzothiazyl disulfide	(MBTS)	0.5	pet
-morpholinylmercaptobenzothiazole	(MOR)	0.5	pet
Epoxy resin		1	pet
Balsam Peru		25	pet
p-tert-Butylphenolformaldehyde resin		1	pet
Carba mix		3	pet
-1,3-diphenylguanidine	(DPG)	1	pet
-zinc diethyldithiocarbamate	(ZDC)	1	pet
-zinc dibutyldithiocarbamate	(ZBC)	1	pet
Formaldehyde		1	aqua

Appendix 3 (continued)

Compound	Conc. % w/w	Vehicle
Fragrance mix	8	pet
-cinnamic alcohol	1	pet
-cinnamic aldehyde	1	pet
-eugenol	1	pet
-hydroxycitronellal	1	pet
-α-amylcinnamic aldehyde	1	pet
-geraniol	1	pet
-isoeugenol	1	pet
-oak moss absolute	1	pet
Ethylenediamine dihydrochloride	1	pet
Quaternium-15	1	pet
Primin	0.01	pet

Index of chemicals

Samenvatting, conclusies, aanbevelingen

SAMENVATTING EN CONCLUSIES

In dit proefschrift worden de resultaten van een aantal studies gepresenteerd, die als doel hebben: (i) het voorkomen van bijwerkingen van cosmetica en toiletartikelen; (ii) de (kwantitatieve) rol van contactallergie hierbij; en (iii) de aard van de oorzakelijke allergenen, te onderzoeken.

Hoofdstuk 1 geeft een algemene inleiding op het gebied van cosmetica. Gegevens worden gepresenteerd over het gebruik (kwantitatief) van cosmetica en toiletartikelen; over de meest toegepaste bestanddelen; en over het spectrum van gepubliceerde bijwerkingen. Enkele belangrijke aspekten van de cosmetica wetgeving in de EEG worden samengevat.

In *Hoofdstuk 2* worden de resultaten van 2 epidemiologische studies naar de aard en de frequentie van bijwerkingen van cosmetische produkten gepresenteerd. Tevens worden de gegevens van 2 andere onderzoekingen, waarin geselecteerde groepen van dermatologische patiënten epicutaan werden getest met conserveermiddelen en parfumgrondstoffen, belicht. Het doel hiervan was de frequentie van contactallergie voor deze cosmetica ingredienten vast te stellen, en om allergenen te identificeren die in aanmerking komen om aan een " cosmeticum-reeks" toegevoegd te worden.

A (Hoofdstuk 2.3). Een groep van 1609 personen van 33-64 jaar werd ondervraagd over het optreden van bijwerkingen van cosmetica en toiletartikelen. 196 (12,2%) van hen gaven aan in de voorafgaande 5 jaren zo'n bijwerking te hebben ondervonden. Vrouwen schreven de meeste reakties toe aan zeep, gelaatscreme, deodorant, shampoo en oogschaduw. Bij mannen stond zeep ook op de eerste plaats, gevolgd door aftershave, deodorant en badschuim. De meeste reakties waren gelokaliseerd in het gelaat, op de handen en onder de oksels. Het merendeel van de patiënten (63%) loste het probleem op door het gebruik van de verdachte produkten te staken, en een ander merk te gebruiken. De conclusies van deze studie en literatuurgegevens zijn:

- Bijwerkingen van cosmetica en toiletartikelen zijn niet zeldzaam; in een periode van 1-5 jaar kunnen deze optreden bij 10% van de volwassen bevolking.

- De meeste bijwerkingen zijn mild van aard; niettemin raadpleegde 30% van de patiënten in deze studie de huisarts.
- Produkten die bij vrouwen de meeste reakties veroorzaken zijn: zeep, deodorant, (gelaats)cremes, shampoo, oogcosmetica en badschuim. Bij mannen zijn dit: zeep, aftershave, deodorant en doucheschuim.
- Vrouwen rapporteren bijna tweemaal zovaak bijwerkingen als mannen; dit verschil wordt grotendeels veroorzaakt door cosmetica die op het gelaat worden aangebracht.
- Het meerendeel der bijwerkingen wordt veroorzaakt door orthoergische invloeden (irritatie).
- Personen met een atopische aanleg hebben wellicht een verhoogde kans op het ontwikkelen van bijwerkingen door cosmetica en toiletartikelen t.g.v. irritatie.

B (Hoofdstuk 2.4). Een groep van 982 vaste cliënten van schoonheidsspecialistes werd ondervraagd over het optreden van bijwerkingen van cosmetica en toiletartikelen. 245 (26%) van hen gaven aan in de voorafgaande 5 jaren zo'n bijwerking te hebben ondervonden. De meeste reakties waren veroorzaakt door huidverzorgingsprodukten, produkten voor de hygiëne (zeep, shampoo, badschuim etc.), oogcosmetica, deodorant/antitranspiratiemiddel, en gelaatsmakeup. Met als doel de kwantitatieve rol van contactallergie vast te stellen werden 150 van deze vrouwen epicutaan getest met de Europese standaardreeks en een reeks van 15 cosmetica allergenen. In de standaardreeks werden slecht enkele positieve reakties gezien op allergenen die in cosmetische produkten kunnen voorkomen: parfummengsel (3), wolalcoholen (3), formaldehyde (2), Perubalsem (1) en colofonium (1). In de cosmeticum-reeks werden slechts 3 reakties gezien, allen op Kathon CG. De diagnose "cosmeticum-allergie" werd gesteld bij 3 patiënten (2%), terwijl deze diagnose bij 7 (5%) als "mogelijk" werd beschouwd. De conclusies van dit onderzoek zijn:
- Minder dan 10% van de bijwerkingen van cosmetica en toiletartikelen wordt veroorzaakt door contactallergie. Het meerendeel der reakties is het gevolg van irritatie door produkten voor de hygiëne zoals zeep, shampoo, badschuim en door deodorant.
- Irritatie van cosmetica en toiletartikelen kan zich manifesteren als verergering van preëxistente huidziekten zoals seborrhoisch eczeem en acne.
- Personen met een atopische aanleg hebben een verhoogd risico op het ontwikkelen van bijwerkingen door cosmetische produkten ten gevolge van irritatie.

C (Hoofdstuk 2.5). 179 patiënten verdacht van cosmeticum-allergie werden epicutaan getest met een reeks van 16 parfumgrondstoffen en 9 conserveermiddelen. Bij 67 (37%) van hen werden een of meer positieve reakties

gezien. Bij de parfumgrondstoffen werden de meeste reakties gezien op isoeugenol, oakmoss, geraniol, α-amylcinnamicalcohol, en een mengsel van α-hexylcinnamic aldehyde en α-amylcinnamic aldehyde. Het parfummengsel in de Europese standaardreeks detecteerde bijna 80% van de gevallen van contactallergie voor niet in het mengsel aanwezige parfumgrondstoffen.
In de groep van conserveermiddelen scoorden Kathon CG en quaternium-15 het hoogste aantal positieve reakties.
De conclusies van deze studie zijn:
- Kathon CG en quaternium-15 zijn wellicht belangrijke allergenen in cosmetica; nader onderzoek is van belang.
- Het parfum-mengsel in de Europese standaardreeks detecteert meer dan 80% van alle gevallen van parfum-allergie.
- De veelal gebruikte testconcentraties van 2% voor oakmoss, geraniol en isoeugenol zijn te laag om alle gevallen van contactallergie hiervoor aan te tonen. Deze stoffen dienen apart in een hogere concentratie getest te worden bij verdenking op allergie voor parfumgrondstoffen.

D (Hoofdstuk 2.6). Twee groepen van 627 en 501 patienten die verdacht werden van contactallergie werden getest met reeksen van conserveermiddelen. Benzoëzuur, benzalkoniumchloride, DMDM hydantoin, Kathon CG en alkyltrimethylammoniumchloride scoorden meer dan 1% positieve reakties. De testconcentraties van benzoëzuur, benzalkoniumchloride en alkyltrimethylammoniumchloride waren marginaal irriterend, zodat een aantal "positieve" reacties mogelijk toxisch (fout- positief) waren geweest. De reakties op de formaldehyde-donor DMDM hydantoin waren het gevolg van allergie voor formaldehyde. De conclusie van deze studie is dat Kathon CG een plaats verdient in een "cosmeticum screening-reeks".

Hoofdstuk 3 beschrijft de resultaten van een retrospectief en van een prospectief onderzoek naar de allergenen in cosmetica. Er wordt een samenvatting gegeven van door de auteur gepubliceerde gevallen van cosmeticumallergie door zelden of niet eerder beschreven contactallergenen (Hoofdstuk 3.5).

A Retrospectief onderzoek (Hoofdstuk 3.3). Tussen 1981 en 1985 werden 49 patiënten met cosmeticumallergie onderzocht. Dit aantal was 0.3% van het totaal aantal nieuwe patiënten, en 3.5% van de patiënten die wegens verdenking op contactallergie epicutaan waren getest. Het gelaat was het meest frequent aangedaan. Bijna de helft van alle verantwoordelijke cosmetica (45%) waren huidverzorgingsprodukten. Daarna volgden haarcosmetica (10%), scheerprodukten (10%) en nagelcosmetica (8%). 20 van de patiënten werden getest met alle bestanddelen van de verdachte produkten. Bij 22 andere patiënten kon de aard van de oorzakelijke allergenen

met hoge mate van waarschijnlijkheid worden vastgesteld aan de hand van de resultaten van het testen met de Europese standaardreeks en/of additioneel geteste cosmetica-allergenen. In totaal werden 21 (groepen van) cosmeticumingrediënten geidentificeerd als allergenen. Parfums (-grondstoffen) veroorzaakten 55% van alle reakties. Conserveermiddelen/ antimicrobiële stoffen waren verantwoordelijk voor 20% van de allergische reakties. In deze categorie werden de meeste reakties veroorzaakt door Kathon CG. 8% van de cosmeticum-allergieën was veroorzaakt door de emulgator oleamidopropyldimethylamine. De conclusie van dit onderzoek is dat parfumgrondstoffen en conserveermiddelen de belangrijkste oorzaken zijn van cosmeticumallergie in Nederland tot 1985.

B Prospectief onderzoek (Hoofdstuk 3.4). In een periode van 17 maanden (1986-1987) werden 119 patiënten met cosmeticum-allergie onderzocht. Dit aantal was 0.6% van alle nieuwe patiënten, en 5.8% van de patiënten die wegens verdenking op contactallergie door de auteur epicutaan waren getest. Het gelaat en de oogleden waren het meest frequent aangedaan. Meer dan de helft van alle reakties (56%) was veroorzaakt door huidverzorgingsprodukten. Daarna volgden nagelcosmetica (13%), parfums (8%), haarcosmetica (6%), deodorantia (5%) en cosmetica voor de lippen (4%). 81 patienten werden getest met alle, en 38 met een of meer bestanddelen van de verdachte cosmetische producten. In totaal werden 53 cosmeticumallergenen geidentificeerd.
Verreweg het belangrijkste contactallergeen was Kathon CG, dat verantwoordelijk was voor de allergie bij 33 patiënten (28%). Daarop volgden tolueensulfonamide/formaldehyde hars (15 patiënten, 13%) en oleamidopropyldimethylamine (13 patiënten, 11%). Bij 15 patiënten was de cosmeticumallergie veroorzaakt door de (niet nader gespecificeerde) parfumfraktie. De conclusie van deze studie is dat conserveermiddelen, parfumgrondstoffen en emulgatoren de belangrijkste groepen van voor cosmeticumallergie verantwoordelijke bestanddelen zijn in Nederland. De belangrijkste allergenen zijn Kathon CG, tolueensulfonamide/formaldehyde hars en oleamidopropyldimethylamine.

In *Hoofdstuk 4* wordt de rol van Kathon CG bij cosmeticum- allergie toegelicht. In 1986 werd Kathon CG 100 ppm in water door de leden van de Commissie Contactdermatosen aan de routinereeks toegevoegd, met als doel de prevalentie van allergie voor het conserveermiddel te bepalen. 3114 patiënten verdacht van contactallergie werden getest. 155 van hen (5,0%) hadden een positieve reaktie op Kathon CG; bij 109 (3,5%) was deze reaktie relevant voor de klachten van de patiënt. Bij een onderzoek naar de aanwezigheid van Kathon CG in cosmetica, bleken 59 (23%) van de 253 onderzochte produkten met dit middel geconserveerd. De conclusie van de studies, in dit hoofdstuk besproken, is dat de aanwezigheid van

Kathon CG in een hoeveelheid van 7 ppm aktieve ingrediënten of meer in cosmetische produkten die op de huid blijven ("stay-on products") een duidelijk risico in zich bergt op contactallergische reakties. Geadviseerd wordt om Kathon CG aan de Europese standaardreeks toe te voegen.

In *Hoofdstuk 5* wordt beschreven dat oleamidopropyldimethylamine een belangrijke oorzaak is van cosmeticumallergie in Nederland. Alle gevallen van allergie voor deze cationische emulgator waren veroorzaakt door één merk baby body lotion, dat 0,3% oleamidopropyldimethylamine bevat. De klinische gegevens van 12 patiënten allergisch voor de emulgator worden besproken. De meeste patiënten (allen vrouwen) hadden de baby body lotion al jaren gebruikt, zowel als "vochtinbrengende creme" alsook voor het verwijderen van gelaats- en oogmakeup. Bij 10 patiënten (83%) was het eczeem, veroorzaakt door de baby body lotion, gelocaliseerd op het gelaat, m.n. rond de ogen. Berekend werd dat per jaar 1 op de 700-1000 personen door het gebruik van de baby body lotion allergisch wordt voor oleamidopropyldimethylamine. In een ander onderzoek werden 13 patiënten, bekend met allergie voor oleamidopropyldimethylamine epicutaan getest met een reeks van verwante emulgatoren van het amide-amine type. Bij één patiënte werd geen enkele reaktie gezien op deze stoffen, maar de overige 12 hadden tenminste 4 reakties op de verwante allergenen. De meeste reakties werden geconstateerd op ricinoleamidopropyldimethylaminelactaat en tallowamidopropyldimethylamine (11 patiënten, 85%); daarna volgden lauramidopropyldimethylamine met positieve reakties bij 9 van 12 geteste patiënten (75%), en myristamidopropyl dimethylamine bij 6 patiënten (46%).

AANBEVELINGEN

De resultaten van de studies die in dit proefschrift beschreven worden hebben een aantal praktische implicaties voor de fabrikant van cosmetica en voor de dermatoloog:

1. Het merendeel der bijwerkingen van cosmetica en toiletartikelen berust op irritatie. Derhalve verdient het onderzoek naar de irritatiepotentiaal van cosmeticabestanddelen en cosmetische produkten (nog) meer aandacht. Aangezien atopici een verhoogd risico hebben op het ontwikkelen van bijwerkingen door cosmetica t.g.v. irritatie, verdient het aanbeveling om in een testpanel voor nieuwe produkten veel atopici op te nemen.
2. Het verdient aanbeveling om Kathon CG niet toe te passen in "stay-on" produkten in een concentratie van 7 ppm aktieve ingrediënten of hoger. Nader onderzoek dient gericht te zijn op de antimicrobiële aktiviteit van lagere concentraties van dit conserveermiddel, en op de invloed van concentratieverlaging op de allergiepotentiaal. Combinaties

van lagere concentraties Kathon CG en andere conserveermiddelen dienen onderzocht te worden. Het conserveren van produkten die niet op de huid blijven ("rinse-off products") met Kathon CG in een concentratie van 5 ppm of lager kan gecontinueerd worden, omdat dit geen onacceptabel risico op sensibilisatie in zich bergt.

3. Het verdient aanbeveling om oleamidopropyldimethylamine niet in stay-on producten in een concentratie van 0,3% of hoger toe te passen, vooral niet wanneer deze op beschadigde huid of rond de ogen geappliceerd kunnen worden. De allergiepotentiaal van verwante emulgatoren van het amide-amine type dient nauwkeurig onderzocht te worden, alvorens deze toe te passen in stay-on cosmetica.
4. Ofschoon de risico-*index* waarschijnlijk laag is, is het nagellak bestanddeel tolueensulfonamide/formaldehyde hars een belangrijke oorzaak van allergie voor cosmetica. Onderzoek op dit terrein dient gericht te zijn op de ontwikkeling van harsen van dezelfde kwaliteit, maar met een lagere allergiepotentiaal. De aanwezigheid van formaldehyde in nagelverharders die tolueensulfonamide/ formaldehyde hars bevatten verhoogt mogelijk de kans op sensibilisatie voor de hars.
5. Het verdient aanbeveling om Kathon CG in een concentratie van 100 ppm in water op te nemen in de standaardreeks van allergenen die als routine getest wordt bij patiënten die verdacht worden van contactallergie.
6. Een reeks van allergenen die als routine getest wordt bij verdenking op cosmeticumallergie kan als volgt worden samengesteld (aan te passen aan lokale omstandigheden):

2-Broom-2-nitropropaan-1,3-diol (conserveermiddel)	0,25% in petrolatum
Chlooracetamide (conserveermiddel)	0,2% in petrolatum
Diazolidinylureum (conserveermiddel)	2% in water
Eugenol (parfumgrondstof)	5% in petrolatum
Glycerylthioglycollaat (permanent) *	2,5% in petrolatum
Hydroxycitronellal (parfumgrondstof)	4% in petrolatum
Imidazolidinylureum (conserveermiddel)	2% in petrolatum
4-Isopropyldibenzoylmethaan (UV-filter)	2% in petrolatum
Kathon CG (conserveermiddel)	100 ppm in water
Oleamidopropyldimethylamine (emulgator) *	0,4% in water
Phenylsalicylaat (UV-filter, smaakstof)	1% in petrolatum
Propolis (moisturiser)	10% in petrolatum
Propyleenglycol (moisturiser) *	5% in water
Tolueensulfonamide/formaldehyde hars (hars)	10% in petrolatum

* cave toxische reakties bij plakproeven

Curriculum vitae

De auteur van dit proefschrift werd geboren op 2 april 1951 te Deventer. Na het behalen van het diploma gymnasium-beta aan het Alexander Hegius Gymnasium te Deventer, ving hij in 1969 aan met de studie geneeskunde aan de Rijksuniversiteit Groningen. Na het behalen van het arts-examen in december 1975 en na het voltooien van de opleiding tot dermatoloog aan de kliniek voor huid- en geslachtsziekten van het Academisch Ziekenhuis Groningen in december 1979, vestigde hij zich als dermatoloog in vrije praktijk in het Carolus en het Willem-Alexander Ziekenhuis te 's-Hertogenbosch. Het onderzoek dat de basis vormt van dit proefschrift werd daar uitgevoerd in de jaren 1984-1987.