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Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Sensitisation caused by exposure to cosmetic products

Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety

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SUMMARY

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has on the request from the Norwegian Food Safety Authority (Mattilsynet) assessed if sensitisation caused by exposure to cosmetic products should be considered as an adverse health effect. The opinion further deals with differences between food products and cosmetics in terms of sensitisation. The task has been assessed by the Scientific Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics (Panel 4).

Contact with allergens in many cosmetic products could lead to sensitisation of consumers and occupational groups, such as hairdressers. Skin sensitisation and subsequent allergic contact dermatitis following use of cosmetic products is mainly type IV reactions (cell-mediated). Type I sensitisation and allergic response (IgE-mediated) predominate in the gut or respiratory system. However, type I and IV sensitisation may occur at all sites. In a recent report from the Norwegian Institute of Public Health it is concluded that adverse reactions caused by the use of cosmetic products could constitute a significant health problem. The adverse reactions are often diagnosed as allergic contact dermatitis.

According to the Cosmetics Directive 76/768/EEC, Article 2, "*a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use"*. It has not been clear whether sensitisation related to cosmetics should be included in the term adverse effect in the same way as toxic effects, such as reproductive effects, carcinogenicity, mutagenicity etc. So far, both the Member States of the European Community and the cosmetic industry have been of the opinion that allergic issues related to the use of cosmetics could be properly dealt with through labelling of the products. A similar situation appears for foods, where accurately labelled food products (e.g. nuts, shellfish) could cause serious health effect for some consumers. However, as there are some basic differences between food allergy and allergic contact dermatitis, it could be questioned whether it is correct to compare cosmetic products and food products when addressing this problem.

According to the terms of reference of the present opinion, the VKM Panel 4 was requested to answer the following two questions:

1) In terms of sensitisation, should cosmetic products be considered differently than food products?

Food allergy is often transient as tolerance develops in the majority of cases, while sensitisation to cosmetics is regarded as permanent. Most food allergens are naturally present in foods which are commonly consumed, and sensitisation will occur in genetically susceptible individuals. On the other hand, individuals who are proven sensitised to a cosmetic ingredient may all, if sufficient doses are applied, react to the chemical in question. Furthermore, it is often difficult for individuals sensitised to cosmetic ingredients to avoid/protect themselves from the sensitising compound due to their extensive use in cosmetics, household products, textiles and the working environment of a variety of occupations, such as hairdressers and health care workers.

Allergic reactions to both food and cosmetics require a sensitisation phase. However, since naturally occurring food allergens are inevitably connected with traditional human nutrition,

they cannot be eliminated from the market. In contrast, cosmetic ingredients, as well as food additives causing allergic reactions may be avoided.

Food allergens naturally present in food should thus be considered differently than cosmetic ingredients.

2) Should sensitisation caused by exposure to cosmetic products be considered as an adverse health effect?

In terms of sensitisation caused by cosmetics, the type IV reactions induced by skin sensitizers are well characterised, and are used as basis for the present consideration. However, the conclusions presented are valid for sensitisation by different routes of exposure and for both type I and type IV reactions.

There is a causal relationship between the topical exposure to a skin sensitizer and the subsequent events of skin sensitisation, elicitation, and the eventual manifestation of clinical allergic contact dermatitis. Importantly, this implies that the risk of evolving allergic contact dermatitis is absent when exposure to the skin sensitizer is avoided or kept below the dose-threshold. Even though it appears to be a threshold dose for sensitisation, this dose depends on a number of host and exposure factors, and there are no generally recognised methods to determine possible threshold doses. Elicitation of allergic responses occurs at considerably lower doses than those causing sensitisation. The capacity of a substance to cause allergic contact dermatitis can be predicted by its capacity to cause skin sensitisation. Allergic contact dermatitis is inevitably connected with the exposure to the skin sensitizer and its intrinsic potential to cause skin sensitisation. In principle, skin sensitisation is not different from other toxicological hazards. Therefore, skin sensitisation is a topic in general toxicological testing and risk assessment of chemicals including ingredients of cosmetics.

Skin sensitisation is a critical and necessary event in the aetiology of allergic contact dermatitis. It represents an acquired and irreversible immunological change, which make the body more susceptible to the skin sensitizer, and which increases the risk of developing allergic contact dermatitis.

In conclusion:

- Allergic responses are considered adverse health effects. Sensitisation is a prerequisite for allergic responses and strongly increases the risk of an allergic response.
- Sensitisation caused by exposure to cosmetic products must therefore be considered as an adverse health effect.

Recommendations:

- In order to significantly reduce the risk of sensitisation to cosmetic ingredients, the exposure to substances with extreme and strong sensitising potency present in cosmetic products should be avoided. Exposure to moderate sensitizers should be minimized.
- Information to the consumer about the content of ingredients is beneficial in order to avoid elicitation of sensitised individuals.
- Quantitative risk assessment methods which may improve the risk characterisation of sensitising cosmetic ingredients should be further developed and validated in terms of both sensitisation and elicitation.

SAMMENDRAG

Vitenskapskomiteen for mattrygghet (VKM) har på oppdrag fra Mattilsynet vurdert om sensibilisering forårsaket av eksponering for kosmetiske produkter skal betraktes som en helseskade. Uttalelsen fra VKM omhandler også forskjeller og likheter mellom sensibilisering forårsaket av kosmetiske produkter og sensibilisering fra mat. Vurderingen er gjennomført av Faggruppen for tilsetningsstoffer, aroma, matemballasje og kosmetikk (Faggruppe 4).

Kontakt med allergener i mange kosmetiske produkter kan føre til at forbrukere og enkelte yrkesgrupper (for eksempel frisører) blir sensibilisert. Sensibilisering og påfølgende allergisk kontakteksem (kontaktdermatitt) som følge av kosmetikkbruk er hovedsakelig type IV-reaksjoner (cellemediert). Type I-sensibilisering og allergisk respons (IgE-mediert) dominerer i mage/tarmsystemet og i respirasjonssystemet. Både type I- og type IV-sensibilisering kan imidlertid forekomme alle steder. I rapporten "Etablering av et system for rapportering og registrering av alvorlige hudreaksjoner på grunn av bruk av kosmetiske preparater" utgitt av Nasjonalt folkehelseinstitutt i 2006, konkluderes det med at det er grunn til å mene at kosmetikkbivirkninger utgjør et ikke ubetydelig helseproblem. Helseeffekter forårsaket av kosmetiske produkter er ofte diagnostisert som allergisk kontakteksem.

Kosmetiske produkter skal i henhold til kosmetikkdirektivet (76/768/EEC, artikkel 2) ikke medføre helsefare ved normal bruk, eller ved bruk som med rimelighet kan forutses. I sammenheng med forvaltningen av kosmetiske produkter er det derfor viktig å ha en klar oppfatning av hva som skal oppfattes som helseskade. Så langt har det vært uklart om sensibilisering skal inkluderes i begrepet på linje med toksiske effekter som for eksempel effekt på fosterutvikling, kreftfremkallende effekt, mutagenisitet etc. Både EUs medlemsland og kosmetikkindustrien har hittil vært av den oppfatning at allergiske reaksjoner relatert til bruk av kosmetiske produkter ivaretas tilstrekkelig gjennom merking av produktene. En tilsvarende problemstilling finnes for mat, der lovlige og korrekt merkede matvarer (for eksempel nøtter eller skalldyr) kan forårsake svært alvorlige helseeffekter hos enkelte forbrukere. Ettersom det er grunnleggende forskjeller mellom matvareallergi og allergisk kontakteksem kan det likevel stilles spørsmål om hvorvidt det er riktig å sammenlikne kosmetiske produkter med mat i denne sammenheng.

I henhold til oppdragsteksten fra Mattilsynet har VKMs Faggruppe 4 besvart følgende to spørsmål i denne uttalelsen:

1) Bør kosmetiske produkter vurderes forskjellig fra mat når det gjelder sensibilisering?

Matvareallergi er ofte forbigående siden det i de fleste tilfellene utvikles toleranse, mens sensibilisering til kosmetiske produkter betraktes som en vedvarende effekt. De fleste matallergener finnes naturlig i mat og konsumeres verden over. Genetisk mottakelige individer vil kunne bli sensibilisert. På den annen side kan alle individer som har blitt sensibilisert for en kosmetisk ingrediens reagere, hvis de utsettes for tilstrekkelig høye doser av det aktuelle stoffet. Med bakgrunn i at flere sensibiliserende stoffer kan være i utstrakt bruk i kosmetiske produkter, forbrukerprodukter, tekstiler og i arbeidsmiljøet til enkelte yrkesgrupper (for eksempel frisører og arbeidere i helsesektoren), er det ofte vanskelig for individer som er sensibilisert for kosmetiske ingredienser å beskytte seg mot et sensibiliserende stoff.

Allergiske reaksjoner forårsaket av både mat og kosmetiske produkter krever en sensibiliseringsfase. Naturlig forekommende matallergener kan imidlertid ikke fjernes fra markedet siden de er uunngåelig forbundet med tradisjonell human ernæring. På den annen side

kan kosmetiske ingredienser, så vel som tilsetningsstoffer i mat, som forårsaker allergiske reaksjoner unngås.

Matallergener som finnes naturlig i mat bør derfor vurderes forskjellig fra kosmetiske ingredienser.

2) Bør sensibilisering forårsaket av eksponering for kosmetiske produkter betraktes som en helseskade?

Når det gjelder sensibilisering forårsaket av kosmetiske produkter, er type IV-reaksjoner indusert av hudsensibiliserende stoffer godt karakterisert og derfor brukt som grunnlag for denne vurderingen. Konklusjonene gjelder imidlertid også for sensibilisering via andre eksponeringsveier og både for type I- og type IV-reaksjoner.

Det er en årsakssammenheng mellom eksponering for et hudsensibiliserende stoff og den påfølgende sensibiliseringen, utløsningen av allergisk reaksjon (elisiteringen), og endelig allergisk kontakteksem. Det er viktig å merke seg at denne årsakssammenhengen innebærer at risikoen for å utvikle allergisk kontakteksem er borte når eksponering for det hudsensibiliserende stoffet unngås eller holdes under terskeldosen for sensibiliserende effekt. Selv om det synes å være en terskeldose for sensibilisering, avhenger denne dosen av en rekke ulike faktorer, og per i dag finnes det ingen anerkjente metoder for å bestemme mulige terskeldoser for sensibiliserende stoffer. Utløsning av allergiske reaksjoner forekommer ved betydelig lavere doser enn de som forårsaker sensibilisering. Et stoffs evne til å medføre allergisk kontakteksem kan forutsies ut i fra dets evne til å forårsake hudsensibilisering. Allergisk kontakteksem er uunngåelig forbundet med eksponering for et sensibiliserende stoff og dets iboende evne til å forårsake sensibilisering av huden. Sensibilisering av huden er i prinsippet ikke forskjellig fra andre toksikologiske farer. Det er derfor inkludert som et eget punkt i generelle toksikologiske tester og i risikovurdering av kjemikalier, herunder kosmetiske ingredienser.

Hudsensibilisering er en kritisk og nødvendig faktor i sykdomsutviklingen av allergisk kontakteksem. Det representerer en ervervet og irreversibel immunologisk forandring som gjør kroppen mer følsom for et sensibiliserende stoff, noe som igjen øker risikoen for å utvikle allergisk kontakteksem.

Konklusjon:

- Allergiske reaksjoner er å anse som en helseskade. Sensibilisering er en forutsetning for å utvikle allergiske reaksjoner, og det øker risikoen for å utvikle en slik reaksjon betydelig.
- Sensibilisering forårsaket av kosmetiske produkter må derfor betraktes som en helseskade.

Anbefalinger:

- For å oppnå en betydningsfull reduksjon av risikoen for å bli sensibilisert ved bruk av kosmetiske produkter, bør eksponering for ingredienser med et ekstremt eller sterkt sensibiliserende potensial unngås. Eksponering for moderat sensibiliserende stoffer bør reduseres.
- For å unngå utløsning av allergisk reaksjon (elisitering) hos sensibiliserte individer, vil det være gunstig med informasjon til forbruker om hvilke ingredienser et produkt inneholder.
- Kvantitative risikovurderingsmetoder, som kan forbedre risikokarakteriseringen av sensibiliserende kosmetiske ingredienser, bør videreutvikles og valideres både med tanke på sensibilisering og elisitering.

CONTENTS

CONTRIBUTORS

Persons working for VKM, either as appointed members of the Committee or as *ad hoc* experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has appointed an *ad hoc* group consisting of both VKM members and external experts to answer the request from the Norwegian Food Safety Authority. The members of the *ad hoc* group are acknowledged for their valuable contribution to this opinion.

The members of the *ad hoc* group are:

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The report from the *ad hoc* group has been discussed and approved by the VKM's Scientific Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics.

Assessed by:

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1. BACKGROUND

Skin contact with allergens in many cosmetic products could lead to sensitisation of consumers and occupational groups, such as hairdressers. Skin sensitisation may trigger allergic contact dermatitis (cell-mediated reaction (type IV)) or an allergic skin reaction caused by the same mechanisms as respiratory allergy (IgE-mediated reaction (type I)).

Some allergic reactions, following both types of sensitisation, could result in severe health effects. Admissions to hospital and sick leave have been reported due to adverse reactions to hair dyes, which could contain some extreme sensitising substances (Søsted *et al.*, 2002; SCCP, 2007). Primary sensitisation through skin contact may also result in IgE production and thus lead to an allergic reaction in the respiratory system after inhalation. Anaphylaxis has been reported in countries within the European Economic Area (EEA) and periodic disability for work is common.

Fragrance ingredients and preservatives are widely used in nearly all cosmetic products on the market. It is therefore very difficult to point out a special product being responsible for causing contact allergy. However, the use of permanent hair dyes is likely to be of special concern (Berg, 2004; SCCP, 2007). Nearly all incidents which have resulted in admissions to hospital or the accident and emergency unit following adverse effects to cosmetics in Norway, have been related to the use of permanent hair dyes.

Market surveys in Europe, USA and Japan, indicate that hair dying has become much more prevalent during the last ten years. Some of the reasons for this are that the hair dying is done at a younger age and the proportion of men dying their hair is increasing (McFadden *et al*., 2007). Data from Denmark show that 75% of women and 18% of men reported that they have used hair dyes. The median age at first hair dying was 16 years (Søsted *et al.*, 2005).

The EU Scientific Committee on Consumer Products (SCCP) adopted on 19 December 2006 a memorandum on hair dye substances and their skin sensitising properties. Twenty-seven of the 46 hair dye substances assessed were found to fulfil the EU criteria for classification as skin sensitizer (R43). Further categorisation of skin sensitising potency showed that 10 of the classifiable hair dye substances are extreme sensitizers, 13 are strong, and 4 are moderate sensitizers. Contact allergy and allergic contact dermatitis caused by hair dyes is an important and increasing health problem to consumers and society, often causing acute and severe dermatitis on the face, scalp and neck (SCCP, 2007).

It should be noted that also a lot of consumer products other than cosmetics contain fragrance ingredients and preservatives. Individuals being sensitised could therefore be affected by this problem throughout their lives. As much as 15-20% of the population within the EEA could be sensitised for a chemical substance, and the yearly incidence has been estimated to 0.7% by the European Surveillance System on Contact Allergies (ESSCA) http://www.ivdk.gwdg.de/essca/.

In a recent report from the Norwegian Institute of Public Health it is concluded that adverse reactions caused by the use of cosmetic products could constitute a significant health problem (FHI, 2006). During a period of almost 18 years, eczema has been the most frequent adverse reaction reported through the Swedish Cosmetic Adverse Reaction Monitoring System. The

Norwegian Food Safety Authority frequently receives inquiries from individuals reporting adverse reaction caused by use of cosmetic products verified by medical doctors. The adverse reactions are often diagnosed as allergic contact dermatitis.

According to the Cosmetics Directive 76/768/EEC, Article 2, a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use (EC, 1976). For the administration of cosmetic products, it is therefore important to have a clear understanding of what should be considered as an adverse effect. It is not clear whether sensitisation should be included in the term adverse effect in the same way as toxic effects, such as reproductive effects, irritation, carcinogenicity, mutagenicity etc. A similar situation appear for food products, where the Norwegian Food Safety Authority does not ban accurately labelled food products, even if they could cause serious health effects for some consumers (allergy to nuts, shellfish etc). However, as there are some basic differences between food allergy and allergic contact dermatitis, it could be discussed whether it is correct to compare cosmetic products and food products when addressing this problem. Relatively few people are afflicted by food allergy, which also often could be inherited. On the other hand, everybody could be sensitised and then be at risk for an outbreak of allergic contact dermatitis.

So far, both the Member States of the European Community and the cosmetic industry have been of the opinion that allergic issues related to the use of cosmetics could be properly dealt with through warnings printed on the label of the products. The warning "Can cause allergic reaction" is mandatory for 25 out of the 65 hair dye substances regulated by the Cosmetic Directive 76/768/EEC.

In light of the many severe adverse reactions now being observed in the Norwegian Cosmetic Adverse Reaction Monitoring System, the Norwegian Food Safety Authority has requested a scientific opinion from VKM related to whether sensitisation caused by exposure to cosmetic products should be considered as an adverse health effect.

2. TERMS OF REFERENCE

The Panel on Food Additives, Flavourings, Processing Aids, Materials in contact with Food and Cosmetics is requested to answer the following questions in relation to sensitisation caused by exposure to cosmetic products

1. *In terms of sensitisation, should cosmetic products be considered differently than food products?*
2. *Should sensitisation caused by exposure to cosmetic products be considered as an adverse health effect?*

3. OPINION

3.1 Introduction

3.1.1 Definition of cosmetic products

Cosmetic Directive 76/768/EEC (EC, 1976)
Cosmetic products are any substance or preparation intended to be put in contact with the various external parts of the human body or with the teeth and the mucous membranes of the oral cavity, mainly for cleaning, perfuming, changing their appearance and/or correct body odour and/or for protection and/or for maintaining one's person in good condition.

Definition of cosmetic products in Norway (Kosmetikklova, 2005)

a. *Cosmetics and toiletries*
   Products that come in contact with the body surface (skin, hair, nail, lip and external genitals), teeth or mucous membranes of the oral cavity.
b. *External healthcare preparations*
   Products that come in contact with the body surface, teeth or mucous membranes of the oral cavity with a view to prevent, alleviate or treating health problems that are not caused by disease.
c. *Tattoo products*
   Products that are used to gain permanent or long lasting pattern, drawing etc. or colour on skin (including permanent make-up).
d. *Injection products*
   Products that are injected into the skin to change the appearance of the skin in other ways than mentioned in litra c.

3.1.2 Use of cosmetic products

There is a widespread use of cosmetic products. Soaps, shampoos, conditioners, moisturisers, deodorants, shaving products and tooth paste are products that most people use (Figure 1). Commonly, a person is exposed to a large number (50-100) of different chemicals even before leaving the bathroom in the morning. Almost without exception, the whole population and all age groups are using cosmetic products. Even infants and small children are exposed to cosmetic products through the use of moisturiser, baby oil, soap and shampoo. Hair dying as fashion (as opposed to the more traditional usage to cover gray hair) is common both among women and men and even among teenagers (from as early as 11 years of age) (Søsted *et al.*, 2005). Furthermore, both permanent and temporary tattoo (e.g. black henna tattoo) has become increasingly popular in the last decades. Temporary tattoos are also applied on children.

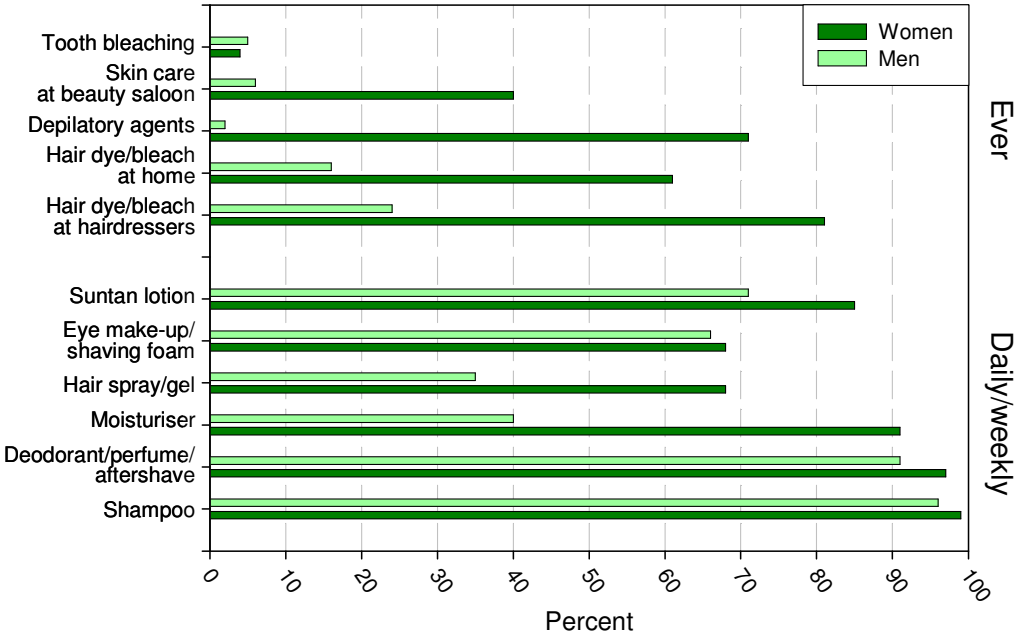

Figure 1. The percentage of women and men in Norway using cosmetic products daily/weekly or ever. The results are corrected for gender, age, and place of residence (n=1126). (Modified from Berg, 2004).

The use of cosmetic products seems to be increasing. Table 1 shows the sales figures for cosmetic products to consumers on the Norwegian market between 2003 and 2007 (The Norwegian Association of Cosmetic, Toiletries and Fragrance suppliers (KLF), 2008).

Table 1. The Norwegian cosmetic market 2003 - 2007. Figures in mill. NOK (modified from www.klf.no).

Product	2003	2004	2005	2006	2007
Total skin care	***1500***	***1645***	***1795***	***1895***	***2120***
Skin creams (face and body)	1275	1395	1515	1515	1655
Cleansing products/face tonic	225	250	280	380	465
Sun care	***240***	***255***	***300***	***365***	***355***
Total hair care	***1825***	***1870***	***1940***	***2075***	***2215***
Shampoo	665	690	730	760	780
Balsam	270	275	280	305	330
Styling products	520	530	540	560	595
Hair colouring/bleaching/permanents	370	375	390	450	510
Total colour cosmetics	***1180***	***1255***	***1330***	***1425***	***1565***
Nail products	95	100	90	85	85
Lip products	365	380	385	395	410
Eye make-up	445	475	520	560	635
Face make-up	275	300	335	385	435
Total fragrances	***405***	***420***	***450***	***500***	***560***
Women's fragrances	270	275	295	330	370
Men's fragrances	135	145	155	170	190
Total hygiene	***1825***	***1955***	***1965***	***2030***	***2030***
Shaving products (not incl. razors, blades etc.)	90	95	105	105	105
Hair removal products	40	45	55	55	55
Tooth paste	330	370	350	365	365
Mouth wash	30	30	35	30	30
Bath and shower products, incl. toilet soap	760	805	810	850	850
Deodorants, antiperspirants	425	440	445	455	455
Foot care products	25	25	25	25	25
Children's care	125	145	140	145	145
Total all groups	**6975**	**7400**	**7780**	**8290**	**8845**
Growth vs. last year (%)		6.1	5.1	6.6	6.7

3.1.3 Adverse reactions from cosmetic products

In this opinion, an adverse health effect caused by cosmetic products is defined as a harmful reaction that occurs from normal or reasonably foreseeable use of the product. Examples of adverse health effects are allergic/irritative contact dermatitis, photo-allergic/toxic contact dermatitis, anaphylactic shock, conjunctivitis, urticaria, cosmetic acne, hypo-/hyper-pigmentation, itching, corrosive scalp injury, acute hair loss, loosening of nails from the nail bed, and irritation of the mucous membrane of the oral cavity.

Even though there is a widespread use of cosmetic products, there are few studies on the occurrence and nature of adverse effects in the general population (Berg, 2004; De Groot *et al.*, 1987; Guinot *et al.*, 2006; Willis *et al.*, 2001). Based on 1126 telephone interviews of Norwegian women and men, 18-71 years of age, the National Institute of Consumer Research published a report on adverse effects from cosmetic products (Berg, 2004). Seventy-one percent of the women and 53% of the men reported to have experienced discomfort,

afflictions or damages/hurts from the use of cosmetics. A total of 34% of the women and 21% of the men reported the adverse effects to be 'unpleasant' or 'very unpleasant'. In a UK epidemiologic study on sensitive skin, 57% of women and 31.4% of men (> 18 years of age) had experienced an adverse reaction against a personal care product at some stage in their life (Willis *et al*., 2001). These studies indicate that adverse effects against cosmetic products are common in the general population. Since most reactions are often mild and transient, most consumers do not consult a physician but stop using the suspected item. Diagnosed or reported cases of cosmetic dermatitis probably represent only a fraction (i.e. the most serious cases) of the total cases occurring. In the Norwegian study, only 17% of the women and 9% of the men reporting adverse effects visited a physician (Berg, 2004).

In Sweden, the Medical Products Agency introduced a monitoring system for adverse reactions to cosmetics in 1989. Between 1989 and 1994, they evaluated 191 reports concerning adverse effects of 253 cosmetic products (Berne *et al.*, 1996). The top-ranking product category was moisturisers, followed by hair care products and nail products (Figure 2). The majority of the adverse effects reported involved only the skin. Ninety percent were eczematous reactions, in which the majority of all cases were classified as contact allergy. This was an unexpectedly high proportion, since irritant eczemas are probably the most common type of cosmetic adverse effect. However, these patients seldom seek medical advice (Berne *et al.*, 1996). The products that most often gave adverse effects in the Norwegian study were deodorants, perfumes and aftershaves. After adjusting for the frequency of use, there were only small differences between genders (Table 2) (Berg, 2004).

Occupational contact dermatitis (OCD) constitutes up to 30% of all occupational diseases and 90-95 % of the occupational skin diseases (Diepgen and Weisshaar, 2007). Incidence and prevalence of allergic OCD seem to be equal or higher than irritant OCD (Antezana and Parker, 2003; Kucenic and Belsito, 2002). The average incidence rate of registered OCD is around 0.5 to 1.9 cases per 1000 full-time workers. Wet work (hairdressing, health care work and cleaning) as well as manicure and aromatherapy, are occupations with a high risk of OCD (Amado and Taylor, 2006). In North Bavaria (Germany) the incidence of work-related skin-disease for hairdressers was 97.4 cases per 10 000 workers per year from 1990-1999. Furthermore, for hairdressers and barbers the incidence rates of irritant and allergic contact dermatitis were 46.9 and 67.2, respectively. Similar incidence rates for health care workers were 4.0 and 3.7, respectively (Diepgen, 2003).

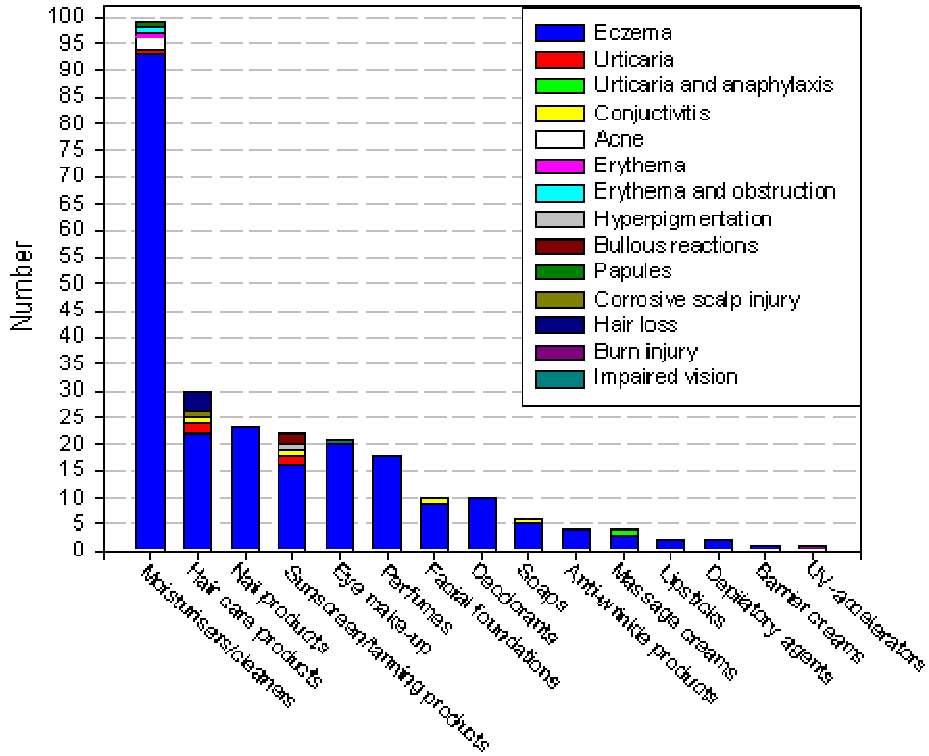

Figure 2. Reported adverse effects of cosmetic products in relation to product categories – overview from the Swedish Medical Products Agency 1989–1994. Based on 191 reports and 253 cosmetic products (modified from Berne et al., 1996).

Table 2. The percentage of adverse effects in proportion to the population using the products on daily/weekly basis (Modified from Berg, 2004).

Product	Female (%)	Male (%)
Deodorant	38	39
Eye make-up	35	
Moisturiser	32	20
Depilatory agents	28	
Hair shampoo	21	18
Hair spray/gel etc.	17	17
Shaving foam		9
Sunscreens	9	3

3.1.4 Prevalence of allergic contact dermatitis

Fragrances and preservatives are ingredients that most often cause allergic contact dermatitis (Berne *et al.*, 1996; Biebl and Warshaw, 2006; Diepgen and Weisshaar, 2007). In groups of unselected individuals, the frequency of positive responses to fragrance mix was 1-2% in a Danish study (Nielsen and Menné, 1992; Nielsen *et al.*, 2002) and 1.8% in a Norwegian study (Dotterud and Smith-Sivertsen, 2007).

In dermatitis patients examined by dermatologist in 10 different centres in Europe, 5-12.8% of the patients had positive patch tests to fragrance mix (Bruynzeel *et al.*, 2005). Similar data collected by the Information Network or Departments of Dermatology (IVDK) multicentre project from 1996 to 2002 shows that between 8.9% and 13.5% had positive patch test results to fragrance mix (n = 59 298), 9-11.5% positive reactions to Balsam of Peru (n=59 334), and 1.6-4.4% positive reactions to Oil of turpentine (n=59 478) (Schnuch *et al.*, 2004). Patients undergoing patch testing with preservatives as part of the investigation for contact dermatitis in 9 UK centres showed that formaldehyde and methylchloroisothiazolinone/methyl-isothiazolinone had the highest positivity rates (2.0%) and chlorozylenol the lowest (0.2%). Paraben mix on the other hand had the highest irritancy rate (0.36%). Other important ingredients are *p*-phenylenediamine and related hair dyes (Marks *et al*., 1998; Schnuch *et al.*, 1997; Søsted *et al.*, 2005). Multicentre studies show that between 3.9% and 4.8% of the patients had positive patch test results to *p*-phenylenediamine (Bruynzeel *et al.*, 2005; Schnuch *et al.*, 1997). The results based on about 1686 patch tests performed in five hospitals in Norway confirm results found in the multicentre studies (Table 4).

Table 4. Patch test results of ingredients used in cosmetics. Modified from NOLAR (a Norwegian register on patch test results from five hospitals).

Allergen	**Frequency (%)**
Phenylenediamine	3.3
Colophony	3.9
Paraben	1.3
Butylphenol	0.8
Formaldehyde	3.3
Fragrance	9.8
Quaternium	2.1
Methyldibromoglutaronitrile	2.9

3.1.5 Definition of sensitizers

The allergic response is an immune reaction with a sensitisation (induction) and an elicitation (effector) phase, as opposed to an irritative response which is primarily a non-immunological reaction that do not involve a sensitisation phase. In this opinion, the focus is on adverse effects due to allergic responses.

According to the Directive 1999/45/EC, relating to the classification, packaging and labelling of dangerous preparations, sensitizing substances and preparations are defined as: *"substances and preparations which, if they are inhaled or if they penetrate the skin, are capable of eliciting a reaction of hypersensitisation such that on further exposure to the substance or preparation, characteristic adverse effect are produced"*. Allergens are such substances, also referred to as sensitizers.

Proteins or peptides are alone capable of triggering an immune response. Low molecular weight chemicals cannot by themselves induce sensitisation and elicit an adaptive immune response, but have to be linked to protein-carriers to elicit antibody or T cell responses. These molecules are generally referred to as haptens. Some haptens may spontaneously form bonds with the protein-carrier. However, some molecules, called prohaptens, are transformed into reactive haptens by metabolic processes in the skin. In this way, harmless molecules are converted into derivatives with allergenic properties. The metabolic processes involved are

mainly based on oxido-reduction reactions and enzymatic hydrolysis. Prohaptens play an important role in contact allergy because of their number and their highly reactive nature after biotransformation. Harmless molecules may also be chemically modified during storage and handling (i.e. by non-enzymatic processes). These molecules are called prehaptens if transformed by e.g. heat and oxygen, and photohaptens if transformed by light (Lepoittevin, 2006).

3.1.6 Sensitizers in cosmetic products

Allergic skin reactions are most often caused by cosmetics that remain on the skin – "stay-on" or "leave-on" products (e.g. moisturisers, hair dyes, nail cosmetics, deodorants, perfumes, facial and eye make-up). "Rinse-off" or "wash-off" products are removed from the skin after a short period, and therefore less commonly elicit allergic reactions (White and de Groot, 2006). There are few systematic investigations on the sensitising potential of cosmetic ingredients, but fragrances and preservatives have emerged as the most common causative ingredients (Biebl and Warshaw 2006). Examples of fragrances, preservatives and other ingredients that may act as sensitizers are listed in Table 3. Fragrances are widely used in commercial products and there has been an increased use of plant extracts in so-called "natural" products. Formaldehyde is now rarely used as a preservative in cosmetics because of its sensitising potential. However, despite decreased use in cosmetic products the sensitivity levels remain high probably because of continued use in cleaning products and the use of formaldehyde donors (Biebl and Warshaw, 2006; Wilkinson *et al*., 2002).

Table 3. Examples of potential sensitizers in cosmetic products (modified from White and de Groot, 2006).

Type of ingredients	Example of ingredients
Fragrances	Amyl cinnamal Cinnamyl alcohol Cinnamal *Evernia prunastri* (oak moss) Eugeniol Geraniol Hexyl cinnamal Hydroxycitronellal Iso-eugenol
Preservatives	Formaldehyde Formaldehyde donors: Quaternium-15 Imidazolidinyl urea Diazolidinyl urea 2-Bromo-2-nitropropane-1,3-diol 1,3-bis(hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione (DMDM hydantoin) Iodopropynyl butylcarbamate Methylchloroisothiazolinone/methylisothiazolinone Methyldibromo glutaronitrile Parabens
Hair dye ingredients	*m*-Aminophenol Basic blue 99 Henna 1-Hydroxyethylamino-3-nitro-4-aminobenzene N-(b-Hydroxyethyl)-2-nitro-4-hydroxyaminobenzene 1-Hydroxy-3-nitro-4-aminobenzene Naphtalenediol 2-Nitro-*p*-phenylenediamine *p*-Phenylenediamine *N*-Phenyl-*p*-phenylenediamine Pyrocatechol Resorcinol Toluene-2,5-diamine
UV-filters	Anthranilate Benzophenone Cinnamate Dibenzoylmethane *p*-aminobenzoic acid (PABA) Salicylate
Emollients/emulsifiers/surfactants	Cocamidopropyl betaine Hydrolyzed proteins Lanolin and derivates Propylene glycol
Antioxidants	Butylated hydroxyanisole Butylated hydroxytoulene *t*-Butylhydroquinone Gallates Tocopherol (vitamin E)

3.2 Allergy caused by exposure to cosmetic products

Allergy is defined as immunologic hypersensitivity. There are four main types of hypersensitivity reactions (I-IV). Type I-III are antibody-mediated and are distinguished by the different classes of antibody involved and the types of antigens recognized (Type I: IgE and soluble antigens; Type II: IgG/IgM and cell or matrix associated antigens; Type III: IgG/IgM and soluble antigens). Type IV is T cell-mediated ($CD4^+$ T cells and soluble antigens; $CD8^+$ (cytotoxic) T cells and cell-associated antigens). Cosmetic products may cause type I or IV reactions. Therefore, this opinion will discuss only these types of hypersensitivities.

3.2.1 Sensitisation and elicitation

Clinical allergy develops in two steps: The induction (sensitisation) phase and the effector (elicitation) phase (Figure 3). Sensitisation may occur alone without being followed by elicitation, and thus, many sensitised individuals may never experience allergic symptoms.

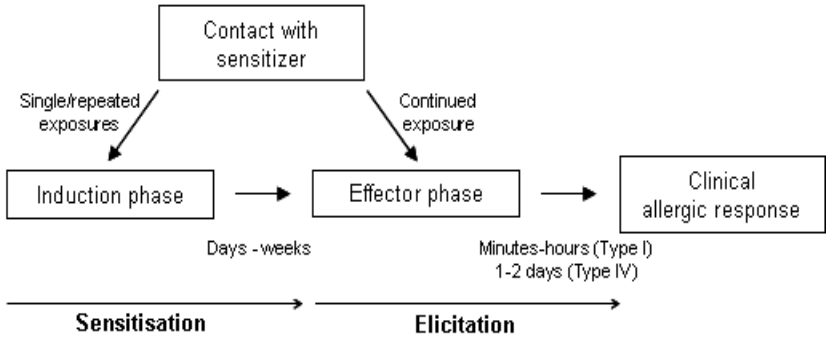

Figure 3. Flow chart showing the causal relationship between sensitisation and clinical allergic contact dermatitis.

Type I and type IV reactions

Type I immediate hypersensitivity reactions are characterised by the production of allergen-specific IgE-antibody (Figure 4). During the sensitisation phase, antigen-presenting cells present the allergen, and signals are generated that cause differentiation of naive T helper (Th) cells into activated Th_2 cells. Next, cytokines secreted by the Th_2 cells together with co-stimulatory surface antigen signals lead to activation of B cells, immunoglobuline switch and production of antigen-specific IgE by plasma cells. IgE is a cytophilic immunoglobuline and thus binds to receptors on cells like mast cells and basophil granulocytes. On renewed contact, the specific allergen enters the body and couples to cell-bound IgE. The bridging of two IgE-molecules by the allergen signals the mast cells/basophil granulocytes to release potent mediators and thus elicit symptomatic allergic responses. The elicitation may occur within few minutes after renewed contact with the allergen. Allergens triggering a type I response are mainly low molecular weight water soluble proteins such as pollen, or food allergens entering the body through the respiratory or gastrointestinal tract. However, type I sensitisation through the skin may also occur.

Type IV delayed-type hypersensitivity reactions are cell-mediated and characterised by activation of antigen-specific effector T cells which are stimulated by antigen-presenting cells

(Langerhans' cells) in the skin. This occurs as a delayed immune response, and the subsequent proliferation and differentiation of specific T cells take place over several days and weeks leaving a high amount of effector and memory T cells in the blood circulation of the sensitised individual (Figure 4). Th_1 cells play a role in the activation and differentiation of cytotoxic T cells in the sensitisation phase. The elicitation phase is initiated by renewed allergen contact. In this phase, cytotoxic T cells are important effector cells causing tissue injury and release of pro-inflammatory cytokines. Th_1 cells do also play a role by producing pro-inflammatory cytokines. The elicitation may occur within 24-48 hours after renewed contact with the allergen. Allergens that trigger type IV responses are mainly low molecular weight chemicals (haptens) entering the body through the skin.

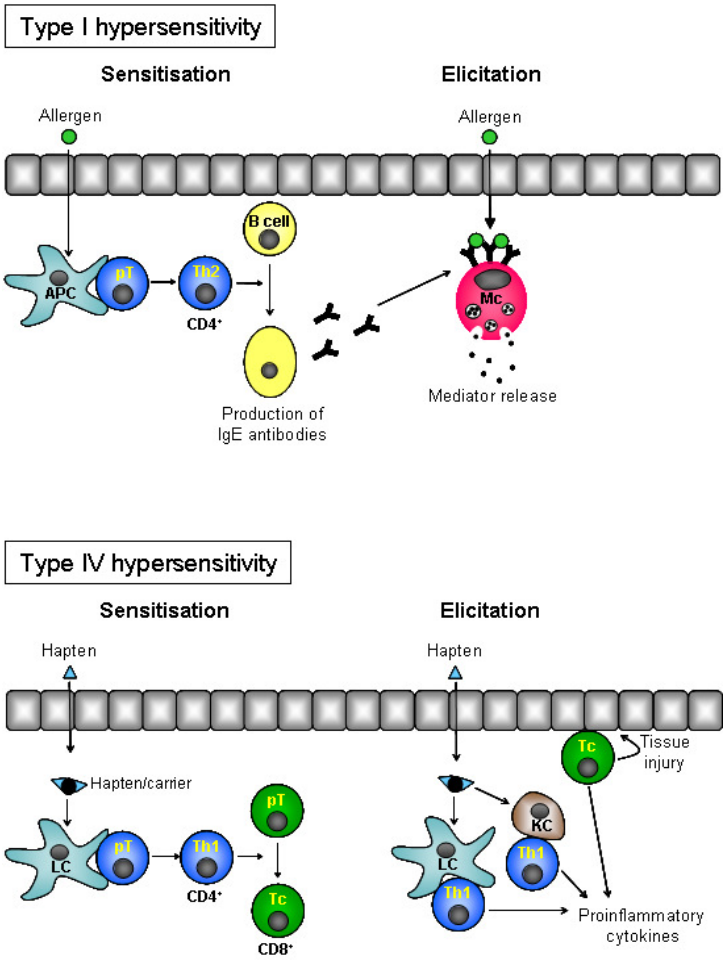

Figure 4. Schematic presentation of type I and IV hypersensitivity reactions. APC: Antigen presenting cell; KC: Keratinocyte; LC: Langerhans cell; MC: Mast cell; pT: precursor T cell; Th: T helper cell; Tc: Cytotoxic T cell.

Clinical manifestations

Sensitisation precedes elicitation of symptoms, but sensitised individuals are not necessarily symptomatic. It is not exactly clear why some sensitised persons will experience an allergic response and others not, but regulatory T cells may play an important role in this process. This is true for both type I and type IV responses. When sensitisation has been established, symptoms/reactions may be elicited by lower concentration of the sensitizer.

Clinical reactions with allergic origin due to the use of cosmetic products are most often contact dermatitis, but contact urticaria, angioedema, photoallergy, anaphylaxis and systemic contact dermatitis may also occur. Allergic contact dermatitis and photoallergic reactions are mainly of type IV origin, whereas allergic contact urticaria and anaphylaxis are caused by type I reactions (Figure 5) (Bieble and Warshaw 2006; Lange-Asschenfeldt *et al.* 2004; Orton and Wilkinson 2004; Oshima *et al.,* 2001; Sahoo *et al.,* 2000).

Systemic contact dermatitis can occur when patients sensitised to an allergen is re-exposed orally or by inhalation to the same substance. Symptoms usually appear on the skin as flare-up of previous eczema, vesicular hand eczema and as a generalized rash, but general symptoms (fever, malaise etc.) are also occasionally seen. Symptoms may appear a few hours or 1-2 days after experimental provocation. This suggests that more than one type of immunological reaction may be involved. Butylated hydroxyanisole, formaldehyde and sorbic acid are cosmetic ingredients that have been shown to cause systemic contact dermatitis (Veien *et al.*, 2008).

Epidermal exposure to protein antigens may selectively drive Th_2 type responses and thus promote sensitisation to foods upon gastrointestinal exposure (Strid *et al.,* 2005). Lauriere and co-workers demonstrated primary sensitisation and IgE-production to hydrolyzed wheat proteins used in cosmetics (Lauriere *et al.,* 2006). Subsequent reactions to foods containing hydrolysed wheat proteins were in most cases preceded by topical application of the hydrolysed wheat products.

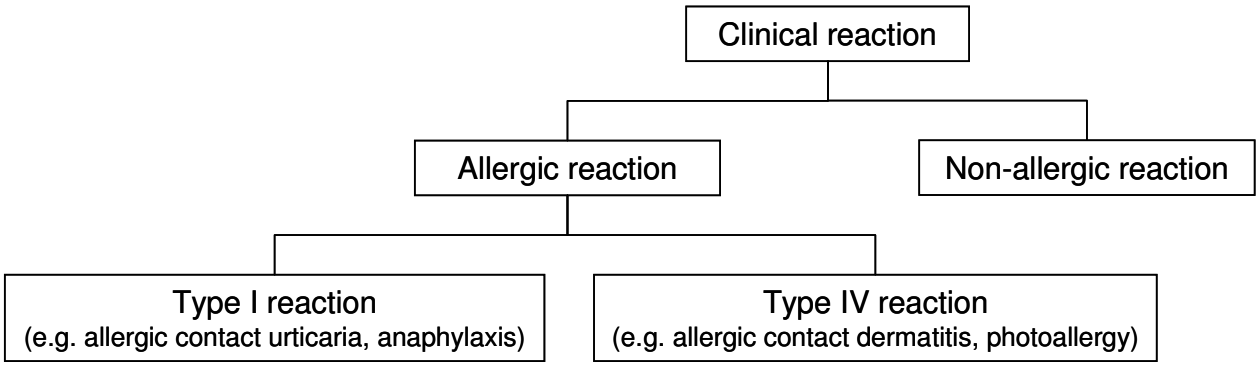

Figure 5. Schematic overview over clinical reactions due to the use of cosmetic products.

Type I

Allergic contact urticaria is an immediate but transient localised swelling and redness that occurs on the skin after contact with a sensitizer. Symptoms from this often IgE-mediated response may be burning, stinging and itch, including urticaria and angioedema (Orton and Wilkinson, 2004). Urticaria is an eruption characterised by transient wheals due to acute dermal oedema from extravascular leakage of plasma, whereas angioedema signifies a larger area of oedema involving the dermis and subcutis (Gawkrodger, 2008a). Allergic contact urticaria has been reported following the use of several cosmetic ingredients (Niinimaki *et al.*, 1998; Orton and Wilkinson, 2004).

Anaphylaxis is an acute systemic allergic reaction, involving more than one organ system, including urticaria, angioedema, and/or hypotension. The severity of an anaphylactic reaction can vary from mild symptoms to sudden death. There are some case reports on anaphylactic

reactions after the use of hair dye (Oshima *et al.*, 2001; Sahoo *et al.*, 2000) and UV filters (Lange-Asschenfeldt *et al*., 2004).

Type IV

Allergic contact dermatitis is the most common allergic response to skin sensitizers, and it is characterised by a delayed reaction that consists of varying degrees of erythema, oedema, and vesiculation. The reaction is generally confined to the site of contact with the sensitizer. However, in severe cases the reaction may extend outside the contact area. The allergen may also be transmitted from the fingers so unexpected sites can be affected (e.g. eyelids, genitals). A large number of different sensitizers may cause allergic contact dermatitis, in which fragrances, preservatives, dyes and lanolins are the most important types of ingredients. (Gawkrodger, 2008b; Marzulli and Maibach, 2008).

Photoallergy is a type IV reaction that may occur when ultraviolet radiation converts a topically applied chemical into a sensitizer. Symptoms appear on the sun-exposed skin and are commonly manifested as eczema. The reaction may also spread onto unexposed sites but the exposed area tends to remain most severe. Photoallergens can be found in i.e. fragrances and in sunscreens. Although skin responses triggered by ultraviolet radiation can be of allergic origin, non-immunological phototoxic reactions are the most common reactions (Bieble and Warshaw, 2006; Palmer and White, 2006).

3.2.2 Characteristics of the sensitizer influencing sensitisation

Sensitisation and elicitation occur only above threshold doses. The magnitude of the immune response depends on the sensitizer's:

- Ability to penetrate the epithelium
- Potency
- Exposure dose, frequency and duration

The ability of a sensitizer to penetrate the epithelium is a factor influencing their ability to sensitise and elicit allergic responses. Consequently, both molecular weight and tertiary structure of the proteins in question are important.

The potency (the relative ability of a sensitizer to induce sensitisation) of a substance and its ability to penetrate the epidermis are basic factors in the risk assessment of a substance as a sensitisation agent. There is a great variation in sensitising potency of different substances. Notably, para-phenyldiamine (PPD) is denoted as a strong to extreme sensitizer.

Sensitisation for type IV allergy shows a somewhat peculiar dose-response relationship. The sensitising potency is determined by the amount of chemical per unit area (dose) required for the acquisition of skin sensitisation in a previously naive individual (van Loveren *et al.*, 2008). This means that a given amount of a sensitizer has a higher sensitising capacity if concentrated on a small area of skin rather than applied to a larger area. The dose is usually reported as micrograms of substance per square centimetre of exposed skin. A recent study from Thailand indicate that frequent, short duration exposure to a lower dose of PPD increased the risk of sensitisation compared to infrequent, long duration use of higher doses (Basketter, 2006). The allergenic component of PPD accumulates in the skin, making the cumulative exposure to several smaller doses equivalent to larger, single time exposure

(White *et al.*, 2007a). However, once sensitised, individuals can react to lower doses of a sensitising substance. In type I allergy, the total sensitisation dose may be low, and a tolerance dose high, although tolerance is also known to be induced by repeated low doses of the allergen. In addition, the dose-response relationship may vary between different sensitizers. There is no known relationship between dose and area of application for type I sensitisation, as it is in type IV allergy.

Cross-reactivity
Cell receptors that recognize sensitizers are highly specific, and the recognition is dependent on both the molecular structure and the size and spatial geometry of the molecule. The term cross-reactivity may often be misused. However, true cross-reactivity between two molecules may occur when 1) two molecules are chemically and structurally similar, 2) a molecule is metabolised into a compound which is similar to another molecule, and 3) two different molecules are both metabolised to similar compounds. It may be difficult to identify cross-reactivity because of the possibility of co- or poly-sensitisation. Furthermore, the metabolism of molecules can be complex, and two completely different molecules can be converted to derivatives that have a similar structure (Leopoittevin, 2006).

An example of cross-reactivity between different sensitizers is formaldehyde and various formaldehyde donors such as quaternium-15, imidazolidinyl urea, diazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol and DMDM hydantoin (Figure 6). Because formaldehyde is a ubiquitous substance, sensitisation may be caused by exposures from other sources than cosmetics, for example household products, disinfectants, textiles and paint.

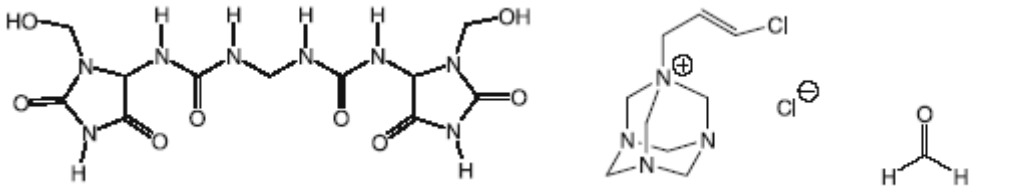

Figure 6. Chemical structure of some cross-reacting chemicals.

Examples of true cross-reactivity between proteins are IgE-mediated cross reactions between pollens and fruits/vegetables where similarity between the cross-reactive epitopes on the proteins may lead to cross-reactions (e.g. Bet v 1 in birch and Mal d 1 in apple).

3.2.3 Individual characteristics influencing sensitisation

Some of the most important factors influencing sensitisation are:

- Skin characteristics
- Atopy
- Gender
- Age
- Genetic susceptibility

The barrier abilities of the skin may differ inter- and intra-individually. Skin responsiveness differs by anatomical site. Regional differences in absorption are substantial, and occlusion may promote the penetration of allergenic substances into the skin. Inherent dry skin may be more susceptible to allergens and irritants. Shaving and exposure to irritants, including excess use of water, may traumatize the skin resulting in an increased risk of sensitisation.

It is hypothesized that skin barrier dysfunction may facilitate entry of allergens through the skin and thus lead to systemic sensitisation. Barrier-disrupted skin as can be seen in atopic individuals seems to be well suited for induction of potent Th_2 responses with production of allergen-specific IgE (Strid and Strobel, 2005). Thus, in children with atopic dermatitis and damaged skin barrier entrance of proteins/peptides through the skin is particularly important and should be avoided. In adults, hydrolysed collagen used in hair conditioners has been shown to cause allergic contact urticaria, especially in subjects with atopic eczema (Niinimäki *et al.*, 1998). Furthermore, adult atopic individuals have a higher risk of developing irritative contact dermatitis, notably hand eczema, due to the impaired skin barrier function. On the other hand contact allergy to haptens with oral and skin exposure seem to be reduced in patients with atopic dermatitis compared to persons without atopic dermatitis. Possible explanations may be that atopic dermatitis patients may be efficient at tolerizing haptens orally and inefficient at tolerizing proteins, secondary to their atopic status. Furthermore, that oral tolerance of haptens may antagonize tolerance of food proteins and lead to an immunological shift towards atopy (hapten-atopy hypothesis) (McFadden *et al.*, 2008).

It has been shown that women have a stronger cell-mediated immune response than men. However, it is likely that the higher prevalence of contact allergy observed in women mainly is due to more frequent exposures to allergens and thereby more frequent subclinical sensitisation (Veien, 2006).

The influence of age on predisposition of contact sensitisation is not fully understood. IgE-mediated allergy is more prominent in childhood and early adulthood. In the elderly, IgE-mediated reactions are rare. The skin barrier function may be decreased in both infants and elderly. Allergic contact dermatitis in children has been considered rare compared with the occurrence in adults. However, recent work shows that patch test positivity in children is increasing. There is little information in the literature on patch testing in the elderly. Patch testing in a large number of patients >65 years with suspected allergic contact dermatitis showed that the sensitisation rate was significantly lower in elderly patients than in 20- to 40-year-olds except for some substances particularly used in the formulation of topical treatment of age-related diseases, i.e., leg ulcer and xerosis (Piaserico *et al*., 2004; Machet *et al*., 2004).

There are many studies on the genetic basis for atopy, and these studies show that IgE-mediated diseases are associated with a complex network of interacting genes that have diverse functions and act in multiple pathways. However, the number of genes that contribute to these phenotypes are still unknown (Reviewed in: Heinzmann and Deichmann, 2001; Ober and Hoffjan, 2006). There are fewer studies on genetic susceptibility for developing allergic contact dermatitis, and there is a lack of conclusive evidence from clinical studies. However, some findings suggest a possible relationship between allergic contact dermatitis and polymorphisms in genes coding for tumor necrosis factor α, IL-16 and HLA class III (Blömeke *et al*., 2008; Orecchia *et al*., 1992; Reich *et al*., 2003; Westphal *et al*., 2003). Although some individuals may be more easily sensitised than others due to their genetic background, the total number of sensitised individuals in the population probably depends upon the degree of cutaneous exposure (Agner and Menné, 2006).

Polysensitisation seems to indicate a subset of individuals (with a phenotype) at greater risk of developing contact allergy due to an increased susceptibility to sensitisation to weaker allergens (whereas when exposed to stronger allergens, this susceptibility seems to be overridden) (Schnuch, 2008).

Tolerance induction

Food allergy can partly be explained by late or no onset of normal tolerance. Presently the notion that tolerance may be achieved through daily intake of small amounts of the incriminated food is prevailing. Not all food allergic children become tolerant, however, and the age when tolerance is achieved may be very different. How contact with food allergens through skin application will influence the course of food allergy has been explored and primary sensitisation through epicutaneous application has been demonstrated at least in a mouse model (Strid *et al.*, 2004). Furthermore, it has been demonstrated that epicutaneous exposure to peanut protein, especially on barrier-disrupted skin, prevents normal tolerance induction and may also modify existing tolerance (Strid *et al.*, 2005). The mechanism involved is development of a strong Th_2 immune response with production of IL-4 and allergen-specific IgE. However, these studies involved large quantities of peanut protein on the skin. Skin care products usually contain peanut oil in which only very small amounts of protein are present. The clinical relevance of peanut oil in skin care products are probably negligible (Ring and Möhrenschlager, 2007).

In a non-sensitised individual, oral/gut exposure to allergens may initiate tolerance by the activation of regulatory suppressor T cells. For example, ear piercing easily leads to sensitisation against nickel. However, if it is preceded by oral nickel contact via orthodontic braces, tolerance may be induced with a resistance to the subsequent acquisition of skin sensitisation by piercing or use of bracelets etc. Propyl gallate is an antioxidant added to cosmetic products, especially lipsticks. It is known as a strong skin sensitizer, but few have been sensitised which may be due to a tolerance achieved through oral exposure to the antioxidant (E310) in fatty food. Now, the prevalence of allergic contact dermatitis to propyl gallate is increasing concomitantly with the reduced use of this antioxidant by the food industry (Perez *et al*., 2008). Likewise, a possible development of oral tolerance to fragrance chemicals used in perfumes and skin-care products through toothpastes has been discussed (White *et al.*, 2007b). On the other hand, animal models of oral tolerance to contact allergens indicate that cutaneous exposure to small, sub-sensitising doses of contact allergens might negate subsequent attempts to induce tolerance by oral administration. If applicable to humans, contact allergens in consumer products used by children may inhibit development of natural tolerance through dietary exposure (White *et al.*, 2007b).

3.3 Regulation of allergens in cosmetics and food

3.3.1 Cosmetics

The safety of cosmetic products is based on the safety of their ingredients and that the products are used under normal or reasonable foreseeable conditions. The safety evaluation procedure and toxicological testing of cosmetic ingredients is regulated in the Cosmetic directive 76/768/EEC (EC, 1976) and further described in the SCCPs Notes of Guidance for Testing of Cosmetics Ingredients and Their Safety Evaluation (SCCP, 2006). These guidelines include the toxicological test procedures described in the Dangerous Substances

Directive 67/548/EEC. Among the test procedures described are animal models used to identify skin sensitizers (see Appendix). According to the abovementioned directive 67/548/EEC and directive 1999/45/EC, relating to the classification, packaging and labelling of dangerous preparations, substances and preparations shall be classified as sensitising and assigned the symbol "Xi" (harmful) and the risk phrase "R43, may cause sensitisation by skin contact":

- if practical experience shows the substance or preparation to be capable of inducing a sensitisation by skin contact in a substantial number of persons.
- where there are positive results from an appropriate animal test.

Interestingly, even though a cosmetic ingredient is identified as a skin sensitizer that qualify to be labelled R43, the Cosmetic Directive 76/768/EEC (EC, 1976) is not using labelling with the risk phrases of Directive 67/548/EEC. Other product categories where the regulation does not use these risk phrases are medical products and tobacco products.

3.3.2 Food

Appropriate labelling is used in order to prevent serious allergic food reactions. Annex IIIa of EU Directive 2003/89/EC, amending Directive 2000/13/EC, as regards indication of the ingredients present in foodstuffs, lists foods that trigger allergies and certain intolerances. On the packaging labels of ready-to-eat foods (pre-packed or processed) the common allergens must be listed: cereals, crustaceans, eggs, fish, peanuts, soybeans, milk, shell fruit, celery, mustard, sesame seeds, sulphur dioxide and sulphites. Exempted from this labelling are so-called "loose products" such as bread, bakery products, sausage and cheese which are sold over the counter in bakeries, butcher shops, canteens etc. by sales staff to the consumer (BfR, 2007).

Food additives are regulated by a framework directive (Council Directive 89/107/EEC) and three specific directives for sweeteners, colours and food additives other that colours and sweeteners, respectively. Food additives may only be authorised if there is a technological need for their use, they do not mislead the consumers, and they present no health hazard to the consumers. Prior to their authorisation, food additives have been evaluated for their safety by the European Food Safety Authority (EFSA) according to criteria given in the guidance document on submission for food additive evaluations by the EU Scientific Committee for Food (SCF) (EC, 2001). This guidance was endorsed by EFSA on 9 July 2003. Tests of immunotoxicity and allergenicity are mentioned in the guidance document, but are not part of the core studies that normally have to be carried out. The need for such studies is decided in each case.

Flavourings are substances used to give flavour and/or odour to food. Flavourings are regulated by Council directive 88/388/EEC, which defines various types of flavourings, such as; natural, natural-identical or artificial flavouring substances, flavouring preparations of plant or animal origin, and process flavourings which evolve flavour after heating and smoke flavourings. There are no specific requirements for allergy testing in the safety evaluation of flavourings.

Food made from genetically modified organisms (GMOs) can only be allowed on the EU market once they have received authorisation based on the EU regulation on genetically

modified food and feed (Regulation (EC) No1829/2003). The safety evaluation performed by EFSA includes comprehensive allergy tests.

Novel foods and food ingredients are assessed by EFSA in accordance with Regulation (EC) No. 258/97 before authorisation is given. The guideline calls for an assessment of potential to induce allergy without making any specific proposals about the type of tests required.

3.4 In terms of sensitisation, should cosmetic products be considered differently than food products?

Food allergy may be IgE-mediated (type I) or cell-mediated (type IV) immunologic reactions. Type I allergy constitutes the risk of life-threatening anaphylaxis, while type IV are delayed eczemateous reactions. Food allergens are natural substances used (consumed) in their natural context (fruits, nuts, meats, milk products), and only moderately processed (boiled, fried, etc.) or separated/refined (grain milled to flour, casein separated from milk, etc.). Allergy to cosmetic products is usually cell-mediated (type IV) as in allergic contact dermatitis, although type I reactions also may be involved. The majority of contact allergens are synthesised chemicals or technically isolated and refined substances (metals, plant-derived substances). Food allergens that occur naturally in a product can be difficult or not feasible to eliminate, while additives in food or ingredients in cosmetics may be avoided. Food allergy is often transient as tolerance develops in the majority of cases, while sensitisation to cosmetics is regarded as permanent.

Food allergens are commonly consumed and thus sensitisation will occur in genetically susceptible individuals. As a rule, tolerance to foreign proteins in food is achieved during the first year of life, although some children do not become tolerant and thus may experience adverse reactions for a shorter or longer period. However, for some allergens (for instance nuts or fish), the allergy may be permanent. The sensitisation process may occur *in utero* or during the first years of life, and is dependent on genetics and environmental factors (diet). Although all sensitised individuals will carry the risk of clinical reactions, only about 30 – 40% will react to food. Although clinical food allergy may constitute a major health problem with the risk of life-threatening anaphylactic reactions, it pertains only to a very small percentage of sensitised individuals.

Some cosmetic products are used to improve appearances and are not absolutely necessary for human existence, whereas others are necessary products for modern way of life (soap, toothpaste etc.). One would, however presume compounds used for hygienic purposes or general well-being to be without appreciable risk for health damage. Sensitisation to cosmetics may occur in all individuals but certain risk factors apply. Individuals who are proven sensitised will all react to the chemical in question, if sufficient doses are applied. However, a positive patch test reaction does not automatically indicate a related clinical problem. Contact allergies are often considered lifelong. It can be difficult for sensitised individuals to avoid/protect themselves from the sensitizer due to the wide use in cosmetics, household products, textiles and the working environment of a wide variety of occupations, such as hairdressers and health care workers.

With respect to regulation, food allergens and cosmetics have different legal status. The regulation of food additives, as well as novel food and genetically modified organisms (GMO) is comparable to that of cosmetic ingredients in the way that it is based on a pre-

authorisation assessment. Labelling legislation regarding natural foods is only pertinent in their capacity to induce allergic reactions in already sensitised individuals.

In summary, allergic reactions to both food and cosmetics are similar because they require a sensitisation phase. However, since naturally occurring food allergens are inevitably connected with traditional human nutrition they cannot be eliminated from the market. On the other hand, cosmetic ingredients, as well as food additives causing allergic reactions may be avoided. Food allergens are not feasible to eliminate and should thus be considered differently than cosmetic ingredients and food additives.

3.5 Should sensitisation caused by exposure to cosmetic products be considered as an adverse health effect?

The following considerations are directed to skin sensitisation because of the absence of validated predictive tests for exposure via other routes (e.g. inhalation and oral). The considerations are also confined to skin sensitizers leading to type IV reactions. These reactions are well studied, and good animal models are developed to identify such sensitizers. Furthermore, the legal documents on skin sensitisation mainly refer to knowledge about type IV reactions even though they also regulate sensitizers leading to type I reactions. The reason for this is that the mechanisms and dose-response relationships for type I reactions are not well characterised, and that there are no standardised animal tests for such reactions (see Appendix). However, the conclusions presented are valid for sensitisation by different routes and for both type I and type IV reactions.

There is a causal relationship between the topical exposure to a skin sensitizer and subsequent skin sensitisation, elicitation, and the eventual manifestation of clinical allergic contact dermatitis (see Figure 3). Repeated exposures at adequate dose levels make the body more susceptible to the skin sensitizer. Hence, skin sensitisation represents an acquired and irreversible immunological change that increases the risk of developing allergic contact dermatitis. Importantly, skin sensitisation is not confined to particular sensitive individuals. Although there is inter-individual variability in response pattern, as in any toxicological endpoint, all individuals in the population will become sensitised by a potent skin sensitizer at a sufficiently high exposure. The main difference between sensitisation and systemic toxicity endpoints is that for skin sensitisation the adequate descriptor of exposure is dose per skin area, expressed as nanomoles or micrograms per square centimetre per day (van Loveren et al., 2008). In principle, skin sensitisation is not different from other toxicological hazards. Thus, skin sensitisation is a critical and necessary event in the aetiology of allergic contact dermatitis, and the health effect is prevented when the cause (skin sensitizer) is avoided, or the exposure is below dose-threshold.

In recent years these causal relationships have been experienced in the human population when novel preservative in cosmetics have been introduced on the marked (the so-called Dillarstone effect) (Dillarstone, 1997). After an initial lag phase there is an outbreak of allergic contact dermatitis. Then, after recognition of the causes of the epidemic, the use of the preservative declines, and so does the number of cases with allergic contact dermatitis. In Denmark it was observed a significant decreasing trend in the frequency of positive patch tests to the preservative methyldibromo glutaronitrile after it was banned in cosmetics (Johansen *et al.*, 2008).

Skin sensitisation is considered as a significant hazard and is included as an endpoint in general toxicological testing and risk assessment of chemicals including ingredients of cosmetics (see Appendix). The problem so far is that methods of dose-response/potency assessment and quantitative risk assessment are not satisfactory. Although SCCP has evaluated the potency of several ingredients, fully quantitative risk assessments have not been performed. In the Memorandum on hair dye substances and their skin sensitising properties (SCCP, 2007), they have examined the hair dyes on the marked and classified them according to the Directive on dangerous substances 67/548/EEC and a further potency gradation (see Appendix). Of the adopted opinions on 46 hair dyes substances, 10 were categorised as extreme, 13 as strong and 4 as moderate skin sensitizers, all fulfilling the EU criteria for classification as a skin sensitizer (R43). In other words, these products should if they were not cosmetics be labelled with the risk phrase "R43, may cause sensitisation by skin contact".

There is a strong need for novel approaches to determine quantitative risk of skin sensitizers to cope with the situation. Such methods are currently under development and a report from a WHO/IPCS workshop on the topic has recently been published (van Loveren *et al.,* 2008). The International Fragrance Association (IFRA) has developed a new exposure-based methodological approach to assess the sensitisation risks and identify concentration limits for fragrance substances. This quantitative risk assessment (QRA) approach is based on the potency, dose-threshold and exposure of the skin sensitizer, like QRA for other threshold effects for cosmetic ingredients. It may be summarised in brief as presented on the homepage of IFRA (http://www.ifraorg.org).

In 2008, the European Commission requested SCCP to critically review the QRA methodology presented by IFRA to answer whether the QRA approach is appropriate to assess the sensitisation potential of fragrance substances in cosmetic products and set restrictions for use on the basis of this approach. SCCP was also asked whether this approach could be used for assessing the risk posed by sensitising cosmetic ingredients other than fragrances. The SCCP opinion on dermal sensitisation quantitative risk assessment (Citral, Farnesol and Phenylacetaldehyde) was adopted on 24 June 2008 and the initiative and development of a QRA approach from the industry was welcomed. However, SCCP emphasized that they could not endorse the industry proposed QRA approach for setting safe dose thresholds of exposure to the three ingredients in question, since the model had not been validated, and no strategy of validation has been suggested. Further, there is no confidence that the levels of skin sensitizers identified by the dermal sensitisation QRA are safe for the consumer. Even if the QRA strategy has been developed for fragrance ingredients, SCCP stated that it could in principle be applied to other cosmetic ingredients provided that the concerns stated in their opinion are addressed (SCCP, 2008).

In summary, there is a causal relationship between the exposure to a skin sensitizer, the subsequent events of skin sensitisation, elicitation, and the eventual manifestation of allergic contact dermatitis. Importantly, this causality implies that the risk of evolving allergic contact dermatitis is absent when exposure to the skin sensitizer is avoided or kept below the dose-threshold. In principle, skin sensitisation is not different from other toxicological hazards. Skin sensitisation, which represents permanent reduced resistance to a skin sensitizer and an enhanced risk of developing allergic contact dermatitis, must therefore be considered an adverse health effect. Future validated QRA methods might improve the risk characterisation of sensitising cosmetic ingredients.

4. CONCLUSIONS

In terms of sensitisation, should cosmetic products be considered differently than food products?

- Skin sensitisation and subsequent immune reactions following use of cosmetic products is mainly type IV. Type I sensitisation predominate in the gut after oral exposure. However, type I and IV sensitisation occur both in the gut and in the skin.
- It is often difficult for individuals sensitised to cosmetic ingredients to avoid/protect themselves from the sensitising compound, due to its extensive use in cosmetics, household products, textiles and the working environment of a variety of occupations, such as hairdressers and health care workers.
- Food allergy is often transient as tolerance develops in the majority of cases, whilst sensitisation to cosmetics is regarded as permanent.
- Most food allergens are naturally present in food and universally consumed and thus sensitisation will occur in genetically susceptible individuals. Although all sensitised individuals will carry the risk of clinical reactions, only about 30 – 40% will react to food. On the other hand, individuals who are proven sensitised to a cosmetic ingredient may all, if sufficient doses are applied, react to the chemical in question.
- In terms of sensitisation, allergic reactions to both food and cosmetics are similar because they require a sensitisation phase. However, since naturally occurring food allergens are inevitably connected with traditional human nutrition they cannot be eliminated from the market. On the other hand, cosmetic ingredients, as well as food additives causing allergic reactions, may be avoided.
- Food allergens naturally present in food should be considered differently than cosmetic ingredients.

Should sensitisation caused by exposure to cosmetic products be considered as an adverse health effect?

- There is a causal relationship between exposure to a skin sensitizer and clinical allergic responses. Elicitation of an allergic response requires prior sensitisation.
- Skin sensitisation is an acquired and irreversible immunological change. It appears to be a threshold dose for sensitisation. However, the threshold dose depends on a number of host and exposure factors, and there are no generally recognised methods to determine possible threshold doses.
- Elicitation of allergic responses occurs at considerably lower doses than those causing sensitisation.
- Allergic responses are considered adverse health effects. Sensitisation is a prerequisite for allergic responses, and strongly increases the risk of an allergic response.
- Sensitisation caused by exposure to cosmetic products must therefore be considered as an adverse health effect.

5. RECOMMENDATIONS

Sensitisation to cosmetic ingredients is common in the general population and may have serious consequences for those affected. Sensitisation to cosmetic ingredients may also have negative consequences for the tolerance to other consumer products, as well as occupational exposure to the same or cross-reacting sensitizers.

- In order to significantly reduce the risk of sensitisation to cosmetic ingredients, the exposure to substances with extreme and strong sensitising potency present in cosmetic products should be avoided. Exposure to moderate sensitizers should be minimized.
- Information to the consumer about the content of ingredients is beneficial in order to avoid elicitation of sensitised individuals.
- Quantitative risk assessment methods, which may improve the risk characterisation of sensitising cosmetic ingredients, should be further developed and validated in terms of both sensitisation and elicitation.

GLOSSARY

The explanations of the different terms in the glossary are mainly based on the proposals of the World Allergy Organisation Nomenclature Review Committee (Johansson *et al.*, 2004) and the European Academy of Allergy and Clinical Immunology (Johansson *et al.*, 2001). The website of the New Zealand Dermatological Society (www.dermnetnz.org), the website www.thefreedictionary.com, Merriam-Webster's Medical Dictionary (www.merriam-webster.com) and the Oxford Dictionary of Biology (5th edition) have also been used to define some of the terms in the glossary. The definition of sensitizers is according to Directive 1999/45/EC, as explained earlier in the opinion.

Antigen:	Any substance capable of inducing a specific immune response and of reacting with the products of that response, i.e. with specific antibody or specifically sensitised T lymphocytes, or both.
Allergen:	An antigen capable of causing an allergic reaction.
Allergy:	A hypersensitivity reaction initiated by specific immunologic mechanisms.
Anaphylaxis:	A severe, life-threatening generalized or systemic hypersensitivity reaction. The term allergic anaphylaxis should be used when the reaction is mediated by an immunological mechanism; i.e. IgE, IgG and immune complex complement-related. Anaphylaxis from whatever non-immunological cause should be referred to as non-immunological anaphylaxis. Full-blown anaphylaxis includes urticaria (hives) and/or angioedema (tissue swelling) with hypotension (low blood pressure) and bronchospasm (asthma).
Angioedema:	A skin reaction characterised by a sudden pronounced swelling of the skin and mucous membranes. All parts of the body may be affected but swelling most often occurs around the eyes and lips. Angioedema is very similar and can co-exist with urticaria, but affects deeper layers of the skin and is more painful and has a slower resolution.
Atopy:	A personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, and/or eczema.

$CD4^+$: T cell with CD4 receptor that recognizes antigens on the surface of a virus-infected cell and secretes lymphokines that stimulate B cells and killer T cells.

$CD8^+$: T cell with CD8 receptor that recognizes antigens on the surface of a virus-infected cell and binds to the infected cell and kills the cells.

Conjunctivitis: An inflammation or redness of the lining of the white part of the eye and the underside of the eyelid (conjunctiva). IgE-mediated allergic conjunctivitis commonly accompanies allergic rhinitis and is termed allergic rhinoconjunctivitis.

Contact dermatitis: An acute or chronic skin inflammation resulting from contact with an irritating substance or allergen. ***Allergic contact dermatitis*** is mediated by immunological mechanisms, predominantly Th_1 lymphocytes in close contact with the skin. It arises some hours after contact with the responsible material, and settles down over some days providing the skin is no longer in contact with it. If no immune mechanisms are involved, the reaction is called ***non-allergic contact dermatitis***, but terms like ***irritant*** or ***toxic contact dermatitis*** can also be used. This reaction occurs when chemicals or physical agents damage the surface of the skin faster than the skin is able to repair the damage. The reaction is often well demarcated with a glazed surface but there may be redness, itching, swelling, blistering and scaling of the damaged area. This may be indistinguishable from other types of contact dermatitis. ***Systemic contact dermatitis*** can occur after exposure to sensitizers through oral uptake.

Contact urticaria: See urticaria.

Cross-reaction: A reaction which occurs when antigenic determinants on different molecules of quite different sources are identical, so that antibody or cell-bound antigen-receptors directed against one antigen also reacts with another.

Cytotoxic T cells: A large differentiated T cell that attacks and lyses target cells bearing specific antigens.

Dermatitis: The umbrella term for a local inflammation of the skin. The terms dermatitis and eczema are often used interchangeably. In some cases the term eczematous dermatitis is used. Ezcema, contact

	dermatitis and other forms of dermatitis (including e.g. photosensitive dermatitis, seborrheic eczema) are all subgroups of dermatitis.
Eczema:	An acute or chronic inflammation of the skin. ***Acute eczema*** refers to a rapidly evolving red rash which may be blistered and swollen. ***Chronic eczema*** refers to a longstanding irritable area. It is often darker than the surrounding skin, thickened (lichenified) and much scratched. ***Atopic eczema*** is linked to raised circulating IgE levels and occurs in genetically predisposed people who have an atopic tendency. This means they may develop any or all of three closely linked conditions; atopic dermatitis, asthma and hay fever (allergic rhinitis).
Epidermis:	The outer protective layer of the skin, mostly consisting of flat, scale-like cells called squamous cells.
Gastrointestinal tract:	The digestive organs and structures, including the stomach and intestines.
Hapten:	A substance that is capable of inducing an allergic reaction only when it is bound to a carrier protein or other antigenic molecules.
Hypersensitivity:	Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons.
Hypersensitivity reactions:	An inappropriate and excessive reaction to an allergen (as pollen or certain foods). Severity ranges from mild allergy to severe systematic reactions leading to anaphylactic shock.
Immunoglobulin:	Any of a group of large glycoproteins that are secreted by plasma cells and that function as antibodies in the immune response by binding with specific antigens. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM.
Incidence:	The extent or rate of occurrence, especially the number of new cases of a disease in a population over a period of time.
Phenotype:	The observable properties of an organism, as determined by both genetic makeup and environmental influences.

Photo-allergic/toxic contact dermatitis:	A toxic or allergic reaction that occurs when certain chemicals are applied to the skin and subsequently exposed to the sun.
Prevalence:	The total number of cases of a disease in a given population at a specific time.
Sensitizers:	Substances and preparations which, if they are inhaled or if they penetrate the skin, are capable of eliciting a reaction of hypersensitisation such that on further exposure to the substance or preparation, characteristic adverse effect are produced (definition according to Directive 1999/45/EC). Allergens and hapten-carrier complexes are such substances.
T helper (Th) cells:	A T cell that participates in an immune response by recognizing a foreign antigen and secreting lymphokines to activate T cell and B cell proliferation, that usually carries CD4 molecular markers on its cell surface. Th_1 cells may be defined through their cytokine production, i.e. IL2 and IFN γ and others. Th_2 cells produce among others IL-4, IL-5 and IL-13. Th_1 cells protect against intracellular pathogens, activate phagocytes and produce delayed hypersensitivity responses, while Th_2 cells protect against extracellular pathogens, activate eosinophils and are responsible for IgE-mediated hypersensitivity.
Tolerance:	Unresponsiveness to an antigen that normally produces an immunological reaction.
Urticaria:	Urticaria refers to a group of disorders characterised by the rapid appearance of wheals and/or angioedema. The release of chemicals such as histamine from mast cells in the skin causes small blood vessels to leak and results in tissue swelling. The wheals are itchy and often surrounded by a red flare. The wheals have a fleeting nature and may last a few minutes or several hours. Urticaria that develops through immunological mechanisms (IgE-mediated) after locally topical contact with an allergen, are referred to as allergic contact urticaria.

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APPENDIX

Classification and categorisation of skin sensitizers

Skin sensitizers are regulated in documents produced by EU, OECD and WHO/IPCS (van Loveren *et al.,* 2008). The EU Scientific Committee on Consumer Products (SCCP) has reflected on this regulation in two memorandum documents (SCCP 2005; 2007). The following overview is based on these references.

Directive 67/548/EEC and 1999/45/EC regulate the classification and labelling of dangerous substances and preparations. According to these directives substances and preparations shall be classified as sensitising and assigned the symbol "Xi" and the risk phrase "R43, may cause sensitisation by skin contact":

- if practical experience shows the substance or preparation to be capable of inducing a sensitisation by skin contact in a substantial number of persons
- where there are positive results from an appropriate animal test.

The default concentration value for labelling of preparations with R43 is 1%. Preparations containing >0.1% of a classified sensitizer must have the warning phrase "Contains xxx (name of the substance) May cause an allergic reaction".

The Cosmetic Directive 76/768/EEC (EC, 1976) is not using labelling with the risk phrases of Directive 67/548/EEC.

Animal test methods used in harmonised classification of substances, according to their potential to cause skin sensitisation (Directive 67/548/EEC and 1999/45/EC) are the Guinea Pig Maximisation Test (GPMT), the Buehler test, and the Local Lymph Node Assay (LLNA). The same animal test methods are used for evaluating cosmetic ingredients in accordance with the Cosmetic directive 76/768/EEC (EC, 1976) and the SCCP Notes of Guidance for Testing of Cosmetic Ingredients and Their Safety Evaluation (SCCP, 2006). As yet, there is not a validated *in vitro* test method accepted for skin sensitisation. Positive results from the OECD guideline animal tests (OECD 406 and OECD 429) sufficient to classify a substance with R43 are:

- GPMT: if at least 30% of the animals have a positive response
- Buehler test: if at least 15% of the animals have a positive response
- LLNA: if at least a 3-fold increase in proliferative counts is induced, compared to vehicle-treated controls (stimulation index $SI \geq 3$).

Further categorisation of substances classified with R43 into three groups according to allergen potency (extreme, strong and moderate) has been proposed by an expert group nominated by the Technical Committee of Classification and Labelling in EU (Basketter *et al.,* 2005; ECB, 2002a; 2002b). Such potency classification of skin sensitizers is based on EC3 values (estimated concentration of a chemical required to produce a 3-fold stimulation of draining lymph node cell proliferation compared with concurrent controls) in the LLNA, on

intradermal induction concentration in the GPMT, and topical induction concentration in the Buehler test. When EC3 values are available from more than one study, the lowest value should normally be used. Where multiple animal data sets lead to different categorisation of the same substance, the higher potency category should apply.

There are also ongoing discussions within the new European Community Regulation on chemicals and their safe use (REACH) on whether sensitizers should be classified according to potency gradation (REACH Implementation Project (RIP) 3.6, Working Group 2, ECBI/20/08 Rev.1)

Human test results are also used for regulatory purpose such as classification with R43, limitations, and approval to use (EC, 1994; 2003). The application of test results is specified in Annex VI of Directive 67/548/EEC. The following evidence (practical experience) is sufficient to classify a substance with R43 (SCCP, 2005):

- positive data from appropriate patch testing in more than one dermatological clinic study, or
- epidemiological studies showing allergic contact dermatitis caused by the substance or preparation. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small, or
- positive data from experimental studies in man.

The following is sufficient to classify a substance with R43 when there is supportive evidence:

- isolated episodes of allergic contact dermatitis, or
- epidemiological studies where chance, bias or confounders have not been ruled out fully with reasonable confidence.

Supportive evidence may include:

- data from animal tests performed according to existing guidelines, with a result that does not meet the criteria given in the section on animal studies but is sufficiently close to the limit to be considered significant, or
- data from non-standard methods, or
- appropriate structure-activity relationships.