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Allergens in Consumer Products

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Abstract

Allergens in consumer products

Many consumer products contain substances that can cause an allergic reaction, such as contact dermatitis or contact eczema. A reaction can also occur due to allergen exposure through the airways. However, little is known about this type of reaction. The main causes of contact dermatitis are nickel contained in jewellery and fragrances in cosmetics. Products containing preservatives and some types of wax can also be the cause of an allergic reaction. Both the degree to which the user is exposed to the substance and its concentration are important factors in determining how the reaction will develop.

The Food and Consumer Product Safety Authority (VWA) commissioned the RIVM to make an inventory on the degree to which people suffer discomfort from skin and other allergies due to substances in consumer products. Contact dermatitis is relatively common in the Netherlands compared to other conditions such as asthma, hay fever and food allergies. Allergic conditions belong to the most common chronic conditions occurring in Europe.

Limit values have been set by law for a number of allergenic substances contained in products, but these have not yet been based on a quantitative risk assessment. A quantitative approach determines which dosage level can induce a reaction. Knowledge of this critical dosage level is essential in order to set safe limit values of allergens in a particular product.

Two quantitative methods are currently under development, but these are not yet ready to be used in daily practice. It is particularly important that exposure to more than one product (aggregated exposure) is included in this methodology to a satisfactory extent.

Key words:
allergens, consumer products, contact allergy, legislative limit values, quantitative risk assessment

Rapport in het kort

Allergenen in consumenten producten

Veel consumentenproducten bevatten stoffen die een allergische reactie van de huid kunnen veroorzaken (contact dermatitis of contacteczeem). Ook kan een reactie ontstaan bij blootstelling via de luchtwegen, maar hierover is weinig bekend. Grootste veroorzakers van contact dermatitis zijn nikkel in sieraden en geurstoffen in cosmetica. Daarnaast kunnen conserveermiddelen en harssoorten in producten een allergische reactie veroorzaken. Zowel de sterkte van de stof als de mate waarin de gebruiker eraan blootstaat zijn van belang voor de aard van de reactie.

In opdracht van de Voedsel en Waren Autoriteit (VWA) heeft het RIVM geïnventariseerd in welke mate mensen last hebben van (huid)allergie door stoffen in consumentenproducten. Contact dermatitis komt in Nederland relatief veel voor vergeleken met astma, hooikoorts en voedselallergie. Allergische aandoeningen behoren tot de meest voorkomende chronische ziekten in Europa.

In de wet zijn limietwaarden voor een aantal allergene stoffen in producten vastgesteld. Deze limietwaarden zijn vooralsnog niet gebaseerd op een kwantitatieve risicobeoordeling. Bij een kwantitatieve aanpak wordt vastgesteld bij welke dosis een reactie optreedt. Dit is essentieel om veilige limietwaarden van allergenen in een product af te leiden.

Er zijn twee kwantitatieve methoden in ontwikkeling, die in de praktijk nog niet bruikbaar zijn. Het is vooral belangrijk dat blootstelling via meerdere producten (geaggregeerde blootstelling) op een adequate manier wordt meegenomen in deze methodiek.

Trefwoorden:
allergenen, consumentenproducten, contact allergie, wettelijke limietwaarden, kwantitatieve risicobeoordeling

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List of abbreviations

γ-methylionone	3-methyl-4-(2,6,6-trimethyl-2-cyclohexe-1-yl)-3-buten-2-one
AEL	acceptable exposure level
AHTN	6-acetyl-1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydronaphtalene
BEUC	European consumer's organisation
BHT	butylated hydroxytoluene
BIT	1,2-benzisothiazolin-3-one
CE-DUR	clinical epidemiology-drug utilisation research
CEL	consumer exposure level
CMI/MI (Kathon CG)	5-chloro-2-methyl-4-isothiazolin-3-one/ 2-methyl-4-isothiazolin-3-one
DALY	disability adjusted life years
DIY	do-it-yourself
DNCB	dinitrochlorobenzene
DST	dermal sensitization threshold
EC3	estimated concentration to produce SI≥3
ELINCs	European list of notified chemical substances
EPA	Environmental Protection Agency
ESS	European standard series
EU	European Union
GHS	globally harmonised system
GMT	glyceryl monothioglycolate
GPMT	guinea pig maximization test
HICC (Lyral)	hydroxyisohexyl-3-cyclohexene carboxaldehyde
HMPCC	hydroxyl-methyl-pentyl-cyclo-hexene-carboxaldehyde
HMT	human maximization test
HRIPT	human repeat insult patch test
IFRA	International Fragrance Association
INCI	International Nomenclature of Cosmetic Ingredients
IVDK	German information network of departments of dermatology
LC	Langerhans cell
Lilial®	butylphenyl methylpropionial
LLNA	local lymph node assay
LOEL	lowest observed effect level
MDGBN (Euxyl K400)	methyldibromoglutaronitrile
MTI	2-methyl-4,5-trimethylene-4-isothiazolin-3-one
NESIL	no-expected-sensitization-induction-level
NO(A)EL	no observed (adverse) effect level
PPD	para-phenylene diamine
QRA	quantitative risk assessment
QSAR	quantitative structure activity relationship
REACH	Registration, Evaluation, Authorisation and restrictions of CHemical substances
RIFM	Research Institute for Fragrance Materials
SAF	sensitization assessment factor
SCC(NF)P	Scientific Committee on Consumer (Non Food) Products
SCHER	Scientific Committee on Health and Environmental Risks
SI	stimulation index

TDA	toluene-2,5-diamine
TDI	toluene diisocyanate
TTC	Threshold of Toxicological Concern
VWA	Nederlandse Voedsel en Waren Autoriteit, Dutch Food and Consumer Products Safety Authority
WMS	Wet Milieugevaarlijke Stoffen

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Summary

The aim of the current document is to provide more insight in the different aspects that are related to allergies due to the use of consumer products. Consumers are exposed to allergenic compounds via various consumer products such as cosmetics, toys and detergents. To protect consumers from allergenic effects, different policy measures are implemented, varying from a ban, labeling, concentration limits and consumer education. The Dutch Food and Consumer Products Safety Authority (VWA) initiated a project to investigate the size of the problem caused by allergens in consumer products, with the purpose to indicate the importance of controlling allergenic substances in consumer products and to point the direction of possible further investigations in this field.

From the present inventory it is clear that a lot of consumer products like cosmetics, toys, clothing and textile, and scented products contain chemical allergens that have the potential to induce either contact dermatitis or respiratory allergy in consumers. Also products that are known to cause allergy in an occupational setting, such as cleaning products and detergents, do-it-yourself and hair-dye products are frequently used in a domestic setting where they may also induce or elicit allergic reactions.
Compounds with an allergenic potency that are found in consumer products are metals like nickel and chromate; a large group of fragrances like isoeugenol, d-limonene, oak moss and Peru balsam; preservatives like isothialozinones, methyldibromoglutaronitrile, CMI/MI, and formaldehyde; (hair) dyes like para-phenylene diamine (PPD) and resins and solvents like colophonium. The main product groups responsible for induction of contact dermatitis in consumers were metallic accessories and cosmetics.
In addition, an inventory on market studies as performed mostly in Denmark and the Netherlands was made on various consumer product types. These data give insight into the use of certain compounds, the frequency and used concentrations. Allergens that are most frequently found in consumer products are the fragrances d-limonene, linalool, Lilial® and geraniol and the preservative group of the parabens.
Allergic diseases are among the most common chronic disorders in the Western countries. From occupational allergies such as occupational asthma and contact dermatitis it is known that they can severely impair the quality of life over a prolonged period of time, causing loss of productivity.
In general, the prevalence of contact dermatitis (3.7% in men and 5.4% in women in the Netherlands) is relatively high when compared to other allergic diseases such as asthma, rhinitis and food allergy (3-5%, 1.5-3% and 1-3%, respectively). In European epidemiological studies it was demonstrated that the prevalence of contact dermatitis was in the range of 7-28% and an important part of this was caused by nickel (7-19%) and cosmetics and fragrances (3-4%). A substantial part of the cases are caused by allergens present in consumer products. The specific contribution of the various substances in consumer products to this prevalence of contact dermatitis was mapped in this document. After combining all data, the most prevalent allergenic substances causing contact dermatitis in patients appeared to be nickel, fragrance mix I, Peru balsam, cobalt chloride, potassium dichromate, colophonium, PPD and thiurams. Unfortunately, only very little information is available with respect to respiratory allergies caused by allergens present in consumer products.
To predict the sensitizing potential of a substance, different validated animal models can be used, while also information of human patch tests might be useful. Sensitizers can be classified as either stronger or other sensitizers. From the inventory on potency, it was shown that the most potent sensitizers are CMI/MI, PPD, methylisothiazolinone, formaldehyde, benzoisothiazolinone, potassium dichromate, nickel and isoeugenol. It is important to realize that sensitizing potency plays an important role in the risk of getting sensitized, but that exposure dose and frequency are involved in this too. Nickel, for instance, is the most important skin sensitizer in humans. The potency of nickel is moderate, but other

factors, like exposure via ear piercings, play an important role in the risk of sensitization. For some (extremely) weak sensitizers, such as d-limonene and parabens, it has been demonstrated that although these chemicals are abundantly present in products, they are rare causes of contact dermatitis. In contrast, strong sensitizers, like isoeugenol and oak moss, are not often present in consumer products, but are categorized as frequent sensitizers in patients. Hence, for strong and weak sensitizers the risk of getting sensitized seems to depend predominantly on skin sensitizing potency of the chemical, but for the group of moderate sensitizers other factors, such as exposure are of importance too.
To protect the consumer from sensitization, several types of regulations are in force in the EU. First there is prohibition of the use or presence of some allergens in cosmetics and toys. Furthermore, two different types of limits are used: 1) Maximum limit values, e.g. for nickel and preservatives, and 2) Limits of declaration, for fragrances in cosmetics and for all sensitizers in preparations.
However, limits are in most cases mainly based on practical choices, and not based on a quantitative risk assessment. Furthermore, declaration limits might prevent already sensitized people from elicitation (and thus complaints) by avoiding products with the specific sensitizer on the label, but they do not necessarily protect new sensitization cases. Apparently, the current legislation is not sufficient to prevent the occurrence of contact dermatitis and a better control of the exposure to sensitizers in consumer products is needed.
This can be reached by derivation of safe limit values for sensitizers in consumer products by the use of an adequate and quantitative risk assessment (QRA) approach for sensitizers. Currently, Industry has proposed two approaches: QRA (demonstrated for fragrances) and the Threshold of Toxicological Concern (TTC) for skin sensitizers based on derivation of a no-expected-sensitization-induction-level (NESIL) and the subsequent use of different sensitization assessment factors (SAFs). These methods, still under development, are an important step forward in quantification of safe levels when compared to the traditional risk assessment of sensitizers, which is only a hazard (yes or no) assessment. One of the major drawbacks is that the risk is determined per compound per product and aggregated exposure (exposure via different products or sources) is not taken into account. Furthermore, essential for a solid risk assessment, a more scientific basis is needed on the used assessment factors specific for sensitization on intraspecies, interspecies, duration and matrix effects. These approaches are both focused on dermal sensitization. Additionally, respiratory allergy needs attention, also because the relationship between dermal and respiratory sensitization is not clear which can lead to an additional risk.

In conclusion, a substantial part of consumer products contain allergenic substances resulting in relatively high prevalences of contact dermatitis. Despite the current legislation, contact dermatitis is still a problem. What is urgently needed is the derivation of safe limits of frequently used allergens in consumer products by the use of a validated QRA method which also takes aggregate exposure into account. Therefore the QRA method needs to be further developed and improved. Also a monitoring system is needed for the effectiveness of the QRA method. In addition, information on the levels of sensitizers in consumer products and frequency of use is needed in combination with prevalences of contact dermatitis, including time trends. This is important for the determination of the impact of legislation on prevalence of contact dermatitis. For those consumers already sensitized, prevention of complaints is possible using labeling. To make things easier for the consumer, labeling should be simplified, for instance by the use of codes instead of the difficult chemical names.
Currently there is a lack of information on the effects of inhalation exposure of sensitizers. However, the large number of consumer products that are available in spray (trigger or air space spray) form, which contain several sensitizers, will lead to respiratory exposure. Therefore, more information needs to become available on the effects of this exposure in terms of respiratory sensitization and elicitation, for example in patients with contact dermatitis.

Samenvatting

Het doel van het huidige rapport is om het inzicht te krijgen in de verschillende aspecten die gerelateerd zijn aan allergie door het gebruik van consumentenproducten. Via allerlei producten zoals cosmetica, speelgoed en was- en reinigingsmiddelen kunnen consumenten aan allergenen worden blootgesteld. Om de consument te beschermen tegen allergieën worden diverse maatregelen getroffen variërend van een verbod, etikettering, het vaststellen van concentratielimieten tot consumentenvoorlichting. De Nederlandse Voedsel en Waren Autoriteit (VWA) heeft een project geïnitieerd om de omvang van het probleem dat veroorzaakt wordt door allergenen in consumentenproducten in kaart te brengen. Dit met het doel om het belang van de beheersing van allergene stoffen in consumentenproducten aan te geven en om richting te geven aan eventueel toekomstig onderzoek op dit gebied. De bevindingen van deze inventarisatie staan beschreven in dit document.

Uit de huidige inventarisatie blijkt dat veel consumentenproducten zoals cosmetica, speelgoed, kleding, textiel en geurproducten chemische stoffen bevatten die de potentie hebben om of contact dermatitis of respiratoire allergie te veroorzaken. Ook producten waarvan bekend is dat ze allergische effecten op de werkvloer veroorzaken, zoals was- en reinigingsmiddelen, doe-het-zelfproducten en haarverf worden vaak door consumenten gebruikt alwaar ze ook allergische reacties kunnen induceren of ontlokken. Stoffen met een allergene potentie die in consumentenproducten voorkomen zijn metalen zoals nikkel en chromaat; een grote groep geurstoffen zoals isoeugenol, d-limoneen, oak moss, en Peru balsam; conserveermiddelen zoals isothialozinonen, methyldibromoglutaronitrile, CMI/MI, en formaldehyde; (haar) kleurstoffen zoals para-phenylene diamine (PPD) en harsen en oplosmiddelen zoals colofonium. De belangrijkste productsoorten die verantwoordelijk zijn voor het induceren van contact dermatitis in consumenten zijn metalen accessoires (op kleding en juwelen) en cosmetica.
Voor de verschillende productgroepen zijn in Denemarken en Nederland markstudies uitgevoerd om meer inzicht te krijgen in het gebruik van de verschillende stoffen, de frequentie waarmee ze in consumentenproducten voorkomen en de gebruikte concentraties. Allergenen die het meest in consumentenproducten voorkomen zijn de geurstoffen d-limoneen, linalool, Lilial® en geraniol, en voor de groep van conserveermiddelen de parabenen.

Allergische aandoeningen behoren tot de meest voorkomende chronische ziekten in de westerse wereld. Vanuit werkgerelateerde allergieën is bekend dat de kwaliteit van leven als gevolg van astma en contact dermatitis verslechtert over een langere periode met verlies van productiviteit als gevolg.
Over het algemeen is de prevalentie van contact dermatitis in Nederland (3,7% in mannen en 5,4 % in vrouwen) relatief hoog ten opzichte van de prevalentie van andere allergische aandoeningen zoals astma, neusverkoudheid en voedselallergie (respectievelijk 3-5%, 1,5-3% en 1-3%). Europese epidemiologische studies laten een prevalentie van contact dermatitis van 7-28% zien en een belangrijk deel hiervan wordt veroorzaakt door nikkel (7-19%) en cosmetica en geurstoffen (3-4%). Een substantieel deel van de gevallen worden dus door allergenen in consumentenproducten veroorzaakt. De specifieke bijdrage van de verschillende stoffen aan deze prevalenties van contact dermatitis is in dit document in kaart gebracht. Hieruit blijken de meest prevalente allergenen voor contact dermatitis in patiënten nikkel, geurstoffen mix I, Peru balsem, cobaltchloride, kaliumdichromaat, colofonium, PPD en thiuramen te zijn. Er is heel weinig bekend over respiratoire allergie als gevolg van allergenen in consumentenproducten.

Om de sensibiliserende potentie van een stof te voorspellen kunnen verschillende gevalideerde diermodellen worden gebruikt. Daarnaast kan ook informatie uit humane plak testen bruikbaar zijn. Sensibiliserende stoffen kunnen worden ingedeeld in ‘sterker’ en ‘anders’. Met anders worden de matig

en zwak potente sensibiliserende stoffen bedoeld. Vanuit de inventarisatie die gemaakt is voor de potentie, blijkt dat CMI/MI, PPD, methylisothiazolinone, formaldehyde, benzoisothiazolinone, kaliumdichromaat, nikkel en isoeugenol de hoogste sensibiliserende potentie hebben. Het is hierbij van belang om te realiseren dat sensibiliserende potentie weliswaar een grote rol speelt in het risico om gesensibiliseerd te raken, maar dat ook dosis en frequentie van blootstelling hierin een rol van betekenis spelen. Nikkel bijvoorbeeld is een bekende sensibiliserende stof voor de huid. De potentie van nikkel is matig, maar de relatief hoge blootstelling zoals via piercings resulteert toch in een hoog risico voor sensibilisatie. (Extreem) zwakke allergenen zoals d-limoneen en parabenen die veel in consumentenproducten voorkomen, veroorzaken weinig gevallen van contact dermatitis. De sterk potente allergenen zoals isoeugenol en oak moss komen zeer zelden voor, maar worden in de patiënten vaak als sensibiliserende stof geïdentificeerd. Dus voor sterke en zwak sensibiliserende stoffen is het risico om gesensibiliseerd te raken voornamelijk afhankelijk van de potentie, terwijl voor de matig potente stoffen naast de potentie voornamelijk de blootstelling belangrijk is.

Om de consument tegen sensibilisatie te beschermen zijn in de EU verscheidene soorten regelgeving van kracht. Ten eerste is er een verbod op de aanwezigheid en het gebruik van sommige allergenen in cosmetica en speelgoed. Daarnaast worden twee verschillende typen van limieten gehanteerd:
1) Maximale limiet waarden, zoals voor nikkel en conserveermiddelen en 2) Declaratielimieten, voor geurstoffen en alle sensibiliserende stoffen in preparaten. Deze beide limieten zijn in de meeste gevallen gebaseerd op praktische overwegingen en niet op een kwantitatieve risicobeoordeling. Declaratielimieten zorgen ervoor dat personen die al gesensibiliseerd zijn het product met de specifieke substantie kunnen vermijden en zo een elicitatiereactie kunnen voorkomen. Deze declaratielimieten beschermen echter niet tegen de inductie van een nieuwe sensibilisatiereactie omdat de stof, mits gedeclareerd, er in theorie tot 100% in mag zitten. Omdat contact dermatitis ondanks de huidige wetgeving nog steeds een probleem is, is de huidige wetgeving blijkbaar niet voldoende voor de bescherming tegen het voorkomen ervan. Er is een betere controle nodig op de blootstelling aan sensibiliserende stoffen in consumentenproducten.

Dit doel kan worden bereikt door veilige limietwaarden voor sensibiliserende stoffen in consumentenproducten af te leiden door middel van een adequate en kwantitatieve methode van risicobeoordeling (QRA) voor sensibiliserende stoffen. Op dit moment heeft de industrie twee benaderingen voorgesteld: QRA (geïllustreerd voor geurstoffen) en de threshold for toxicological concern (TTC) methode die de drempel vaststelt waarboven vanuit toxicologisch oogpunt reden tot zorg kan zijn. Deze beide methoden zijn opgesteld voor sensibiliserende stoffen voor de huid en zijn gebaseerd op de afleiding van een no-expected-sensitization-induction waarde (waarde waarbij geen inductie van sensibilisatie wordt verwacht, NESIL). Daarnaast worden verschillende sensibilisatie assessment factoren (SAF's) toegepast. Deze methoden, die nog steeds in ontwikkeling zijn, zorgen voor een belangrijke stap voorwaarts in de kwantificering van veilige waarden voor sensibiliserende stoffen vergeleken met de traditionele methoden waarin alleen maar een ja/nee-antwoord wordt gegeven. Een van de grootste nadelen is echter dat het risico wordt vastgesteld per stof per product en dat geaggregeerde blootstelling (blootstelling via verschillende producten) niet wordt meegenomen. Verder is voor een betrouwbare risicobeoordeling een meer wetenschappelijke basis nodig voor de gebruikte assessmentfactoren met name voor de specifieke factoren voor intraspecies, interspecies, duur van blootstelling en matrix-effecten. Naast dermale sensibilisatie waarop beide methoden nu gericht zijn, moet er ook aandacht zijn voor sensibilisatie via respiratoire blootstelling. Vooral omdat de relatie tussen dermale en respiratoire sensibilisatie nog niet helder is en dit kan leiden tot een extra risico.

Concluderend kan worden vastgesteld dat een substantieel deel van consumentenproducten allergenen stoffen bevatten die resulteren in een relatief hoge prevalentie van contact dermatitis. Ondanks de huidige wetgeving is contact dermatitis nog steeds een groot probleem. Het afleiden van veilige

limietwaarden voor vaak gebruikte allergenen in consumentenproducten is daarom hoognodig. Dit kan door gebruik te maken van een kwantitatieve risicobeoordeling die ook rekening houdt met geaggregeerde blootstelling. Daarom moet de methode zoals nu voorgesteld door de industrie verder ontwikkeld en verbeterd worden. Ook is een systeem nodig om de effectiviteit van de QRA-methode te monitoren. Bovendien is meer informatie nodig over de concentraties van sensibiliserende stoffen in consumentenproducten in combinatie met prevalentiecijfers van contact dermatitis, inclusief trends in de tijd. Dit is belangrijk omdat op deze manier de invloed van wetgeving op prevalenties kan worden gevolgd. Consumenten die al gesensibiliseerd zijn kunnen klachten vermijden door geen producten te gebruiken waar de allergenen in zitten waar zij gevoelig voor zijn. Dit kunnen zij controleren door gebruik te maken van de productinformatie op het etiket of de bijsluiter. Om het voor de consument makkelijker te maken moet de informatie op de etiketten versimpeld worden bijvoorbeeld door het gebruik van codes in plaats van de complexe chemische namen.
Er is momenteel een gebrek aan informatie over de effecten van blootstelling aan sensibiliserende stoffen via inhalatie. Toch zijn er veel consumentenproducten bekend die beschikbaar zijn in spray vorm, die allergene stoffen bevatten en dus tot respiratoire blootstelling aan allergenen kunnen leiden. Meer informatie over effecten na inhalatoire blootstelling met betrekking tot respiratoire sensibilisatie en elicitatie, bijvoorbeeld in patiënten met contact dermatitis, is noodzakelijk.

1 Introduction

Allergic diseases, most commonly occurring as rhinitis, asthma, food allergy and atopic dermatitis are among the biggest causes of health problems worldwide. In developed countries allergic diseases are among the most common chronic disorders, affecting up to 15-30% of the population (European Allergy White Paper, 1997). Various genetic and environmental factors play a role in the development of allergies, including the quality of housing, different feeding habits and our changed industrial and chemical environment. Although the understanding of allergies has improved considerably in the last decades, changes in environment and lifestyle has lead to new allergies which may reach wide proportions in the future. Allergies can severely impair the quality of life over a prolonged period of time, causing loss of productivity and workdays leading to major economic repercussions. In many countries allergic diseases have, apart from being responsible for high costs of health care, a major negative impact on the burden of socio-economic costs (European Allergy White Paper, 1997).

Allergies can be provoked by different external stimuli. Pollen and house dust mites are involved in the development of rhinitis, food contains several known allergens that can induce food allergy and contact dermatitis may be caused by various components in consumer products like cosmetics, cleaning products, clothing and toys. Currently, there is limited information on the prevalence of contact allergy due to the use of by consumer products in the Netherlands. In addition, it is unknown what the contribution of the prevalence of contact allergy is to the prevalence of allergic diseases in general, including also asthma, rhinitis and food allergy. Furthermore, the information on the impact of contact dermatitis, in terms of quality of life, work absence and socio-economic costs is scarce.

Within its responsibility to monitor the safety of consumer products, the Dutch Food and Consumer Products Safety Authority (VWA) has initiated a project to gain more insight in several aspects related to allergies due to the use of consumer products. In this document an initial inventory of important categories of allergens in consumer products has been made. In addition, information on the prevalence of contact dermatitis due to consumer products in the general population, as well as which allergens are most prevalent, is collected. Furthermore, an attempt is made to give an impression of the health care expenses and socio-economic costs that is related to contact dermatitis. Finally the information needed to conduct a quantitative risk assessment (QRA) on sensitizers, e.g. information on potency of allergens, thresholds for sensitization, and realistic exposure scenarios, will be discussed.
This inventory aims to provide more insight in the magnitude of the problem of contact dermatitis caused by allergens in consumer products and to identify knowledge gaps. Furthermore, the gathered information will be used to assess whether or not the current legislation is sufficient to protect the consumer for an allergic reaction.

2 Background and definitions

2.1 Allergy

Allergy is defined as an adverse condition which manifests itself following a hypersensitivity reaction towards an otherwise harmless antigen. The type of allergy that is induced is dependent on the route of exposure and the allergen. Exposure to allergens that are present in consumer products occurs predominantly via the skin, for instance via cosmetics or clothing. In addition, some products, e.g. cleaning products and scented products, will lead to exposure via inhalation. After skin contact with chemical allergens, allergic contact dermatitis can develop, whereas after exposure via inhalation, respiratory allergy can be induced.

2.1.1 Allergic contact dermatitis

Allergic contact dermatitis is a type IV or delayed type hypersensitivity reaction, which means that it is an allergic response that is mediated by T cells. As is true for all allergies, contact dermatitis comprises two phases: an induction phase in which the immune system is sensitized and an elicitation phase in which the clinical symptoms manifest themselves. Whether a person develops contact dermatitis is dependent on several factors, related to the chemical and to the host. The most important factors are the potency of the allergen, the dose of the substances (as a function of dose per skin area), the degree of inflammation that is induced, and the condition of the skin, whereas genetic susceptibility plays a minor role in contact sensitization. Potent sensitizers are able to sensitize virtually all exposed individuals, whereas less potent chemicals sensitize only susceptible individuals. In contrast to type I type hypersensitivities, such as asthma or food allergy, the atopic status of a person, e.g. the ability to mount an IgE response, is not involved in the susceptibility for contact dermatitis (Kimber and Dearman, 2002). Chemical allergens are mostly low molecular weight compounds that can only induce sensitization when they are capable of penetrating the skin and binding to proteins in the epidermis. The sensitization and elicitation phases of contact dermatitis are illustrated in Figure 1. After penetrating the skin, the chemical binds to proteins and hapten-carrier complexes are formed, which are recognized and processed by Langerhans cells that migrate to the draining lymph nodes. In the lymph nodes, Langerhans cells present the hapten-carrier complex to T cells, which in turn are activated and start to proliferate and generate so-called memory T cells. These T cells recirculate and gain access to the skin. After a second encounter with the substance, the hapten complex is processed again by Langerhans cells and presented to these circulating memory T cells present in the skin. The activation of these T cells causes a rapid release of cytokines and other inflammatory mediators, leading to a dermal inflammatory response. Clinical symptoms occur 24-72 hours after exposure to the allergen and typical symptoms of contact dermatitis are rash, blisters, hives and itchy burning skin (Kimber et al., 2002).
In irritant, non-allergic contact dermatitis, a non-specific response of the skin is causing the inflammation, typically manifested by erythema, mild edema, and scaling. A corrosive agent causes the immediate death of epidermal cells as manifested by chemical burns and cutaneous ulcers. However, this type of skin disease is out of the focus of this report.

2.1.2 Respiratory allergy

Pulmonary immune reactions can be induced by several exogenous factors. When these responses are provoked by proteins, e.g. pollen, a type I hypersensitivity reaction is induced which involves IgE production. For low molecular weight chemicals conjugated to proteins, that cause pulmonary immune responses the situation is more complex and underlying mechanisms are often unknown. Besides inducing a type I hypersensitivity, certain chemicals can provoke a type IV hypersensitivity response in the lungs. Inhalation of the skin-allergens dinitrochlorobenzene (DNCB), dinitrofluorobenzene and picryl chloride induced in rodents symptoms such as laryngitis, pneumotis, and airway hyperreactivity that were mediated by specific T lymphocytes (Garssen et al., 1991; Buckley and Nijkamp, 1994; Arts and Kuper, 2007). In addition to these specific immune responses, exposure to certain chemicals can provoke asthma-like symptoms as a result of non-specific irritation of the airways. Toluene diisocyanate (TDI) is a chemical known to cause occupational asthma. The precise mechanism is unknown. Since TDI does not induce IgE in all patients, it is thought that either type I or type IV hypersensitivity reactions can be induced. In addition, non-specific irritation of the airways can also occur (Wisnewski and Redlich, 2001). Hence, pulmonary responses elicited by chemical allergens are mechanistically complex and not as unequivocal as responses observed after dermal exposure.

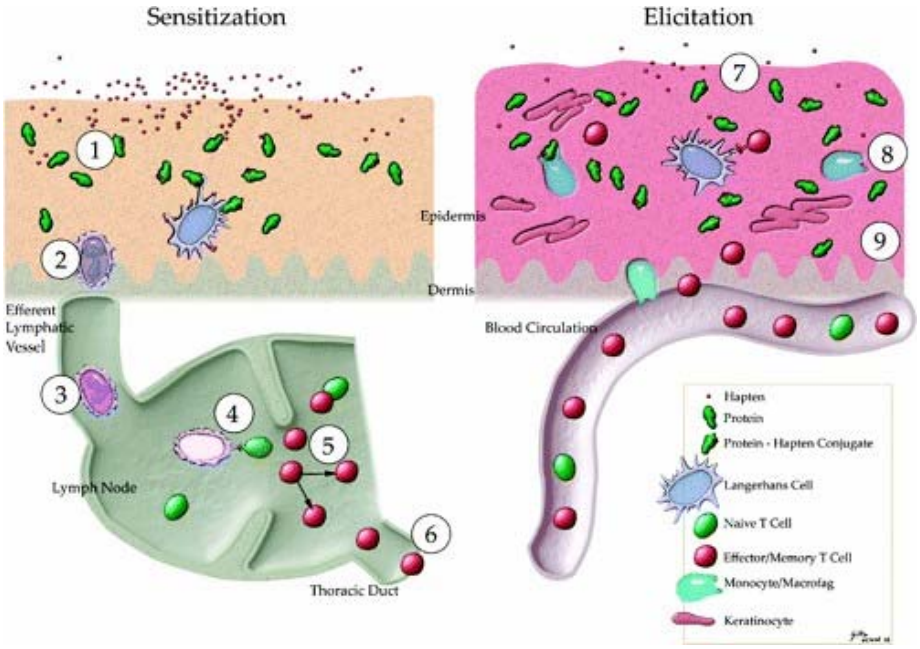

Figure 1: Induction and elicitation of allergic contact dermatitis

* adapted from Karlberg et al. (2008).
(1) Binding of haptens to proteins and other macromolecules. (2) Internalization of hapten-modified proteins. (3) Hapten-induced activation of LCs that migrate and process hapten–protein complexes. (4) Presentation of antigens by LCs to naive specific T-cells. (5) Proliferation of antigen specific T-cells; memory T-cells are formed. (6) Hapten-specific memory T-cells leave the lymph node and enter the circulation. (7) Re-exposure to the hapten. (8) Release of cytokines and chemokines attracting cells to the skin from the circulation. (9) Inflammatory response within 24–48 h, symptoms of ACD.

For general differences between induction (sensitization) and elicitation of contact dermatitis induced by chemicals see also Table 1.

Table 1 Differences between sensitization and elicitation of contact dermatitis (simplified)

	Sensitization	Elicitation
Exposure dose	High(er)	Low(er)
Frequency of exposure	Several	Single
Effect	No symptoms	Allergic reaction on skin

2.2 Legislative aspects of allergens in consumer products

Several legal frameworks exist which are applicable to chemical substances in consumer products. Information relevant for allergens in consumer products is given in the following summary.

2.2.1 General Product Safety Directive 2001/95/EC

In the General Product Safety article 18a of the 'Warenwet' in the Netherlands, it is stated that it is prohibited to sell products of which the trader knows or might expect that they are a danger to the safety or health of humans, taking into account the expected use. This article is based on a European Directive, the European General Product Safety Directive 2001/95/EC.

2.2.2 Current and future classification and labelling Directives

Dangerous Substances Directive 67/548/EC

Substances can be classified based on their hazardous characteristics such as mutagenic, carcinogenic, reprotoxic, irritating or sensitizing properties according to criteria in the Annex VI of the Dangerous Substances Directive 67/548/EC. In the Netherlands, this European Legislation is implemented in corresponding Dutch Act i.e. 'Wet Milieugevaarlijke Stoffen (WMS)'.
Substances can be classified as skin sensitizer (R43) or respiratory sensitizer (R42). A substance is classified as a respiratory sensitizer, when there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or if there are positive results from an appropriate animal test. R42 embraces all materials that are implicated as inducers of occupational asthma, elicited either by immunological or non-immunological mechanisms.
A substance is classified as a skin sensitizer (R43) when there is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons, or if there are positive results from an appropriate animal test. A response is needed in more than 30% of the animals in a test with adjuvant (Guinea Pig Maximization Test (GPMT)), or of more than 15% in a test without adjuvant (Buehler test). When the Local Lymph Node Assay (LLNA) is employed, a three-fold increase in proliferation in the draining lymph nodes compared to the control group (Stimulation Index (SI) ≥3) is used as a cut-off point to designate a chemical as a skin sensitizer (OECD, 2002).
Up to the 29th ATP (Adaption to Technical Progress) meeting, 3,366 substances are listed in Annex I of this Directive. Of these substances, 643 are classified as skin sensitizers, 26 as respiratory allergens and 51 substances are labelled with both R42 and R43. The general concentration limit for

classification as a skin sensitizer is 1%. Specific concentration limits have been set for more than 20 substances classified as skin sensitizers, e.g. formaldehyde 0.2%, glutaraldehyde 0.5%, acrylated 0.5 - 0.2%, isocyanates 0.5 - 0.1%, and CMI/MI 3:1 15 ppm.
The list with classified chemicals (Annex I of Directive 67/548/EEC) is used by some other Directives, resulting in a ban or a specific concentration limit of the use of substances classified. It is included in e.g. the Biocides Directive, the Preparations Directive (1999/45/EC), the Limitations Directive (76/769/EEC), the Cosmetics Directive (76/768/EEC) and the Toys Directive (88/378/EC).

Preparations Directive (1999/45/EC)

The Preparations Directive (1999/45/EC) states that preparations should be classified as sensitizing with R42 when they contain substances which are classified as skin or respiratory sensitizers. For non-gaseous preparations, the preparation should be assigned Xn and R42 (inhalation) or R43 (skin), when the substance is classified with R42 or R43 respectively and present in the preparation in a concentration ≥ 1%. For gaseous preparations, the preparation should be assigned Xn and R42 or R43 when the concentration of the classified substance in the preparation is ≥ 0.2%. Furthermore, for preparations which are not labelled as sensitizing but contain a sensitizing substance, Annex V (9) gives the following restriction: The packaging of preparations containing at least one substance classified as sensitizing and being present in a concentration equal to or greater than 0.1 % or in a concentration equal to or greater than that specified under a specific note for the substance in Annex I to Directive 67/548/EEC must bear the inscription: 'Contains (name of sensitizing substance). May produce an allergic reaction.'

GHS

The Globally Harmonised System of Classification and Labelling of Chemicals (GHS) is the new single, globally harmonized system to address classification of chemicals, labels, and safety data sheets all over the world. It has been developed by several organizations i.e. International Labour Organization (ILO), OECD, and the United Nations Sub-Committee of Experts on the Transport of Dangerous Goods (UNSCETDG) and required a long-term commitment from these organizations involved. The first version of the GHS was adopted in December 2002 by the Sub-Committee on the Globally Harmonized System of Classification and Labelling of Chemicals (SCEGHS). In June 2007 a proposal to implement GHS was accepted by the EU. This EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation will replace aspects of the REACH Regulation (Registration, Evaluation, Authorisation and Restrictions of CHemical substances) which the industry is currently incorporating into its policies. CLP (or in the Netherlands EU-GHS) will replace in time the Directives dealing with classification and labelling of substances and mixtures (67/548/EC and the Preparations Directive 1999/45/EC). The Regulation will become effective in 2009 and the final part in June 2015. Criteria for sensitization in CLP are similar to the ones in the Preparation Directive. One minor difference is that preparations are called mixtures under CLP. See Tables 16 and 17 in Appendix 1 for the CLP classification of sensitizers.
Within the OECD, a scientific issue paper is written on strong versus weak sensitizers. This might lead to subclassification for substances or mixtures in two different categories, category 1A stronger sensitizer and category 1B other sensitizer (OECD, 2008):
For respiratory sensitizers, subcategory 1A, substances should show a high frequency of occurrence in humans and/or severity of reaction within an exposed population; or a probability of occurrence of a high sensitization rate in humans based upon animal or other tests. For subcategory 1B, a substance should show a low to moderate frequency of occurrence in humans and/or severity of reaction within an exposed population; or a probability of occurrence of a low to moderate sensitization rate in humans based upon animal or other tests. For this type of sensitizers, there are no validated animal models.

For skin sensitizers, subcategory 1A, substances should show a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered. For subcategory 1B, a substance should show a lower frequency of occurrence in humans and/or a low potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.
This proposal has been discussed at an OECD meeting in April 2008. After that, it first needs to be accepted for GHS, followed by adoption in European Legislation.

2.2.3 Limitations Directive 76/769/EEC and REACH

The Limitations Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations includes measures for specific substances. One 'sensitizer' example in this regulation is the use of nickel in jewellery. Nickel is allowed in all post assemblies which are inserted into pierced ears and other pierced parts of the human body on the condition that the rate of nickel release from such post assemblies is less than 0.2 $\mu g/cm^2$/week (migration limit).
This European legislation is implemented in corresponding Dutch Acts e.g. the 'Warenwet' for consumer products. The new chemical legislation of REACH has started in 2007. It should regulate all chemical substances within the European Union and will replace (in time) over 60 existing directives and regulations including The Directive for Existing Chemicals, the Directive for New Chemicals, and the Limitations Directive (76/769/EEC). With REACH an integrated system is implemented for the Registration, Evaluation, Authorisation (grant permits) and Restrictions of CHemical substances. Starting point of the proposal is that in the future not the Member States, but Industry is responsible for providing and assessing the information to consider whether use of certain chemicals might be a risk for man or environment.

2.2.4 Specific directives and regulations

Cosmetics Directive (76/768/EEC)

The Cosmetics Directive (76/768/EEC) covers cosmetics and hygiene products, and parts of the Directive focus on the prevention of contact dermatitis.
Annex II of this Directive is a list of 1132 substances (mostly CMR substances) which are not allowed in cosmetic products. Among them are also sensitizers, for example, methyleugenol, with the exception of its presence in natural extracts but still not allowed in higher concentrations than 0.1% in perfume, 0.004% in eau de toilette, 0.002% in perfumed cream, 0.001% in rinse-off products and 0.0002% in leave-on products and products for oral hygiene.
Annex III is a list of substances (about 90) which are allowed with a limit or with special restrictions. Amongst them is the list of 26 allergenic fragrances compiled by the Scientific Committee on Consumer Non Food Products (SCCNFP) (see Tables 2 and 3, chapter 3). The restriction for these fragrances is that products need to be labelled when the concentration is $\geq 0.001\%$ in leave-on, and $\geq 0.01\%$ in rinse-off products. Some oxidative hair dyes with sensitizing properties are included with a specific concentration limit, with the restriction to label the product, and/or with the obligation that is only used by professionals, or not for eye-lashes and brows. Regarding sensitizers, it is important to remark that preservatives (which are frequently found to be sensitizing) are only allowed if they are listed in Annex VI, part 1 of this Directive, or are allowed with a specific concentration limit as specified in Annex VI, part 2. Examples are formaldehyde and paraformaldehyde which are allowed up

to 0.2% or 0.1% for oral hygiene products, and forbidden in sprays, and methylchloroisothiozolinone/ methylisothiazolinone (CMI/MI or Kathon^{R}CG) which is not allowed above 15 ppm.
Furthermore, the use of INCI-names on the labels is obliged. INCI stands for International Nomenclature of Cosmetic Ingredients. With the unique INCI-name persons with an allergy can make a safe choice without a language barrier.

Detergents Regulation 648/2004

The Detergents Regulation 648/2004 follows the rules of classification, packaging and labelling from the Dangerous Substances Directive. Starting in 1989 ingredients in cleaning agents were voluntarily mentioned as groups. The current regulation includes the following provisions on labelling which should be applied to the packaging of detergents sold to the general public. The following weight percentage ranges should be used to indicate the content of the constituents listed below: less than 5%, 5% or over but less than 15%, 15% or over but less than 30%, 30% and more. This is applied for phosphates, phosphonates, anionic surfactants, cationic surfactants, amphoteric surfactants, non-ionic surfactants, oxygen-based bleaching agents, chlorine-based bleaching agents, EDTA and salts thereof, NTA nitrilotriacetic acid and salts thereof, phenols and halogenated phenols, paradichlorobenzene, aromatic hydrocarbons, aliphatic hydrocarbons, halogenated hydrocarbons, soap, zeolites, and polycarboxylates, when where they are added in a concentration above 0.2% by weight. The following classes of constituent, if added, should be listed irrespective of their concentration: enzymes, disinfectants, optical brighteners, perfumes. The final adaptation of this Regulation (2005) included that allergenic fragrances appearing on the list of substances in Annex III, part 1 to Directive 76/768/EEC shall be listed when exceeding concentrations of 0.01%.

***Toy Directive** 1988/378/EEC1*

Council Directive 1988/378/EEC1 regulates the safety of toys in Europe, and currently a revision is proposed in which 38 allergenic substances are banned and 26 other allergenic fragrances are obligatory labelled.

2.2.5 Summary legislation

The above mentioned legislations are intended to protect consumers. However, in almost all cases limits are arbitrarily chosen, and are not based on a quantitative risk assessment. In frameworks determining legislation up till now, no quantitative risk assessments are performed for the endpoint sensitization. Restrictions regarding labelling are aiming to help already sensitized people preventing exposure and thus avoiding elicitation. The question remains whether these limits are sufficient in practice to protect consumers from allergic reactions.

3 Allergens in consumer products

A number of allergenic substances have been identified in a wide range of consumer products. Substances in products that come in contact with skin play an important role as exogenous factors in the triggering of allergenic contact eczemas at work, but also at home. Also respiratory allergy can be induced by substances in consumer products, but information on this is very scarce. In persons that are sensitized to a certain allergen, allergic responses can be induced by other chemicals, that are structurally related, a phenomenon that is called cross-reactivity. For consumer products, most information is available on allergenic substances in cosmetic products, but also information on the presence of such substances in other products like detergents, toys, textiles, and do it yourself products is available. The presence of a substance as such is not always a problem: a substance can exert its sensitizing action only as it is available for dermal contact and/or can be released from its matrix or can enter the lungs.
In this chapter an inventory is made of allergens that were found in (non-food) consumer products (section 3.1) and in addition an inventory is made of the most important product categories that may contain allergenic substances (section 3.2). Also the most frequent cross reactions are mentioned.

3.1 Important categories of contact allergens

The most important allergenic substances in consumer products are schematically pictured in Table 18 (Appendix 2) and presented below in more detail (BfR report 2006, www.huidarts.com , Thyssen et al., 2007a). Five main categories of allergic substances in consumer products can be distinguished: metals, fragrances, (hair) dyes, preservatives and resins/ solvents.

3.1.1 Metals

Nickel

Nickel is a hard, silvery white metal that resists corrosion, even at high temperatures. It was first identified in 1751 by the Swedish chemist Baron Axel Fredrick Cronstedt by attempting to extract copper from niccolite (kupfernickel) (reviewed in Thyssen et al., 2007a). The first report of contact dermatitis caused by nickel exposure (‘galvanization eczema’) appeared in the late 1880s (Blascho, 1889, reviewed in Thyssen et al., 2007a). In 1925, by patch testing, nickel was proven to be the etiological factor for the development of dermatitis in the electroplating industry (Schittemhelm and Stokinger, 1925). In 1931, the first case of nickel dermatitis among consumers of nickel-plated objects worn in direct skin contact was observed (Mc Alester et al., 1931) and after that an accumulation of cases took place, especially among female customers. Products that were responsible for this increase in cases were: nickel-plated suspenders (1930-1960s), metal buttons and zippers in blue jeans (1970s) and jewelry (1980) (reviewed in Thyssen et al., 2007a).
Nowadays, nickel is still used in many industrial and consumer products and is by far the most important contact allergen around the world. For instance in Germany, up to 4.5 million people are sensitized to this allergen (Schnuch et al., 2002). Sources are jewellery, piercings, and clothing accessories, but nickel is also present in household appliances, kitchenware, electric fibres, pieces of equipment and instruments (www.huidarts.com). For individuals that are already sensitized to nickel, oral exposure from cooking utensils and electric kettles may also be relevant (EFSA, 2006).

Recently, because of the regulatory interventions on nickel in Europe (Nickel Directive, 1994) that lead to a diminished nickel release in consumer products, nickel-induced contact dermatitis decreased. However, it still remains the most common allergen in patch tests all over Europe (Uter et al., 2005). In the USA, where no regulation has been introduced, nickel continues to be responsible for clinical disease amongst youngsters (Thyssen et al., 2007a).

Chromium and potassium dichromate

Chromium is a steel grey, lustrous, hard metal that takes a high polish. It was first identified in 1797, and is primarily used not only in metal alloys and plating but also in leather tanning, paint anti-corrosives, ceramics and chemicals (Thyssen et al., 2007a). Historically the most important cause of contact dermatitis from chromium has been occupational exposure to cement. Only trivalent Cr (III) and hexavalent Cr (VI) oxidation states of chromium act as haptens (small molecules which can elicit an immune response only when attached to a large carrier such as a protein). By heating the trivalent compound Cr_2O_3 to 1400-1500°C, Cr (VI) is produced in cement. Also potassium dichromate was shown to be an extreme hapten (reviewed in Thyssen et al., 2007a). After making the addition of iron sulfate (reducing the water soluble chromate content to <2 ppm) to cement compulsory in Denmark, the prevalence of chromium allergy among construction workers in Denmark has decreased (Avnstorp, 1989). In 2005, an EU Directive that restricts the marketing and use of cement containing > 2 ppm Cr (VI) came into force (Chromium Directive, 2005). However, the epidemiology and clinical picture of chromium allergy has changed form an occupational to a consumer problem. Leather products are now responsible for the main chromium exposure (Zachariae et al., 1996). Besides leather clothing, chromium and potassium dichromate are still found in cement and other building materials, glazing, paints, leather gloves and shoes as well as in materials for uniforms. In addition, potassium dichromate is found as a contamination in various substances. Cross reactions between potassium dichromate and chromium III and IV compounds were described.

Cobalt

Cobalt is a metal found naturally in soil, dust, and seawater. It is usually found in association with nickel. Cobalt and its salts have many uses, some of the many sources of cobalt are cobalt blue pigment in porcelain, glass, pottery, ceramics and enamels, cobalt blue in blue and green water, colours paints and crayons, metal-plated objects, clothing accessories such as buckles, buttons and zippers, costume jewellery, and hair dyes. In a review of several European studies from 1972 to 1990, Rietschel and Fowler reported prevalences of cobalt allergy ranging from 4.6% to 7.7%, somewhat lower than prevalences of nickel allergy (7.3% to 17.4%) (Rietschel and Fowler, 1995). Cross reactivity with nickel is possible but occurs not very frequently (www.huidarts.com).

3.1.2 Fragrances

The use of perfumes and fragrances was already described for the civilizations of ancient times in which the use of perfumes was a luxury, reserved for the elite of society. The perfumes were used in connection with mortuary rituals, anointments and - like today – as part of a beauty care (Frosch et al., 1998; Frosell, 1982). The perfumes at that time were produced on the basis of extracts of naturally occurring substances from for instance flowers, trees, herbs and animals secretions. Developments within the chemical industry have made it possible to produce the popular fragrances synthetically. Single fragrant components of a perfume are called fragrances; specific scents of certain perfumes are created by combining different fragrances.

Today, more than 5,000 fragrance substances are frequently used as mixtures, particularly in cosmetics (perfumes, shampoos, creams, shower gel, toothpaste), household products (room fresheners and carpet

shampoo), textiles, shoes and toys. Fragrances have been identified as the most frequent cause of contact dermatitis to cosmetic products (reviewed in SCCNFP, 1999).
In 1999, the Scientific Committee on Cosmetic Products and Non Food products intended for consumers (SCCNFP, now known as SCCP) has identified 24 fragrance chemicals potentially resulting in contact allergy and divided them in two different lists. A list of most frequently reported and well-recognized contact allergens (list A, Table 2) and a list with fragrances less documented as consumer allergens (list B, Table 3).

Table 2 Fragrances - most frequently reported as consumer allergens

Common name	CAS no
Amyl cinnamal	122-40-7
Amylcinnamyl alcohol	101-85-9
Benzyl alcohol	100-51-6
Benzyl salicylate	118-58-1
Cinnamyl alcohol	104-54-1
Cinnamal	104-55-2
Citral	5392-40-5
Coumarin	91-64-5
Eugenol	97-53-0
Geraniol	106-24-1
Hydroxycitronellal	107-75-5
Hydroxymethylpentyl-cyclohexenecarboxaldehyde (HMPCC)	31906-04-4
Isoeugenol	97-54-1

Source: SCCNFP (1999).

Table 3 Fragrances - Less frequently reported as consumer allergens

Common name	CAS no
Anisyl alcohol	105-13-5
Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3
Citronellol	106-22-9
Farnesol	4602-84-0
Hexyl cinnamaldehyde	101-86-0
Lilial®	80-54-6
d-Limonene	5989-27-5
Linalool	78-70-6
Methyl heptine carbonate	111-12-6
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexe-1-yl)-3-buten-2-one (= γ-methylionone)	127-51-5

Source SCCNFP (1999).

It has to be emphasized that fragrance chemicals in this list are probably not the only compounds that can elicit allergenic reactions. Other fragrance chemicals may also be allergenic but are not identified as such due to a lack of data. Two different fragrances mixtures (fragrance mixture I and II) are developed and used to screen for general susceptibility of individuals to fragrances. Components of fragrance mix I are cinnamyl alcohol, cinnamaldehyde, eugenol, alpha-amyl-cinnamaldehyde,

hydroxycitronellal, geraniol, isoeugenol and oak moss absolute (existing of atranol and chloroatranol). Fragrance mix II is composed of alpha-hexyl cinnamaldehyde, citral, citronellol, farnesol, coumarin and hydroxymethylpentylcyclo-hexenecarboxaldehyde. The list of 24 fragrances is in a later stadium completed with oak moss and tree moss. The subdivision of fragrances has recently been adapted by Schnuch et al., (2007) see also Table 4 in chapter 4.

Peru balsam (Myroxylon Pereirae resin)

The natural product Peru balsam is made from the wound exudation of the Peru balsam tree. It is a mixture of chemical substances and its content is therefore varying qualitatively and quantitatively. The perfume materials benzyl cinnamate and benzyl benzoate are among the main components. Apart from this, it contains small amounts of e.g. vanillin. Peru balsam is used as fragrance in cosmetics, shoes and tobacco but also as component of oil paint and medical products for eczema, haemorrhoids and chilblained hands. Cross reactions are possible with for instance colophonium, other fragrances, and turpentine (www.huidarts.com).

3.1.3 Preservatives

Preservatives in consumer products prevent the growth of micro organisms and increase the storage life of the product. Preservatives are common causes of contact dermatitis and in general, the cycle of market introduction of a new preservative in cosmetics is followed, after a delay, by an outbreak of contact dermatitis. This repetitive cycle is called the Dillarstone-effect (Dillarstone, 1997). The group of preservatives contains several chemically different compounds such as isothiazolinones, parabenes, halogen compounds, and formaldehyde liberators. A standard series of preservatives used for diagnosis of occupational contact dermatitis (Kiec-Swierczynska et al., 2006) consists of thiomersal, Euxyl K400 (=MDGBN) formaldehyde, Kathon CG (= CMI/MI), Quaternium-15 (= formaldehyde liberator) and parabens.

Isothiazolinones

Members of this group of preservatives are 1,2-benzisothiazolin-3-one (BIT), 5-chloro-2-methyl-4-isothialzolin-3-one (CMI) and 2-methyl-4-isothiazolin-3-one (MI). Isothiazolinones are substances that have irritating, sensitizing and corrosive characteristics. The use of BIT in cosmetics is currently prohibited (EU Cosmetics Directive).

Preservatives containing CMI/MI have been widely used since the late 1970s in Europe and early 1980s in the USA (Law et al., 1984). They have mostly been used in glues, waxes, paints, varnishes, leather clothing, wood preservatives, mixed water dyes, cosmetics and toiletries. In the 1980s, the first cases of allergic contact dermatitis amongst workers and consumers were reported in Sweden (Bjorkner et al., 1986; Gruvberger, 1997). After that, additional reports of CMI/MI-induced allergic contact dermatitis were published and the prevalence of positive patch test reactions increased in unselected eczema patients (reviewed in Thyssen et al., 2007a). This was attributed to the use of cosmetic leave-on products that contained a concentration of CMI/MI that was within the recommended levels of that time (30 ppm, Fewings and Menne, 1999). Since the 1990s, the recommended level for cosmetic leave-on and rinse-off products was further limited in the EU to 7.5 and 15 ppm, respectively. However, the elicitation threshold for CMI/MI containing solutions is demonstrated to be very low (< 2 ppm, Zachariae et al., 2006), so further monitoring is still necessary. Cosmetics and industrial products containing only MI and not CMI that have been introduced recently still have the potential for eliciting and probably inducing contact dermatitis in humans (Isaksson et al., 2004, Thyssen et al., 2006).

Methyl dibromoglutaronitrile (MDBGN)

In 1983 and 1985, Euxyl® K400 was marketed in Europe for the preservation of industrial and cosmetic products, respectively. The product, a combination of MDBGN and 2-phenoxyethanol (PE) in a 1:4 ratio, was introduced as a potent alternative to CMI/MI. The first case of allergic contact dermatitis in a worker with glue containing MDBGN was reported in 1983 (Mathias, 1983). Allergic contact dermatitis to Euxyl® K400 is almost exclusively induced by MDBGN and only rarely because of PE. The maximum concentration of MDBGN in cosmetic products was regulated in 1986, however, since 1989 increasing cases of MDBGN-induced allergic contact dermatitis from cosmetic products have been reported, in various European countries including the Netherlands (De Groot et al., 1996, Wilkinson et al., 2002). It is generally acknowledged that there has been a risk assessment failure concerning MDBGN. Therefore, an amendment to the European Cosmetic Directive has been added in 2005, restricting the use of MDBGN to rinse-off products only and in a very low concentration. Furthermore, the SCCP recently recommended (SCCP/0863/05) that MDBGN should not be present in any cosmetic product (SCCP, 2005a). However, it is still used for the prevention of decay by bacteria and fungi in detergents and ultrasound gel.

Formaldehyde or formaldehyde liberators

Formaldehyde is a colourless flammable gas with a strong pungent odour. It was first synthesized in 1859 and since 1897 the production of formaldehyde grew significantly (reviewed in Thyssen et al., 2007a). Formaldehyde appears as free formaldehyde, formaldehyde donated from formaldehyde-releasing preservatives and finally as formaldehyde resins. The free and preservative form of formaldehyde is used not only as preservative in household products such as detergents, topical medications, and cosmetics but also in industrial products such as paints, cutting fluids, lacquers and disinfectants. In fact, formaldehyde releasing products have replaced free formaldehyde in most cosmetics and industrials products as they are less frequent sensitizers (Fransway, 1991). However, the main use of formaldehyde is in the form of formaldehyde resins in which formaldehyde is combined with phenol, urea or melamine (see also section 3.1.5). Apart from a variety of cases of occupational sensitization to formaldehyde, consumer sensitization has been observed, mainly for clothing and cosmetics. The decrease in cases observed in the 1970s, when compared to the 1950-1960s, was due to the development of new textile finishes that released less formaldehyde. During the 1980s a decline in the use of formaldehyde in leave-on cosmetics was observed, due to a combination of increasing incidences of formaldehyde sensitization, the EU directive and increasing preservation with CMI/MI. However, nowadays, formaldehyde sensitization remains high as a result of continuous product preservation with formaldehyde and formaldehyde-releasing preservatives (Wilkinson et al., 2002).

Thiurams (Thiuram mix)

This substance mixture consists of the following substances: tetramethylthiuram monosulphide, tetramethylthiuram disulphide, tetraethylthiuram disulphide en dipentamethylenethiuram disulphide. It is used as a vulcanization accelerator in rubber products like rubber gloves, spray and adhesive plasters. Furthermore it is used as preservative in medical products, or insect repellents. Cross reactivity is possible with other carbamates (BfR, 2006).

Thiomersal

Thiomersal (in the US known as Thimerosal) is a mercuric derivative of thiosalicyclic acid that goes by many names. It has been used as a disinfectant (Merthiolate) and a preservative in some vaccines, cosmetics, tattoo inks, eye drops and contact lens solutions. In addition to vaccines and anti-toxins, thiomersal is also used as a preservative in cosmetics, such as makeup removers, eye moisturizers,

mascaras and bleaching creams. Cross reactions are possible with other mercury compounds (www.huidarts.com).

3.1.4 (Hair) Dyes

Contact dermatitis caused by hair dyes is an important and increasing health problem for consumers, hairdressers and society. Hair dyes are causing acute and severe dermatitis on the face, scalp and neck in consumers, and hand eczema in hairdressers.

p-Phenylene diamine

Among the extremely potent skin sensitizers are para-phenylene diamine (PPD) and related compounds that have been used for more than 100 years. More than two thirds of the hair dyes that are currently used contain PPD, a colourless, slightly pink, grey or yellow crystalline solid (lumps or powder). Chemically, it is an aromatic amine that turns red, brown and then finally black on oxidation. PPD has been used as a fur and textile dye, as anti-oxidants in rubber and in paint, varnishes, plastics and henna additive (temporary tattoos). Currently, PPD is mainly used for permanent hair dyeing and is an ingredient in almost every hair colour product on the market, regardless of brand. Hair dyeing with henna became increasingly popular during the 19th century, and introduction of PPD gradually replaced henna as the preferred hair dye in Europe. Because of the sensitization of hair dressers by PPD (Cathelineau, 1898, reviewed in Thyssen et al., 2007a) it was prohibited in Germany in 1906 (Fregert, 1972). One year later, the French chemist Eugene Schueller, founder of L'Oreal, developed a hair colour based on PPD that later caused increasing numbers of contact dermatitis amongst hair dressers. In the 1930s, accumulating cases of contact dermatitis made Bonnevie to suggest that PPD became part of the patch test standard series (Bonnevie, 1936). In the following years, PPD was prohibited in Sweden and France (Fregert, 1972). In the 1960s, hair dyeing became a popular home cosmetic procedure in the USA; the use in the female population increased from 7 to 50% in only 6 years. Today hair dyeing is widely applied (>75% of women use hair dyes) (www.hairproducts.com, Thyssen et al., 2007a).
Under the EU cosmetics directive, PPD is allowed in hair dye products with a concentration limit of 6%. Even though the applied concentration of PPD is usually lower than this limit, sensitization to PPD is high amongst hairdressers and can cause severe contact dermatitis, both in hairdressers and consumers (Health and Safety Executive, 2006). Furthermore, an increase was noted in the frequency of sensitization to PPD among clients using hair dye in Germany between 1995 and 2002 (Thyssen et al., 2007a). Since the use of hair dye is becoming increasingly popular, the permitted PPD use concentration clearly calls for a review. The possibility to decrease the concentration limit for PPD is currently under discussion. Patients reacting to PPD can have cross reactions with other para-substances like azo- and aniline dyes (www.huidarts.com).

Other hair dye substances

Oxidative hair dye formulations contain precursor (p-phenylenediamine, p-aminophenol) and coupler (m-aminophenol, resorcinol) molecules, which are mixed with peroxide under alkaline conditions and applied to the hair. The molecules (precursor and coupler) oxidatively couple to form coloured molecules (oxidative hair dyes) (SCCP, 2005b). So apart from PPD as mentioned in the previous section, more hair dye substances have the potential to give an allergenic reaction. The SCCP and the former SCCNFP have recently assessed the dossiers of 46 of the 117 hair dye substances that are of interest to industry and studied their skin sensitizing properties. Examples of well-known hair-dye substances are toluene-2,5-diamine (TDA), 1-hydroxyethyl-4,5-diaminopyrazole and p-Aminophenol (all precursors) and 4-amino-2-hydroxytoluene, 2,4-diaminophenoxyethanol and 2-methylresorcinol

(all couplers). A detailed overview of the potencies of the 46 investigated hair dye substances (precursors and couplers) is given in Table 30, Appendix 6 (SCCP, 2006a).

Other dyes

Disperse dyes are colorants with low water solubility that, in disperse colloidal form, are suitable for dyeing and printing hydrophobic fibres and fabrics. Azo dyes represent the largest group of disperse dyes that can cause allergy by cross-reaction with structurally similar compounds, including PPD. Azo dyes are mainly present in fibres that are used in textile. Common examples of skin-sensitizing disperse dyes are Disperse Blue 106, 124 and 85 (BfR, 2006).

3.1.5 Resins and solvents

Colophonium

Colophonium is a natural product made from the resin from conifers. It has a variety of applications, such as in glues, paints and printing inks. Furthermore, it is used in paper and cardboard, detergents, and cosmetics such as eye shadow, mascara, shampoo and medical products for external use. Cross reactions are possible with turpentine, Peru balsam, and other fragrances (BfR, 2006, www.huidarts.com).

Epoxy resin

Epoxy resin is used as binding agent in various types of glues and is a component of paints for ships, cars and leather (www.huidarts.com).

Formaldehyde resins

Examples of formaldehyde resins are P-tert.-butylphenol-formaldehyde resin, (ethylene urea) melamine formaldehyde, and urea formaldehyde. These are commonly used as adhesive and binder in plywood, carpeting, paper, pulp, plastic, textile finishing and the wet-strength resin added to sanitary paper products (Thyssen et al., 2007a).

Turpentine oil

Turpentine oil is used as a solvent and diluting agent in varnishes, paints, shoe polishes, resins, and building materials. Cross allergies have been reported between turpentine oil and various fragrances and tea tree oil (www.huidarts.com).

3.2 Relevant consumer products and materials

3.2.1 Clothing (and non-clothing) textiles

Between 1 and 2% of contact allergies in dermatological clinics in Germany are triggered by textiles (BfR Textile Working Group, BfR, 2006). Approximately 7000 preparations of textile auxiliaries and finishing agents are known. Furthermore there are 4000 colorants and dyes handled in textiles of which 50% are azo-dyes. In some cases, carcinogenic and allergenic amines may be released from them after reductive cleavage when applied to the skin (Collier et al, 1993.; Platzek et al, 1999). Highly sensitizing disperse dyes are Disperse Blue 106, 124, and 85 which often are used in combination and can release PPD or p-aminoazobenzene after azo-cleavage. Around 2/3 of all textile related cases of allergy are attributed to disperse dyes (Hatch and Maibach, 1995; Lazarov, 2004). Other important allergens in clothing are potassium dichromate (leather clothes, see below), formaldehyde-releasing resins (wash-and-wear finish) and rubber chemicals like thiurams, dithiocarbamates or benzothiazoles (in rubber bands) (Schnuch et al., 2004a).

3.2.2 Leather clothing including gloves and shoes

Potassium dichromate is one of the most important contact allergens in leather products (BfR, 2006). Also hexavalent (VI) and trivalent (III) chromium appear to be present in leather products like (baby) shoes, (working) gloves, jackets trousers, tops, skirts and hats according to a Danish study in 2001 (Rydin, 2002, see also chapter 5). This is remarkable since it is relatively easy and well-known to produce leather without any hexavalent chromium. Furthermore, azo dyes as well as p-tert-butyl-phenol formaldehyde resin from adhesives may play a role as allergen in shoes.

3.2.3 Cosmetics

Cosmetic products are, as mentioned earlier, together with clothing the most important skin-contact product group. Therefore it is not surprising that high sensitization rates were identified for a number of ingredients of both leave-on and rinse-off cosmetic products in a study on contact allergies caused by consumer products. These ingredients were a combination of fragrances and preservatives such as fragrance mixture, Peru balsam, MDBGN, wool wax alcohols, and CMI/MI (Schnuch et al., 2004a). A market survey on moisturizers on the Swedish market showed that the majority of moisturizers contained at least one of the 9 most common preservatives that can cause an allergic reaction (Gruvberger et al., 1998).
Cosmetic hair products contain, besides fragrances and preservatives (MDBGN, CMI/MI), various hairdresser substances like ammonium per sulphate, PPD, and p-aminophenole as precursors or degradation products of hair dyes and thiurams as rubber ingredients. Because of these ingredients, hair products can lead to face, head en neck eczemas (Schnuch et al., 2004a). The SCCNFP/SCCP also examined hair dyes of which some of them were found to have highly sensitizing properties. Labelling provisions for hair dye substances are taking place at this moment (SCCP, 2006a).
Since fragrances have been identified as the most frequent cause of contact allergy to cosmetic products, the SCCP assessed in 1999 24 special fragrances on their sensitizing properties (list is given in Tables 2 and 3). In its expert opinion of Sept 25th 2001, an initial list of perfumery materials was drawn by the Committee and it strongly recommends restricting the use of these, sometimes highly sensitizing substances or imposes special requirements on their use (SCCNFP, 2001a,b).

The Danish EPA performed several surveys and risk assessments of chemical substances in cosmetics such as deodorants and cosmetic products for children (http://glwww.mst.dk/homepage/). For this last product group, also a Dutch study was carried out. Details of these studies are reported in chapter 5.

3.2.4 Tattoos, permanent make up and henna tattoos

Skin reactions caused by tattoos are mainly allergic reactions. Although skin reactions caused by tattoos rarely occur, they can be rather severe according to the Information Network of Departments of Dermatology (IVDK) in Germany. Besides metal-containing substances in dye mixtures, also sensitizing dyes as well as amines (impurities or cleavage products) in tattooing agents play a key role. In addition, henna tattoos (temporary tattoos) are a major problem, since they are often darkened with the sensitizing p-phenylene diamine (black henna). In the EU, PPD is forbidden in henna tattoos and only permitted in cosmetics for use in oxidating hair dyes. Nevertheless, black henna is frequently used, also for body painting in children (BfR, 2006)

3.2.5 Cleaning products and detergents

Several investigations have shown that cleaning personnel often has hand eczema, due to the combination of wet work and dermal exposure to cleaning agents. In Denmark, cleaning agents for industrial and household use are registered in the Danish Product Register Data Base (PROBAS). In 1992, the most registered cleaning product types containing contact allergens were general cleaners (skin cleaners, hair shampoos,) and floor polishes. Contact allergens found in these product categories were mainly preservatives like isothiazolinones and formaldehyde, and surface active agents like coconut diethanolamide (Flyvholm, 1993). Also, (laundry) detergents are commonly used consumer products that contain allergenic preservatives and fragrances. Recently, both in Denmark and in The Netherlands, surveys on marketed detergents and cleaning products on the market have been carried out. It was found that in both countries allergenic fragrances (and preservatives) were present in the majority of the detergents. Furthermore, there is growing evidence that cleaning workers are at increased risk for developing asthma (Zock et al., 2007), a manifestation of respiratory allergy (see also chapter 2). Specific professional cleaning products have been identified that are associated with asthma including bleach and sprays, products that are also widely applied in private households. Recently, the risk of new onset asthma has been studied in relation to the use of common household cleaners in a domestic setting (Zock et al., 2007). Details of the market surveys on cleaning products are given in chapter 5.

3.2.6 Toys and children's articles

The addition of potential allergenic fragrances to a wide variety of children's articles that in earlier years were only available in unscented versions is increasing. The aim of scent addition is to differentiate them from similar non-scented products in order to make them more attractive. Examples are teddy bears and school articles (speed markers, erasers and pencils, reviewed in Glensvig et al., 2006). In this way, exposure to perfume has increased in children. By playing with toys containing potential allergenic fragrances, children are potentially exposed via skin absorption, inhalation or by ingestion of the substances. It is assumed that due to this intensified contact with perfume and fragrances, the number of children with perfume allergy has increased heavily in recent years. Already in 1999, the SCCNFP proposed that manufacturers should avoid the use of sensitizing fragrances in toys. However, Danish research in 2005 revealed that still in 7 out of 10 toys examined, many of these fragrances were found, although non-sensitizing fragrances are available as a substitute (Glensvig and

Ports, 2006). In addition to fragrances, preservatives that can cause a potential allergic reaction have been found in children's finger-paint (VWA, 2005). For details of these market studies see also chapter 5.

3.2.7 Scented products/ Room fresheners

Scented products are consumer products specifically intended for spreading a pleasant smell. An increasing number of these products is currently available on the market in different applications and their use is growing. A large proportion of the population is using air fresheners in the home and in the car. Scented products can be categorized in the following groups: room perfumes in holders, fragrant candles and wax, ethereal oils, fragrant sachets, sprays, potpourri, fragrant cardboards, toilet bowl rim hangers, incense, ironing perfumes and vacuum perfumes (Park et al., 2006). In addition to fragrance chemicals, scented products often contain other chemicals such as solvents and propellants in sprays. The chemicals that were identified in the emissions from air fresheners are likely to provoke respiratory allergies. In addition, these gaseous compounds can also be absorbed by the skin and lead to skin allergies. Moreover, through adsorption on materials and objects in the room, these primary and secondary compounds increase the risk of contact with the skin and the emergence of skin allergies (reviewed in BEUC, 2005).
In 2003, the Danish EPA mapped chemical substances in air fresheners and other fragrance liberating products. Details of this study on type and amount of fragrances found in various air fresheners are described in chapter 5. Furthermore, the European consumer's organization (BEUC) published in February 2005 the results of a research on emission level of chemicals from 74 air fresheners. It was concluded from this study that the emissions of certain substances such as sensitizing substances give rise to serious concerns. Terpenes, in particular limonene are ever-present in air fresheners: they lead to the formation of oxidization products in indoor air, which are significant allergens in Europe. Therefore the importance of allergies triggered by the appearance of secondary compounds also needs to be taken into consideration. Subsequently, an opinion on this BEUC report was published by the Scientific Committee on Health and Environmental Risks (SCHER). According to the SCHER there is a lack of clarity concerning the associations between disease symptoms and emissions from air fresheners in the BEUC report. Furthermore, data on exposure to emissions from air fresheners are still too limited for an overall risk assessment on air fresheners (SCHER, 2006).

3.2.8 Do-it-yourself products

In a number of do-it-yourself products like paints and lacquers, adhesives and glues, and hardeners a variety of preservatives are found (Flyvholm, 1993; 2005). Overall, the most frequently registered preservatives in do-it-yourself products in Denmark are butylated hydroxytoluene (BHT), formaldehyde, CMI/MI, benzyl alcohol, and benzisothiazolinone. Although these products were initially meant for occupational use, they are also used in private households. In the period 2002-2005, an increase in registration of the majority of preservatives was reported; however, this is most probably due to a change in registration procedure for paints and lacquers (Flyvholm, 2005).
Furthermore, di-isocyanates and acrylates are present in do-it-yourself products. The main exposure to di-isocyanates, known as respiratory sensitizers is however occupational. Di-isocyanates are present in polyurethane foams, paints and glues (Boyd and Mogenson, 2007). Acrylates, like methyl methacrylate and 2-ethyl hexylacrylate, also known from the shop-floor, are present in consumer products like sealants, tape, paints and glues for artificial finger nails (European Chemicals Bureau 2002; 2005).

3.2.9 Rubber products

Two forms of allergies are known in relation to rubber products. On type of allergy is triggered by skin contact with processing aids like vulcanization accelerators. Recently, immediate allergies are described that are triggered by natural latex components (proteins). This form is mainly observed by children who had several operations, or in hospital staff. Aerogenic exposure is seems to be particular important in the case of powered gloves (BfR, 2006).

4 Prevalence and costs of allergies

4.1 Incidence/Prevalence of contact dermatitis in the Netherlands

The prevalence of a disease is the total number of cases in a population at a given time. In The Netherlands in 2000, the prevalence of contact dermatitis in adults was 3.7% in men and 5.4% in women, based on the registration of general practitioners. The incidence, the number of new cases of contact dermatitis in 2000, was 2.1% in men and 3.2% in women (absolute numbers: 167.100 men and 256.500 women). However, these numbers are probably an underestimation, because not all patients that suffer from contact dermatitis will visit their general practitioner (Nationaal Kompas Volksgezondheid). Furthermore, no numbers are available for (very young) children. The prevalence/incidence of contact dermatitis specifically due to allergens in consumer products is also unknown, since the data from general practitioners include both occupational and non-occupational contact dermatitis. In addition, it is unclear in which cases the contact dermatitis is validated by a dermatologist and in which cases irritation can be excluded.

4.2 Frequency of sensitization in patients with contact dermatitis

Several international epidemiological studies have estimated the frequency of contact dermatitis and the contribution of allergens present in consumer products to this prevalence. The multitude of these studies was focussed on sensitization in a selected population of patients with contact dermatitis. The number of studies that have estimated prevalence in the general population is limited. Studies in patients cannot be used to extrapolate the prevalence data to the general population, but they provide insight in which allergens are the most frequent sensitizers. In addition, these studies can give information on the impact of regulatory and preventive decisions by assessing time trends of sensitization to allergens in consumer products.

A large European retrospective multicentre study in 26210 patients with contact dermatitis has established the frequency of sensitization to allergens present in the European standard series, which contains 26 compounds or mixtures that are known as common contact sensitizers, including metals, preservatives, substances in cosmetics, glues, rubber and medicaments. After combining all data, it was shown that nickel (frequency of 17.9%), fragrance mix (9.7%), Balsam of Peru (6.0%), cobalt chloride (5.9%), potassium dichromate (4.6%), colophonium (4.0%), PPD (3.9%) and thiurams (3.2%) were the most frequent sensitizers. Frequencies assessed in Dutch patients in this study showed comparable results, with nickel and fragrance mix being the most important sensitizers (Bruynzeel et al., 2005). An epidemiological survey conducted in Italy between 1984 and 1993 included 43000 patients with contact eczema. Approximately 65% of the cases suffered from non-occupational allergic and irritant contact dermatitis, the other cases were sensitized at the workplace. During this 10 year period, the most important non-occupational sensitizers were nickel, fragrance mix, cobalt chloride and balsam of Peru. The main products that were responsible for induction of non-occupational contact dermatitis were metallic accessories (34%), cosmetics (25.4%), and topical pharmaceuticals (13.2%) (Sertoli et al., 1999).

4.2.1 Preservatives

Preservatives in cosmetics are a common cause of skin sensitization. The contribution of these compounds to contact dermatitis and time trends in frequency of contact dermatitis has been investigated in two studies. Wilkinson et al. (2002) collected data from routine tests in patients performed in clinics in 11 countries during the period 1991-2000. These data demonstrated that in patients the frequency of contact dermatitis induced by formaldehyde and CMI/MI remained stable between 1991 and 2000: an average of 2-2.5% had a positive patch test. Parabens were the preservatives with the lowest prevalence: 0.5-1% which remains stable during this period. For MDBGN a rise in prevalence from 0.7% to 3.5% was observed during this period (Wilkinson et al., 2002). The second study, performed in the UK, assessed the frequency of contact dermatitis induced by preservatives in patients in 2000 and in 2004-2005. It was found that formaldehyde and CMI/MI had the highest rate of positive reactions of all preservatives, with a mean of 2.0% for both preservatives. The prevalence of contact dermatitis to MDBGN decreased significantly in five years from 2.4 to 1.2%. The latter can be explained by prohibition of the use of MDBGN in leave-on products in 2003 and in rinse-off products in 2007, resulting in decreased exposure. Parabens again have a lower prevalence (1% in 2000 and 0.8% in 2004-2005, respectively) (Jong et al., 2007).

4.2.2 Fragrances

Time trends in contact dermatitis due to fragrances have been investigated in several studies, all conducted in patients. In the UK, the prevalence of fragrance allergy was assessed in 25,545 patients between 1980 and 1996. The incidence was 8.5% in females and 6.7% in males. The most prevalent allergen was oak moss (37%). During the study period an increase in prevalence of fragrance allergy to oak moss, isoeugenol, alpha-amyl cinnamic aldehyde and a decrease of sensitivity to hydroxyl-citronellal, cinnamal, and cinnamic aldehyde was observed (Buckley et al., 2000).
The German Information Network of Departments of Dermatology (IVDK) monitors the frequency of contact dermatitis. During the period from 1996 to 2002 they monitored contact dermatitis to fragrance mix, balsam of Peru and turpentine oil in 59,300 patients. The prevalence of contact dermatitis towards all substances tested increased between 1996 and 1998, and declined from 1999 to 2002 from 13.1% to 7.8%. The most frequent allergens in the fragrance mix were oak moss and isoeugenol (Schnuch et al., 2004). A recent study performed in 10,128 patients in Belgium, demonstrated that fragrance allergy shows a fluctuating trend in the period from 1990 to 2005. The frequency of sensitivity to fragrance mix I declined from 13.9% in 1999 to 7.7% in 2005 (Nardelli et al., 2008). These results are in line with the IVKD data (Schnuch et al., 2004b). The percentage of positive reactions to balsam of Peru and colophonium remained relatively stable throughout the years, in the order of 6% and 5%, respectively. In this study it was demonstrated that 2.1% had a positive reaction to fragrance mix II, which contains the more recently introduced fragrances hydroxymethylpentylcyclohexene carboxaldehyde (Lyral®), citral, farnesol, coumarin, citronellol and citronellol and α-hexyl cinnamic aldehyde (Nardelli et al., 2008).

Recently, the IVDK assessed in 21,325 patients the frequency of sensitization to the 26 fragrances which will be labelled according to the current EU regulation. The 26 fragrances were categorized in three groups by using the frequency of positive patch test reactions: (1) important allergens, (2) clearly allergenic compounds but less important in terms of sensitization, and (3) rare sensitizers. In Table 4 an overview is given of these three categories (Schnuch et al., 2007). In this study not all fragrances that need to be labelled according to the SCCNFP (1999) are classified as important sensitizers. Furthermore, some fragrances that are frequently reported sensitizers according to SCCNFP are rare sensitizers in this study, e.g. benzyl alcohol and α–amyl-cinnamic aldehyde. In this study, farnesol was classified as an important sensitizer, whereas the SSCNFP did not list this compound as a frequently

reported sensitizer. The SSCNFP list is based on dermatological data, reflecting clinical experience. The difference with the IVDK study might be caused by a reduced exposure due to the use of less potent fragrances. To support the current EU regulation on labelling of fragrances, it is important to regularly monitor the frequency of sensitization in patients with contact dermatitis. Insight in which fragrances are the most important sensitizers and which are rare or non-sensitizers might eventually lead to a revision of the EU regulation on labelling of fragrances.

Table 4 Categorization of 26 fragrances to be labelled according to EU regulation

Group 1: important sensitizers	Group 2: less important sensitizers	Group 3: rare sensitizers
Oak moss	Cinnamic alcohol	Benzyl alcohol
Tree moss	Citral	Linalool
Hydroxymethylpentylcyclohexene carboxaldehyde (Lyral®)	Citronellol	Methylheptin carbonate
Hydroxycitronellal	Geraniol	α-Amyl-cinnamic aldehyde
Isoeugenol	Eugenol	α -Hexyl cinnamic aldehyde
Cinnamic aldehyde	Coumarin	Limonene
Farnesol	Lilial®	Benzyl salicylate
	Amyl-cinnamic alcohol	γ-Methylionon
	Benzyl cinnamate	Benzyl benzoate
		Anisyl alcohol

Adapted from Schnuch et al., (2007)

4.3 Prevalence of contact dermatitis in the general population in Europe

In Table 20 of Appendix 3, an overview of the data on prevalence of contact dermatitis in the general population of Europe is shown.
The frequency of contact dermatitis in the Danish population was studied in a cross-sectional study performed in 1990 and in a follow-up study in 1998. Of the initial study, 68% (n=365) were patch tested again during follow-up and in this follow-up study new participants were included too. In the subjects that were patch tested in both studies the frequency of contact dermatitis to allergens present in the TRUE test (which contains known contact allergens, e.g. preservatives, metals, medicines, substances in cosmetics, glues and rubber) was 14% in 1990 and 20% in 1998. The majority of positive reactions were induced by nickel, 7% in 1990 and 11% in 1998. For fragrances and substances in cosmetics (colophony, balsam of Peru, parabens, CMI/MI, quarternium 15 and wool alcohols) the frequencies were 1 and 3% in 1990 and 2 and 4% in 1998, respectively. The incidence rates for this period were calculated to be 12%. One of the drawbacks of this study is that subjects were invited for a general health check with emphasis on allergy; therefore an overrepresentation of atopic subjects could be expected (Nielsen and Menne, 1992; Nielsen et al., 2002).

In a study in adolescents aged 12-16 years in Denmark, it was shown that 15.2% had one or more positive patch test reactions. The most frequent sensitizers were nickel, with a frequency of 8.6%, followed by fragrance mix (1.8%), colophony (1%) and thiomersal (1%). Significantly more girls than boys reacted, 19.4% vs. 10.3%. This difference was predominantly caused by the higher frequency of nickel allergy in girls (Mortz et al., 2001).

Studies performed in Norway and Germany report somewhat higher frequencies of contact sensitization. In Norway, two cross-sectional studies demonstrated that 26-28% of the study population had one or more positive patch test reactions. Again, nickel was the most prevalent contact allergen, followed by cobalt and fragrance mix (Dotterud, 2007; Dotterud and Smith-Sivertsen, 2007). In Germany, the prevalence of contact dermatitis was 28%, and the most prevalent sensitizer was fragrance mix (11.4%), followed by nickel (9.9%) and thimerosal (3.2%) (Schafer et al., 2001).

In another Danish study, the CE-DUR method was used to estimate the 10-year prevalence of contact dermatitis in the general population. This approach is a combination of clinical epidemiological (CE) data and drug utilization research (DUR) method. It uses data of patch test sales to calculate the prevalence. The 10-year prevalence was between 5.5-9.7% for all ages and between 7.3-12.9% for adults. The most prevalent allergen was nickel, with a prevalence of 3.7% in adults. The contribution of allergens present in cosmetics was estimated to be 3.6% among Danes of all ages and 4.5% in adults. It was demonstrated that nickel was the most common allergen, followed by fragrance mix, and MDBGN (Thyssen et al., 2007a; Thyssen et al., 2007b).

Recently, a literature survey (Thyssen et al., 2007b) was conducted to assess the prevalence of contact dermatitis in the general population. The median prevalence to at least one allergen was estimated from studies originating from North America and Western Europe that were published between 1966 and 2007 and was estimated to be 21.2% (range 12.5-40.6%).
The variation in prevalence between the different studies and countries as described above and depicted in Appendix 3 can be due to variations in the selected populations, the year of investigation and the variation in methods used. It has been shown that the prevalence of individual allergens was mostly dependent on the year of investigation rather than the country investigated (Thyssen et al., 2007b). One of the reasons can be the development of legislative restrictions, leading to a decrease in prevalence during time (see next section). Furthermore, the age of the population studied is important for the ranking of allergen prevalence; the prevalence of nickel allergy is decreasing with increasing age, while for fragrance mix I it has been shown to be the opposite: contact dermatitis due to fragrance mix I is elevated in older individuals (Thyssen et al., 2007b).

All epidemiological data reported so far are from adults and adolescents. An important issue is whether (young) children are more susceptible for contact dermatitis and can be considered as a sensitive population. Patch results of several studies demonstrate that contact allergy was highly prevalent among infants and young children. A prevalence of contact dermatitis of 72.4 % in children aged 4-12 months, 20% in children between 6 months and 5 years and 50% in children aged less than 18 months, were found in different studies (Röckl et al, 1966; Weston et al., 1986; Bruckner et al., 2000, reviewed in Thyssen et al., 2007b). In addition, a higher prevalence was found in younger children when compared to older children (reviewed in Thyssen et al., 2007b). It is conceived that the prevalence of contact dermatitis should gradually increase through childhood and adolescence because of an increased environmental exposure to contact allergens. So the reliability of patch test results in young children is questionable, maybe caused by a high occurrence of irritating reactions (Thyssen et al., 2007b). The true prevalence of contact allergy is difficult to assess in children.

4.4 Effects of legislation on prevalence of contact dermatitis in time

As has been described above, the prevalence of contact dermatitis for certain substances, has decreased in time. This decrease can be explained by effects of legislation, e.g. banning or restriction of chemicals. The effects of legislation have been reviewed by Wesley and Maibach (2003), see also Table 5. Overall, the evidence suggests a decreasing trend in allergic contact dermatitis to these specific substances after legislation coming into force.
For nickel, legislation was passed in Denmark in 1990, followed by a European Directive in 1994 that recently has been revised (reviewed in Thyssen et al., 2007b). Initially, a limit of 0.5 mg Ni /cm^2 per week (leached out as a response to the corrosion by human sweat) was set, (which was later tightened to 0.2 mg Ni /cm^2 per week). Due to this legislation, the frequency of nickel allergy decreased from 17.1% before to 3.9% after legislation came into force (see Table 5, Jensen et al., 2002). Other studies on the effectiveness of the Nickel Directive show more or less similar results (Johansen et al., 2000; reviewed in Schuur et al., 2008). So, it might be concluded that legislation on nickel is effective.

In hair dressers, an ingredient of acid perms, glyceryl monothioglycolate (GMT), induced a high incidence of sensitization. After withdrawal of this substance a reduction of hairdressers with positive patch tests to GMT from 45% to 20% was observed. The incidence of contact dermatitis due to the use of chromate in cement workers, has also reduced after implementation of an industrial chromate reduction with ferrous sulphate (resulting in a chromate content in cement of ≤ 2 ppm), which became compulsory in Denmark in 1983. The EU Directive on chromate came into effect in 2005 (Avnstrop, 1992; Thyssen et al., 2007b).

Table 5 Changes in allergic contact dermatitis frequency before and after implementation of regulations

Sensitizer	Baseline	'Current'	Comment	Limit value after legislation
Nickel	17.1%	3.9%	Prevalence before and after 1992, OR 3.3 (P=0.004)	0.5 mg Ni /cm^2 per week, recently adapted to 0.2 mg Ni /cm^2 per week
GMT	45%	20%	Forbidden in products	
Fragrance	-	-	Overall, fragrance allergy unchanged (see text)	No limit value, only legislation concerning declaration
Chromate	8.9%	1.3%	-	Chromate content in cement ≤ 2 ppm
Thiuram	-	-	Increase from 1983-88 to 1989 -95 (OR= 2.55, P=0.01). Decrease after 1995, but not statistically significant.	

Adapted from Wesley and Maibach (2003). GMT: glyceryl monothioglycolate, present in acid perms (hairdressing), withdrawn from the German market in 1992.

In the UK it was demonstrated that the prohibition of the use of MDBGN in leave-on products in 2003 and in rinse-off products in 2007, resulted in a significant decrease of prevalence from 2.4% in 2000 to 1.2% in 2005 (Jong et al., 2007).

The use of fragrances in products is not restricted to limit values, legislation concerns only declaration on the label above certain limits. However, due to reduction of concentrations in products or the replacement by other fragrances, prevalence of fragrance allergy fluctuates in time. It should be noted that time trends for fragrances are compound-specific, making patch test results of fragrance mixtures very difficult to interpret. Time trends for fragrances are described in more detail in section 4.2.2 and show that from 1999 there is an decline in prevalence for fragrance mix I, whereas the prevalence for fragrance mix II, which contains more recent introduced fragrances, increased (Nardelli et al., 2008). This indicates on one hand that reductions in concentrations of fragrances in products can lead to decreases in population sensitivity to those specific substances. At the same time, sensitivity to alternative fragrances used in cosmetics and other consumer products is increasing (Buckley et al., 2000).

4.5 Prevalence of chemical respiratory allergy

There is no information available on the prevalence of respiratory allergy induced by chemicals present in consumer products. It is thought that respiratory allergy induced by chemicals occurs less frequently than contact dermatitis. This type of allergy is investigated most extensively in the occupational setting. Chemicals known to cause occupational asthma include the following: di-isocyanates, acid anhydrides, platinum salts and chloramines (Corsini and Kimber, 2007; Baars et al., 2005). There are a few epidemiological studies that have investigated the prevalence of occupational asthma. Bardana Jr. (2008) stated that 9-16% of the asthmatic patients suffered from occupational asthma, whereas in another study, an estimation of at least 10% was determined on the contribution of occupational exposure to the total prevalence of asthma among the working population (Baars et al., 2005).

4.6 Prevalence of contact dermatitis compared to other allergic diseases

The prevalence of contact dermatitis is relatively high when compared to other allergic diseases. To compare prevalences of different allergic diseases in the Netherlands, relevant information could only be derived from the Nationaal Kompas Volksgezondheid and the Dutch Health Council and is mainly based on information from general practitioners. It is estimated that approximately 1-3% of the adult population suffers from food allergy, 1.5-3% from allergic rhinitis and 3-5% from asthma (Table 6). When we compare this with contact dermatitis, as registered by general practitioners, prevalence of contact dermatitis is comparable to that of asthma. In contrast, the epidemiological studies summarized in Table 19 (Appendix 3), show that the prevalence of contact dermatitis in the general population is in the range of 7-28% in adults, which is considerably higher. The contribution of nickel and cosmetic ingredients including fragrances to this prevalence is estimated to be 7-19% and 3-4%, respectively.

Table 6 Prevalence of allergic diseases in the Dutch population

	Prevalence in adults	References
Contact dermatitis	3.7-5.4%	Nationaal Kompas Volksgezondheid
Food allergy	1-3%	Gezondheidsraad, 2007a
Astma	3-5%	Nationaal Kompas Volksgezondheid Gezondheidsraad, 2007b
Allergic rhinitis	1.5-3%	Gezondheidsraad, 2007b

4.7 Costs of allergies induced by consumer products

As mentioned in the previous sections, the prevalence of allergies is increasing in the last decades. Newspapers and internet name the rapidly increasing prevalence and severity of allergies in the Western society (Trouw, June 2006; http://www.allergymatters.nl).
In a workshop in 2003, data on the economic pain of allergy were presented by Postma (2003). A scan of the literature showed that the reliability and relevance of diverse investigations were difficult to judge because of a difference in methods and assumptions. The Allergy White Paper (The UCB institute of Allergy, 1997) is one of the single sources of information drawn up by a group of specialists following a useful and balanced synthesis. Based on information of this paper, the following table (Table 7) concerning the costs of allergy in 1997 was presented:

Table 7 Costs of allergy on yearly base, indicative

	NL % populations	NL direct costs	NL indirect costs	NL total costs	Western Europe total costs
Hay fever	13	54	73	127	3009
Asthma	8	271	586	857	20334
Atopic dermatitis	?	16	16	32	753
Contact dermatitis	?	99	122	221	5232
Urticaria	?	39	-	39	936
Total	**± 25**	**479**	**797**	**1276**	**30264**

Numbers are based on the Allergy White Paper (1997), results of investigations and extrapolation of known data for Western Europe. Costs are in million Euros, price level 1997. Source: presentation on Workshop March 2003 (Postma, 2003)

Direct costs are the costs of visits to the general practitioner or hospital and costs of medication. Indirect costs are more difficult to quantify and include costs of work or school absence by illness, loss of work productivity, early retirement, diets, adaptation of housing and so on.
In 2003, the total costs are estimated to be increased to 2 billion in the Netherlands, due to both an increase in prevalence and inflation. The contribution of contact dermatitis in Western Europe (possible caused by allergens from consumer products) amounts almost 1/5 of the total costs of all allergies (Postma, 2003; Van der Meer et al., 2004).
In Table 8, the direct costs to European society are mentioned according to Mugford and the European Allergy White Paper (Mugford, 2004; European Allergy White Paper, 1997).

Table 8 Direct costs to society of allergy in Europe (in euros)

Asthma	6.4 billion
Contact dermatitis	2.3 billion
Allergic rhinitis	1.3 billion
Food allergies	?

Adapted from Mugford (2004), source: European Allergy White Paper (1997)

The authors of the White Paper recognize the shortage of good-quality data about any of the allergies at this level. Even where data exist, the methodology of cost-of-illness research is not well defined or scientifically validated, and it is often seen and used as a technique for persuading those in power to take notice of this problem. For more trust in the figures, it is important to develop methods that are replicable and useful.
Bramam (2006) reported a total cost of asthma of approximately €17.7 billion euro per year in Europe. Outpatient costs account for the highest proportion of at approximately €3.8 billion, followed by expenses for anti-asthma drugs (€3.6 billion). In-patient care accounts for a relatively minor cost of €0.5 billion. As poor asthma control is responsible for significant work impairment, productivity losses add up to €9.8 billion per year (referenced to European Lung White Book, 2003). The economic burden of asthma disproportionately affects those with the most severe disease. In both Western and developing countries, patients with severe asthma are responsible for approximately 50% of all direct and indirect costs, even though this patient population represents 10 to 20% of all asthma patients. The authors state that globally the economic costs associated with asthma exceed those of tuberculosis and HIV/AIDS.

In 2003, the European Commission published the draft regulation of REACH. This will amend or replace many of the existing EU legislation on chemicals. Various studies tried to estimate the negative and positive effects of the draft regulation. The impact assessments focussed especially on occupational diseases and also included skin diseases and asthma (European Commission, 2003). More recently, a further report on the impact of REACH on occupational health was published with a focus on skin and respiratory diseases. For asthma, they concluded on 40,000 - 80,000 new cases per year in the European Union (consisting of 25 countries). The proportion affected by REACH is about 50% (based on literature data from different countries, ranging from 28 to 84%). For skin disease (occupational dermatitis), the European incidence was estimated at 400 million a year, of which 50% could be potentially prevented by REACH (see Table 9). Health-related quality of life costs were discussed as well as productivity and health service costs.

Table 9 Incidences of asthma and dermatitis and the assumed effect of REACH

	Incidence: nr. of cases / million / year	**Proportion of cases avoided by REACH**
Asthma	200	50%
Dermatitis	200	50%

Adapted from Pickvance et al., (2005)

In the Netherlands, a first exploratory study of RIVM commissioned by the Ministry of Social Affairs and Employment provided an integrated view on the contribution of occupational exposure to chemicals in the burden of disease (Baars et al., 2005). Estimations were made for the contribution of chemical exposure at the workplace to the total occurrence of (amongst others) contact dermatitis. The unit used for these calculations is the DALY. DALY stands for 'Disability Adjusted Life Years', in which premature death and years with disease are weighted and counted up. Based on reviewed

literature, it was assumed that the yearly incidence of contact eczema for workers is 1 per 1000. On the basis of 6,919 million workers in the Netherlands, this estimate results in a yearly incidence of 6,900 (new) cases per year. Supposing that (1) the average worker works 25 year, and (2) 50% of the diagnosed new cases of contact eczema become chronic, the average prevalence is 6,900 x 25 x 50/100 = 86,250. For the calculation of DALYs per year for contact eczema, a weighing factor of 0.07 is used (VTV, 2006). This is the weighing factor of constitutional eczema, since no factor for contact eczema is available. The prevalence results in 6,000 DALYs per year for contact eczema within the worker population caused by exposure to substances under occupational circumstances. In comparison, the total burden of disease in the working population suffering from contact dermatitis is estimated to be 10,000 DALYs. For the potential working population (age group 15-65 years) this is estimated to be 18,600 DALYs (Baars et al., 2005).

Specific information on the costs of allergy caused by substances from consumer products is not available. Estimation of the costs could be quantified, using many assumptions by estimating the burden of disease (in this case, allergy caused by chemicals in consumer products) expressed in DALYs. It is possible to monetize these DALY estimates.
From the study by Baars et al. (2005) it might be concluded that almost half of the total burden of disease of contact eczema is not caused by exposure at work, and thus might result from exposure via consumer products. However, this is a very rough assumption.
Another method to assess the contribution of exposure from consumer products to the allergy burden, might be an estimation of a realistic exposure estimate, performance of a health effect assessment, and establish the burden of disease, as was done in the case of nickel in the report 'Health impact assessment of policy measure for chemicals in non-food consumer products' (Schuur et al., 2008). However, necessary data are scarce and therefore many assumptions have to be made. Another problem is that not for all allergic diseases weighing factors are available. For asthma it is 0.08, but for contact eczema the weighing factor of 0.07 from constitutional eczema must be used since no other factor is available. Furthermore, it should be taken into account that there are many people with contact-eczema who are able to avoid exposure, and thus do not have actual complaints. This also should be addressed somehow.
In summary, with the currently available data, calculation of a cost estimate would result in a very unreliable value.

5 Consumer exposure to allergens

To determine the extent of consumer exposure to allergens in consumer products, it is necessary to have an impression of the levels of the different allergens in consumer products. Therefore market surveys and product sampling of different product groups are valuable. In Denmark, the Danish EPA has been very active in the past years in measuring chemicals in all kinds of consumer products. If possible, also a risk assessment for those ingredients and products was performed (http://glwww.mst.dk/homepage/). Also the Dutch Food and Consumer Products Safety Authority (VWA) has performed surveys on chemicals in consumer products also in order to check compliance to the legal requirements (www.vwa.nl).

Most data available on products containing allergens and levels of allergens in these products refer to fragrances and some preservatives. Also some studies on metals in leather products and detergents are reported. An overview of all available data on fragrances is given in Tables 20-22 of Appendix 4.

5.1 Market studies on the presence of allergenic fragrances

The presence of fragrances is investigated in a large variety of product types like cosmetics, household products, toys and scented products. An overview of the publicly available studies is given below.

5.1.1 Fragrances in cosmetic products

Fragrances in deodorants

Recently, the Danish EPA investigated the presence of selected fragrances and preservatives in 97 deodorants on the Danish market (Rastogi et al., 2007a). First, in almost 70% of the deodorants investigated, one or more of the 26 fragrances that are regulated for labelling, were present according to the ingredients list on the product. Approximately 25% of the deodorants contained 5-17 (a median of 8 per product) of the 26 target fragrances, meaning that there is a considerable allergen load in deodorants on the Danish market. The most potent substances (cinnamal, methyl heptin carbonat and oak moss abs.) were present in a few of the products (1.1% - 4.6%). Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC = HMPCC), hydroxycitronellal and isoeugenol, fragrances that cause many allergic reactions, were present in 33%, 27.3% and 9.1% of the fragrance deodorants respectively (see also Table 20, Appendix 4).
The 23 products selected for further chemical analysis, are in accordance with the regulations, i.e. the contents of fragrance ingredients complied with the labelling on the respective products.
Concentrations of individual fragrances as measured in the products are given in the overview Table 20 in Appendix 4.
In conclusion, fragrance ingredients which are potent allergens and frequently cause allergies in consumers are used as ingredients in deodorants. The most potent allergens were also the most infrequently used ingredients.

Fragrances in perfume products

Furthermore, current exposures to four important fragrance allergens (isoeugenol, hydroxyisohexyl-3-cyclohexen carboxaldehyde (HICC, Lyral), atranol and chloroatranol) were investigated in 25 popular

perfume products on the Danish retail market (Rastogi et al., 2007b). These 4 allergenic fragrances were found in respectively 56, 72, 59, and 36% of the investigated perfumes. The concentrations of isoeugenol were, in all products, below the recommended maximum concentration of 0.02%. HICC was found at a maximum of 0.2%, which is 10-fold higher than the maximum tolerable concentration considered safe by the EU Scientific Committee. The median concentrations of atranol and chloroatranol (components of oak moss abs.) in the investigated products were similar to those found in comparable products in 2003. A significant decrease in the frequency of presence of chloroatranol in the products was observed. A subsequent study of Rastogi and Johansen (2008) showed the presence of considerable amounts of isoeugenol derivates (isoeugenol acetate) in perfumes and after shaves. Isoeugenol-sensitized persons can also be sensitive for these derivates e.g. by skin metabolism into the mother compound (Rastogi and Johansen, 2008).
In contrast to deodorants, there is still a wide-spread exposure to potent fragrance allergens in perfumes.

Fragrances in children's cosmetics

In 2007, the Dutch Food and Consumer Product Safety Authority published a report in which 355 cosmetic products for babies and preschoolers and 400 products for children older than 3 years were investigated on their composition of constituents including potential allergenic fragrances and preservatives (VWA, 2007). According to the label, allergenic fragrances were present in 88% and 78% of the products for babies and children > 3 years, respectively. Twenty-three products for children > 3 years were analysed. Limonene and linalool were found to be the most frequent used fragrances in the products analysed (VWA, 2007). Details on the levels found in the products are given in Table 20, Appendix 4.
Also in Denmark, a large part of investigated cosmetic products for children contained allergenic substances in the form of fragrances, preservatives and/ or colouring agents (Poulsen and Smith, 2007) as obtained from a large survey on children's cosmetics. In total 461 different constituents were found in 208 different products for children in the age of 3-14 years (average is 16 different constituents per product). Similar to the results of the Dutch survey, 74% of the products contained perfume, with a 100% score in the product types deodorants, eau de toilette, hair dyes (rinsing colours), hair styling products and massage oils. One third of the products contained one or more of the 26 fragrances, again limonene and linalool were found most frequently. A quantitative analysis of the 26 fragrances was performed on 17 products. Results on maximum concentrations found are presented in Table 10, in which the maximum measured concentration is only based on a few analysis results of products where the individual fragrance occurs. For the majority of the products it is unknown in which concentration the fragrances occur (only that it is above 100 mg/kg or 0.01%).

More details on concentrations found in consumer products in Denmark are reported in Table 20, Appendix 4. Fragrance levels found by the Danish EPA seem to be higher than in the Dutch survey, however, this can be due to the variation in the amount of products and product types analysed.

Table 10 Overview of maximum concentrations of fragrances in analysed products

	Fragrance (stated with their INCI name)	Maximum measured concentration mg/kg	Occurs in x out of the 208 mapped products
1	Butylphenyl methylpropionial (Lilial ®)	3400	16
2	Hydroxy isohexyl 3-cyclohexene carboxaldehyde (Lyral)	2700	12
3	D-Limonene (limonene)	2200	48
4	Linalool	1100	45
5	Benzyl alcohol	790	20
6	a-isomethylionone	480	12
7	Citronellol	300	22
8	Amyl cinnamal	230	17
9	Benzyl benzoate	210	19
10	Geraniol	180	25
11	Hexylcinnamal	170	21

5.1.2 Fragrances in toys and children's articles

In Denmark, a project was carried out in 2004 to analyze toys and articles for children aged 0-10 years containing scent (Glensvig and Ports, 2006). The content of sensitizing fragrances (24 substances on the EU list supplemented with oak moss and tree moss) as well as the content and emission of other chemical substances were elucidated in 10 selected products. The result of the initial mapping of scented products for children is depicted in Table 11.

In the last column the products are depicted that were further analyzed. Results of the odorant analysis in these products are given in Table 21 of Appendix 4.

In total 18 of the 24 fragrances were detected, in 7 different children's products. Concentrations varied between 0.0001- 0.4%. However, these fragrances should not be present in children's articles, irrespective of concentration. It was recommended by the authors of the report that consumers should avoid these products until the producers have removed the sensitizing fragrances. Furthermore, oak moss and tree moss have not been found in any of the products.

Table 11 Result of the mapping of fragrant toys and children's articles

Overview of products, product series and scents and selection for analysis.

Product type number	Product	Scent	Selected for laboratory experiments and accredited analysis
D01	Soap bubbles	Lemon & Lime, Chocolate chip, Bubblegum, Banana Split, Tropical punch, Strawberries & Cream	Lemon and lime
D02	Rubber figures	The Duke of Puke, Pizza Face Pat, Oli Slick Rick, Dude Boy Doug, Dandy Doo Dave, Clammy Cliff, Zoo Boy Zach, Elephant Drop Eric, Camel Mouth Chris, Monkey Cage Mike, Ra Boy Rob, Winnie the Vulture, Ear Wax Max, Fartasarus Frank, Billy Bob Booger, Toxic Tyler, Spewy Huey, Jurassic Josh, Rotten Onion Ollie, Chill E. Dawg Joey, Never Wash Nick, , Wart Hog Henry	Camel Mouth Chris
D03	Space hoppers	Watermelon, kiwi, citron, orange	
D04	Writing paper	Perfumed scent	Perfume
D05	Mechanical pencil	Apple, grape, kiwi, banana, orange, strawberry	
D06	Eraser lipstick	Apple, grape, kiwi, banana, orange, strawberry	Strawberry scent
D07	Eraser pen	Apple, grape, kiwi, banana, orange, strawberry	
D08	Speed markers	Orange, lemon, strawberry, blackberry, violet, rose, chocolate, pine and two unnamed scents	Lemon (yellow), strawberry (red)
D09	Rabbit	Chocolate	Chocolate
D10	Stacking rings	Apple	
D11	Activity box	Apple	
D12	Soft cube*	Apple	Apple
D13	Cuttlefish	Vanilla	
D14	Soft toy*	Vanilla	Vanilla
D15	Flower	Vanilla	Vanilla

* No longer on the Danish market.

5.1.3 Fragrances in cleaning products and detergents

Fourty-three different, non-cosmetic consumer products were investigated on the presence of fragrances by the Danish EPA (Rastogi, 2002). Mainly dish wash, laundry detergents, and hard and soft surface cleaners were studied (33 products), and 97% of these cleaning products (n=32) contained up to 9 of the target fragrance substances (the 26 fragrances that are regulated for labelling in the EU). Other products investigated in this study were panties, nappies and toilet paper as well as erasers and a doll. Most frequently found fragrances were limonene (67% of all products investigated), Lilial® (56%), hexylcinnamic aldehyde, linalool and γ-methylionone (40% each), benzyl alcohol and coumarin (30% each), benzyl benzoate and citronellol (26% each), benzyl salicylate and geraniol (21% each), eugenol (19%) and citral (16%). All other fragrances were present in < 10% of the products.

Concentrations varied between <0.0001 to 0.7600%. For identification of a trend for use of specific fragrances in product categories, the numbers of products investigated were too small.

In 2006, the Dutch Food and Consumer Product Safety Authority (VWA) carried out market surveillance on detergents (Bouma and Van Peursem, 2006) because of a new detergents regulation (EC 648/2004) that came into force on October 8, 2005. One of the changes in the regulation was the mandatory declaration of allergenic fragrances and preservatives (limit for declaration is 0.01 weight percent). To almost all laundry detergents (94%) fragrances were added, and approximately half of the samples (61%) contained fragrances above 0.01 weight percent. Also in 58% of the products, preservatives were present according to the producing companies. In addition, 52 products were analyzed for allergenic fragrances. More than half of the products contain one or more allergenic fragrance above the 0.01 weight percent, mainly hexyl cinnamal (56%), geraniol (42%), linalool, limonene, and γ-methylionone (40% each), Lilial® (37%), benzyl alcohol (33%), benzyl salicylate and coumarin (27% each), and citronellol (21%). Concentrations varied from 0.0004-0.0795%. On 21 products allergenic fragrances were declared that were not detectable in the product or below the limit for declaration. On the other hand, 7 products contained one or more fragrances in a level higher than 0.01 weight percent, which was not declared on the label. For further detailed information of this study see Table 21, Appendix 4.

5.1.4 Fragrances in scented products/ air fresheners

In order to obtain an overview of the air freshener market, the Danish EPA performed a market survey in different stores and supermarkets that are typical sellers of products for the home and the car. Nineteen air fresheners were selected covering the market and these could be divided in 6 car products (three are suspending, two are electrical for connection on the cars ventilation installation and a spray for all auto textiles) and 13 for use at home. Four of these products are electrical (connected to plug) for the entire house, three are small balls for the vacuum cleaner, two are sprays for all rooms and four products are mainly used in the bathroom (three gel types and a plastic pressure can). In 100% of the air fresheners tested, at least one of the 24 fragrances identified as allergens by the EU's Scientific Committee was detected. Presence of a single fragrance varied from trace levels (0.00035% of methyl heptin carbonate in an electric air freshener) to a large content (6.2% of HMPCC in a bathroom spray). The total content for the vacuum cleaner products vary form 0.6-10%, auto suspending products varied from 0.001-8.4% and in auto products connected to the ventilation system detected presence ranged from 3.7-14%. The highest total content of fragrances was found in liquid samples (0.9-16%) and the lowest content in gel products (0.2-3.3%) (Pors and Fuhlendorff, 2003). Details of this study are depicted in Table 22, Appendix 4.

The European study of BEUC in 2005 reported different fragrances to be present in air fresheners; here emission levels of the fresheners were measured directly in indoor air (BEUC, 2005). Among the natural products, emitted levels of limonene, citral and coumarin were found above background levels. Scented candles emitted most frequently cinnamaldehyde and linalool. Three out of four incense types and six out of nine gel air freshener products tested emitted limonene and only one of both types of fresheners emitted linalool. One of the liquid air fresheners emitted cinnamaldehyde in high concentrations, and again limonene was emitted by nine of the ten products tested. Coumarin, eugenol and Lilial® were found only at low concentrations and emitted by very few products. All of the electric diffuser products tested emit limonene, linalool is emitted by the majority of the products (8/13), Lilial® by two and cinnamaldehyde and benzyl alcohol by just one. Finally sprays, they emit 9 different molecules, limonene (by 17 out of 22 products), linalool by nine and Lilial® by eight. Hydroxycitronellal, geraniol, coumarin, citral, benzyl benzoate and cinnamaldehyde are emitted by

only one spray. In conclusion, the majority of the products tested emit allergens, at concentrations ranging up to 911 µg/ m^3 (limonene in natural product). Certain products combine allergenic substances emitted in concentrations up to 170 µg/ m^3. See also Table 22, Appendix 4.
As already mentioned, emissions of D-limonene were measured by the majority of the air fresheners tested. However, concentrations emitted vary between the different types of air fresheners and some of them also emit L-limonene and some oxidized forms. Concentration ranges are given in more detail in Table 12.

Table 12 Concentration ranges of D- and L-limonene of different air refresheners (µg/m³)

	Natural products	Scented candles	Incense	Gel air fresheners	Liquid air fresheners	Electric diffusers	Sprays
D-limonene	911	1-31	1-19	2-735	1-107	1-499	1-2,003
L-limonene	243	1-5	4	5-92	0.4-26	2-26	1-130

5.1.5 Conclusion on fragrances

The market studies described above and in Tables 20-22 of Appendix 4 show the wide variety of products that contain allergenic fragrances. In total 516 products were analyzed in the different categories as mentioned earlier. When all data are put together, the following ranking of most frequent used fragrances can be made (see Table 13).

Table 13 Most frequently used fragrances in various consumer products

Fragrances	% of products (n=516)	Fragrances	% of products (n=516)
D-limonene	48.3%	Citral	11.6%
Linalool	35.8%	Hydroxycitronellal	10.8%
Butylphenyl methylpropional (Lilial®)	24.8%	Amyl cinnamal	7.9%
Geraniol	22.1%	Anisyl alcohol	7.0%
α-Isomethylionon	21,7%	Cinnamyl alcohol	6.4%
Hexyl cinnamal	21.3%	Farnesol	3.9%
Citronellol	21.1%	Isoeugenole	3.1%
Benzyl salicylate	18.6%	Cinnamal	2.5%
Coumarin	17.0%	Benzyl cinnamate	2.3%
Eugenol	15.7%	Amylcinnamyl alcohol	1.9%
Benzyl alcohol	15.3%	Methyl heptine carbonate	1.0%
Benzyl benzoate	14.7%	Oakmoss	0.8%
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (HICC = Lyral)	12.8%	Treemoss	0.4%

From this table it becomes clear that D-limonene is by far the most used fragrance in consumer products (48.3%), followed by linalool (35.8%) and Lilial® (24.5%). It should be mentioned here that although D-limonene has a low allergenic potency (see also next chapter), air oxidation of D-limonene can create potent allergens (Karlberg et al., 1992). Apart from frequencies, also concentration levels of the different fragrances are of importance in determination of the impact of consumer exposure to

allergens. These concentration levels of the various fragrances in consumer products vary between product types; see also Tables 20-22 of Appendix 4.

5.2 Market studies on preservatives

5.2.1 Preservatives in cosmetic products

Cosmetic products for children also contain potential allergenic preservatives. In the study of the VWA, the most frequently used preservative in the investigated cosmetics for babies and preschoolers as well as for children older than 3 years is a mixture of parabens, with or without phenoxyethanol. Parabens are very mildly allergenic and contents found were below the legal limits. However, in 4 products for babies, the forbidden preservative 1,2-benzisothiazolin-3-one (BIT) was found. Also CMI and MI were detected in 4 baby products without labelling on the product (VWA, 2007).

Preservatives were detected in 63% of the Danish cosmetic products for children. In total, 12 of the 23 applied preservatives are (potential) allergenic. Parabens (methyl- and propylparaben) were the most frequently found preservatives (38 and 34% of the products respectively). Also CMI and MI were found in 7% and quaternium (a formaldehyde liberator) in 1% of the children's cosmetics. None of the analysed CMI/MI levels exceeded the allowed value of 0.0015% (Poulsen and Smidt, 2007). In Appendix 5, the exposure assessment for CMI/MI that was carried out in this survey is described.

In Sweden, the presence of 9 common preservatives was investigated in 100 moisturizers (Gruvberger et al., 1998). Here, parabens were the most common found preservatives, similar to an earlier performed Danish study on preservatives in cosmetic products (Rastogi et al., 1995). The concentrations of parabens did not exceed the maximum concentrations allowed in cosmetics. CMI/MI was only found in 6% of the moisturizers, much lower than in previous studies performed in cosmetics indicating that the manufacturers are intended to use less sensitizing preservatives. However, formaldehyde, which is not recommended for use in moisturizers, was found in 10% of the products. The problem with formaldehyde is that although it may not be intentionally added it can be formed as by product from formaldehyde releasers or as degradation product from polyethylene esters.

5.2.2 Preservatives in toys

In June 2005, the Dutch VWA performed market surveillance on paint for children (VWA, 2005) and found various preservatives like parabens, organic acids (benzoic acid and sorbic acid) and phenoxyethanol. These preservatives are often not declared on the label, although this is required. The limits in EN71-7 (Safety of Toys-Fingerpaints) were however not exceeded for these compounds. In most of the finger paints free formaldehyde was present, with 2 samples exceeding the limit of 0.1%. In 12 samples CMI/MI was detected, in 5 cases above the limit of 0.0015%. Also the prescribed ratio of 3:1 was not applied. BIT, not authorized according to EN71-1 was detected in 2 samples of fingerpaint.

5.2.3 Preservatives in air fresheners

In a study performed by the European Consumers' Organisation (BEUC) emissions of substances from 74 air fresheners were measured. Amongst other substances, the preservative formaldehyde was detected (BEUC report 2005). Only one of the natural products tested did not generate any emission of

formaldehyde. Scented candles frequently emitted formaldehyde (14 out of 16 candles tested), although at very low levels. The concentration of formaldehyde emitted in the air by incense was remarkably high, 6-7 times higher than the limit reference value laid down by the WHO. Such strong emissions of formaldehyde out of incense have been published earlier in a Danish study in 2004 (Eggert and Hansen, 2004). None of the gel air fresheners and only one of the tested liquid air fresheners and sprays released formaldehyde. Electric diffusers emitted low concentrations of formaldehyde. However, it should be noted that electric diffusers may be continuously adding formaldehyde levels to the background noise, and therefore is potentially posing a risk to the health of consumers.

5.2.4 Preservatives in textile

In 1996, formaldehyde concentrations in clothing and non-clothing textile in the Netherlands were determined by the Dutch Food Inspection Department via 'the Japanese method' (Janssen et al., 1998). In summary, it was not possible to detect formaldehyde in 75% of the investigated clothing (levels of <5 ppm) whereas levels of > 50 ppm were found in 3% of the clothing with maximum levels found of 122 ppm. The majority (= 52%) of other (non-clothing) textile products contained no detectable formaldehyde level and in 19% of the products a level of > 100 ppm was found, with a maximum of 754 ppm. A subsequent study (Van Haperen, 1996b cited in Janssen et al., 1998) in non-clothing textile revealed higher levels of formaldehyde in 18% (n=94) of the textile investigated. In 12% of the products levels >100 ppm formaldehyde were found, the maximum was 1975 ppm. These measurements were done in unwashed textile; a 90% decrease of formaldehyde levels after 1 laundry with a further decrease to 5% of the original levels after several laundries has been reported (Janssen et al, 1998). In the Dutch "Warenwet" a decision on formaldehyde in textile is included, with a limit of 120 ppm and a restriction for labelling with 'wash before use' (Date of enforcement 13th of April 2001).

5.2.5 Conclusion on preservatives

Although some studies have been performed on preservatives in consumer products, the product numbers in the described studies are relatively small. An overview such as for fragrances can not be made for preservatives. However, it is clear that the mildly allergenic parabens are frequently used in cosmetics and that formaldehyde can pose a health risk when used in air fresheners, because of the continuous exposure to low levels in indoor air.

5.3 Market studies on transition metals

5.3.1 Metals in leather clothing and other products

Contents of trivalent and hexavalent chromium were studied in leather products in 2001 by the Danish Environmental Agency. They investigated (baby) shoes, (working) gloves, jackets trousers, tops, skirts and hats. Although is it relatively easy to avoid hexavalent chromium in the production process, 35% (15 out of 43) products contained Cr (VI) above the detection limit of 3 mg/kg product, the maximum level found was 14.7 mg/kg in working gloves for the garden. Also in all other aforementioned product categories, products were found with detectable Cr (VI) levels. Since one of the positive products was a baby shoe and babies can be expected to suck on their shoes (like on toys), 2 baby shoes were analyzed

for migration of chromium. The levels found in these two samples do not comply with the standard safety requirements of the European Standard on Safety of Toys EN71 (Rydin, 2002).

5.3.2 Metals in cleaning products and detergents

Levels of the transition metals nickel, chromium and cobalt are present in cleaning products and detergents. In an Italian study, metal levels were investigated in various detergents and were found to be below the recommended level of 5 ppm (reviewed in Basketter et al., 2003). In Table 14, results of an independent analysis of household consumer products are given.

Table 14 Analysis of Ni, Cr, and Co in selected current consumer products

Product type (number)	Ni (ppm)	Cr (ppm)	Co (ppm)
Heavy duty powder (n=9)	0.5	1.1	0.1
Hand wash powders (n=4)	0.9	0.9	0.1
Laundry tablets (n=3)	0.5	0.6	0.2
Heavy duty liquids (n=9)	0.1	0.1	0.1
Machine/ hand wash liquids (n=4)	0.1	0.2	0.1
Hand wash liquids (n=4)	0.1	0.1	0.1
Fine wash liquids (n=2)	0.1	0.2	0.1
Dishwashing liquids (n=9)	0.1	0.1	0.1
Liquid/ powder cleaners (n=6)	0.4	0.4	0.1

Data courtesy of Stazione Sperimentale Oli & Grassi (Basketter et al., 2003)

Additionally, a survey of 95 detergents by the Dutch authorities showed that approximately 90% of the detergents investigated contained < 1ppm Ni, Cr of Co; all were below the recommended level (Gaikema et al., 2002).

5.4 Exposure calculations

5.4.1 Definition of exposure dose

For performance of a quantitative risk assessment, exposure assessment is a crucial component (see also chapter 7). The problem however with determination of exposure is the definition of the exposure dose in humans. Concentration measurements of allergens in consumer products, as described in the previous section, are a prerequisite for the performance of a quantitative exposure assessment and many data are needed. Furthermore, links between the content of a substance in the product (concentration) and actual human exposure are only possible in the case of preparations like paints, detergents and cosmetics. Also the conditions of use must be taken into account. In the case of consumer products like clothing and toys, it is only the proportion of the substance released from the product (migration) that is important for exposure assessment. At the present time there are only few generally accepted methods for migration and scarcely any data available from appropriate measurements. Furthermore the measurement data are not necessarily suitable for exposure assessment. In addition, realistic exposure scenarios for allergens have to be determined.

5.4.2 Aggregate exposure assessment

Human exposure to almost all of the allergens mentioned in this report is resulting from many different sources. Sometimes, exposure may occur only via one product (e.g. a cosmetic product), but in many cases also other cosmetic products and product groups such as detergents or clothing are involved. Establishing an exposure estimate is therefore complex, and requires an aggregate exposure assessment. Aggregate exposure is defined as the total exposure that arises from multiple sources via different pathways and routes. The level of detail, at which aggregation might be done, should be dictated by the scope and purpose of the assessment. Demands for a first tier, screening type of assessment on the required level of detail are much lower than those of an assessment that has to give a realistic quantification of the variation of the exposure in a population (Delmaar and Van Engelen, 2006).
For the performance of a quantitative exposure assessment, many data are needed. Although in the past few years various market studies were carried out in Denmark and The Netherlands, the collected data are not sufficient for a proper aggregate exposure assessment of any of the abovementioned allergens or allergen groups in consumer products.

To provide more insight in the possibilities and difficulties of an exposure assessment, four different examples of exposure calculations (for the preservative methenamine, a polycyclic musk AHTN, the preservative Kathon, and fragrance X) are presented in Appendix 5. These calculations are reproduced from other reports available, and not re-assessed or criticized for their choices. They illustrate that an exposure calculation can be performed at very different levels of detail. Furthermore, many data are needed on e.g. frequency of use, amount used etc. Also correlations between parameters are important in a proper aggregate exposure assessment (to avoid over-conservative estimates). Finally, the exposure calculations demonstrate that data are needed on the actual concentration of sensitizers in the end-product. For a lot of products these data are confidential or are not publicly available which seriously hampers a proper aggregate exposure assessment.
For general toxicity endpoints, exposure estimates are compared to a NOAEL for a certain endpoint. For sensitization, however, it is preferred to have exposure estimates in $\mu g/cm^2$ to compare with possible threshold levels (Robinson et al., 2000; Api et al., 2007; Kimber et al., 2008). This requires additional information on exposure factors (amount in combination with skin area exposed). For more information on threshold levels and quantitative risk assessment for sensitization, see chapters 6 and 7, respectively.

6 Hazard of allergens in consumer products

6.1 Prediction of sensitizing potency

The sensitizing potency of a chemical comprises the intrinsic capacity of a chemical to induce sensitization, and can be expressed by the concentration of the allergen at which sensitization is induced. A chemical with a strong potency induces sensitization at a low concentration; a weaker sensitizer requires higher concentrations. The potency represents the hazard; the risk of sensitization is also determined by the actual exposure encountered. Hence, a weaker potent sensitizer may result in a higher frequency of sensitization, due to an extensive exposure. Nickel is such an example.

6.1.1 Validated animal models used to predict sensitization

To predict the skin sensitizing potential of a substance, different validated animal models are used: the GPMT, the Buehler test and the LLNA (OECD, 1992; OECD, 2002). At present there are no validated animal models available for respiratory sensitizers. However, all respiratory sensitizers investigated so far, were identified with the LLNA (Vandebriel et al., 2000; Dearman et al., 2003).

The GPMT and Buehler test

The GPMT and Buehler test are both performed in guinea pigs. In the GPMT sensitization is induced by intradermal injection of the test substance together with Freund's complete adjuvant. After 6 to 8 days an occluded patch with the test substance is applied to an area on the shoulders for 48 hours. After 12 to 14 days, elicitation is performed on the flank by application of an occlusive patch for 24 hours. Then, after removal of the patch, skin reactions, such as erythema and edema, are scored. A substance is classified as a skin sensitizer if at least 30% of the animals have a positive response (OECD, 1992). For the Buehler test, a patch with the compound is applied topically on the flank for six hours, once a week over a period of three weeks. Two weeks after the final treatment a patch containing the compound is applied again for six hours at a location on the flanks different to where the initial challenges were done. After 24 and 48 hours, erythema and edema are scored. The compound is classified as a skin sensitizer if at least 15% of the animals have a positive response in the Buehler test (OECD, 1992).

LLNA

In the LLNA, the test substance is applied topically on the ears of mice on three consecutive days. On day five the proliferation of lymphocytes is measured in the draining (auricular) lymph nodes, by measuring the amount of radioactivity that is incorporated in the DNA of the proliferating cells. The Stimulation Index (SI) is the ratio of incorporated radioactivity in the lymph nodes of treated versus control mice. This SI is used to discriminate sensitizers from non-sensitizers and a substance is classified as a sensitizer when the SI $\geq$ 3. In addition, the EC3 value, which is the estimated concentration to produce an SI of 3, is used to predict the sensitization potency (Basketter et al., 1999; Van Och et al., 2000). From an animal welfare point of view the LLNA is the preferred method. Additional advantages of the LLNA are that the data obtained are objective and quantitative and that it is possible to assess dose-response relationships, which can be used to calculate potency and thresholds (Gerberick et al., 2007). Limitations of the LLNA are the number of false-positives, for instance strong irritants (Basketter et al., 2007).

6.1.2 Assessment of skin sensitizing potency

It is unethical to assess the potency of substances in humans, but for many chemicals the sensitizing potency has been estimated by using historical data from the human maximization tests (HMT) and the human repeat insult patch test (HRIPT), along with expert judgment. In the LLNA, the EC3 value can be used to assess the potency of a compound (Basketter et al., 1999; Van Och et al., 2000) and it has been demonstrated that this correlated relatively well with human data (Gerberick et al., 2001; Griem et al., 2003; Schneider and Akkan, 2004). In order to classify the hazard of substances with the EC3 value, two different strategies have been proposed (ECETOC, 2003; Basketter et al., 2005). In the EU the proposal of Basketter et al. (2005) is most often used. However, recently an OECD Expert Group on Sensitization Hazards has proposed to use only two categories: stronger sensitizers when the EC3 ≤ 2% and other sensitizers when the EC3 is >2% (OECD Expert Group on Sensitization Hazards, 2008). The aim of this expert group is to harmonize the hazard identification for sensitizers between the different regions of the world. In the future this classification will probably be implemented in the EU and therefore this classification is used in the current report.

6.1.3 Assessment of respiratory sensitizing potency

There are currently no validated animal models to classify respiratory sensitizers, although they can be identified in the LLNA (Vandebriel et al., 2000; Dearman et al., 2003). Human experience is used to identify if a chemical is a sensitizer and also to classify the hazard category. Substances are classified as stronger sensitizers when they frequently induce respiratory allergy or when they induce severe reactions. Chemicals that only moderately induce respiratory allergy or induce less severe reactions are classified as other sensitizers (OECD, 2008).

6.1.4 The potencies of chemical allergens in consumer products

In Tables 29-31 of Appendix 6, potencies for chemical allergens present in consumer products are summarized, in the different substance categories. Table 29 shows available information for fragrances, Table 30 for hair dye substances and Table 31 for metals, preservatives and resins. In most of the published literature, LLNA data are used to calculate skin sensitizing potency. Therefore, the main focus is on EC3 values for potency estimations. However, for hair dye substances, data from a SCCP memorandum on hair dyes (SCCP, 2006a) have been used. In this report, data derived from submissions from the industry are used to categorize the potency of these substances. The potency categorization is based predominantly on LLNA data, but also on data from GPMT and the Buehler test. Therefore, this information is also included in Table 30. These classifications were done according to the proposal of the OECD Expert Group on Skin Sensitization Hazard (2008), categorizing chemicals in two classes: stronger sensitizers (EC3 ≤ 2%) or other sensitizers (EC3 > 2%). Furthermore, if available, the five human potency classes are included in these appendices (strong, moderate, weak, extremely weak, and nonsensitizing) (Basketter et al., 2000).

In Appendix 6, Table 29, it is shown that most fragrances are classified as ‘other’ sensitizers, based on LLNA data, whereas only benzyl salicylate, cinnamal, isoeugenol, and methyl heptine carbonate are classified as stronger sensitizers. In humans, most fragrances are weak sensitizers, with the exception of isoeugenol and methyl heptine carbonate, which are strong sensitizers and cinnamal, hexyl cinnamaldehyde, oak moss and tree moss, which are moderate sensitizers. It is important to note that some fragrances, such as linalool, geraniol and d-limonene are classified as weak sensitizers in humans, but they were able to induce and elicit contact dermatitis. For these fragrances, it has been demonstrated that they have no or weak sensitizing potential in the LLNA. These chemicals are not capable of binding to proteins, and can not sensitize the immune system. However, after oxidation upon

exposure to air, spontaneous oxidation occurs, which results in the formation of protein-reactive oxidation products, such as hydroperoxides and aldehydes (Karlberg et al., 1994; Skold et al., 2004; Hagvall et al., 2007; Skold et al., 2008). By using the LLNA it has been demonstrated that oxidation products of linalool (Skold et al., 2004; Skold et al., 2008) and geraniol (Hagvall et al., 2007) were potent sensitizers, which induced EC3 values that were much lower then those induced by the fragrances themselves. In the GPMT it was demonstrated that hydroperoxides formed after oxidation of limonene were more potent sensitizers than limonene (Karlberg et al., 1994). Oxidized limonene was a frequent sensitizer in patients with contact dermatitis (Matura et al., 2002).
The fragrance coumarin is classified as a non-sensitizer based on LLNA data. In humans, positive patch tests have been observed in patients with atopic dermatitis, but pure coumarin was not able to elicit a positive reaction in the LLNA and was also negative in patients. Possibly, patients react to contaminants with skin sensitizing properties that were present in the coumarin preparations (Vocanson et al., 2006). According to an opinion of the Scientific Committee of Consumer Products (SCCP), coumarin has been shown to elicit allergic contact reactions in humans and should therefore be considered as a sensitizer (SCCP, 2006b).

The potency of 46 hair dye substances is described in a report of the SCCP (SCCP, 2006a). A total of 27 hair dye substances were classified as sensitizers. Further evaluation demonstrated that 23 were classified as stronger sensitizers and 4 as other sensitizers (Table 30, Appendix 6).
In Table 32, potencies of other allergens, such as metals, preservatives and solvents are summarized. Metals generate often false negative results in the LLNA. The potencies of nickel and cobalt were determined in the GPMT, classifying them as other and stronger sensitizers, respectively (Basketter and Scholes, 1992). There is no information on the potency of chromium dichromate, whereas potassium dichromate is classified as a stronger sensitizer. Preservatives are classified as stronger sensitizers in case of CMI/MI, MTI, MDBGN, tetramethylthiuram disulfide, tetraethylthiuramdisulfide, formaldehyde, paraformaldehyde and TDI. BIT, dipentamethylenethiuramdisulfide, tetramethylthiurammonosulfide, dipentamethylenethiuram-tetrasulfide, tetrabutylthiuramdisulfide, 2-chloro-N-acetamide, quartenium-15 and hexamethylenetetramine are classified as other sensitizers (see Table 31, Appendix 6).
In the literature, there is no information on the potency of parabens, colophonium, balsam of Peru and turpentine oil, but colophonium and turptentine have been shown to oxidate upon air exposure, forming oxidation products with sensitizing properties (Brared Christensson et al., 2006).

6.2 Thresholds for skin sensitization

6.2.1 Prediction of sensitization and elicitation thresholds

Skin sensitization and elicitation are both only induced above a certain threshold dose. To estimate thresholds for sensitization, EC3 values derived from LLNA are used. It is important to note that these thresholds are expressed as dose per skin area (in $\mu g/cm^2$), since skin sensitization depends not only on the total dose that is applied, but on the dose that is applied on a certain area of the skin (Friedmann et al., 1983). To calculate murine thresholds, EC3 values are converted to $\mu g/cm^2$ by multiplying it by a factor of 250 (Griem et al., 2003). Historical data from HRIPT and HMT are employed to establish no observed effect levels (NOEL; expressed in $\mu g/cm^2$) or in absence of a NOEL, the lowest observed effect level (LOEL; expressed in $\mu g/cm^2$ divided by a factor of 10). It was shown that murine thresholds correlated reasonably well with human thresholds (Griem et al., 2003; Schneider and Akkan, 2004; Basketter et al., 2005b).

It is important to note that for some chemicals, sensitization can occur after repeated exposure below the threshold dose. For formaldehyde donors, it was shown in mice that prolonged repeated exposure to an EC2 resulted in the induction of SI above 3. One of the characteristics of these chemicals is their reactivity towards proteins resulting in prolonged persistence in the skin (De Jong et al., 2007). In contrast, for the skin sensitizers DNCB, TMTD and benzocaine, prolonged exposure below the EC3 value did not result in positive, e.g. SI >3, lymph node responses (Van Och et al, 2003). Hence, due to physico-chemical characteristics of chemicals, thresholds for sensitization might be lower than the EC3 value.

Thresholds for elicitation are currently not available. It is not possible to extrapolate them from animal studies, since there are no validated and reliable animal models for elicitation. In addition, elicitation responses in humans are complex, since inter-individual variability in thresholds for elicitation exists. Several factors play a role in this and one important factor is the degree of sensitization (Kimber et al., 1999; ECETOC, 2003). Both in humans and in mice, it has been shown that when the sensitization dose was increased, the elicitation threshold decreased (Friedmann et al., 1983; Scott et al., 2002). Thresholds for sensitization are different from elicitation thresholds for the same chemical and in general higher levels are needed for sensitization of naïve individuals than for elicitation of sensitized subjects. Griem et al. (2003) have shown that in humans no correlation could be shown between sensitization and elicitation thresholds, hence, thresholds for sensitization can currently not be used to predict elicitation thresholds.

6.2.2 Sensitization thresholds for allergens in consumer products

In a recent ICCVAM publication, human and murine thresholds for sensitization were assembled by combining data from datasets of human thresholds and LLNA EC3 values as published previously (Griem et al., 2003; Schneider and Akkan, 2004; Basketter et al., 2005a). In Table 15, an overview of these thresholds is presented for allergens in consumer products. The correlation between human and murine thresholds is relatively good, despite the existence of several uncertainties. Therefore, it is too early to use these thresholds to predict safe levels. One of the major concerns is the variability of the human data, derived from historical studies. The high variability is due to the fact that several assumptions had to be made to calculate the thresholds. In most human tests only one dose was tested, and LOEL values had to be extrapolated. In addition, the patch size was not always known, and the size of the application area had to be estimated. Furthermore, these human studies were not conducted according to a standardized protocol and for most allergens results of only one single measurement are available. Hence, the reliability, accuracy and reproducibility are unclear and this may explain the variation between human and murine data (Basketter et al., 2008b).

For ethical reasons it is impossible to determine thresholds in humans, and therefore LLNA EC3 values can be used in order to calculate NOELs for quantitative risk assessment (QRA). The QRA expert group (with members of RIFM and Industry) has proposed to identify hazard by using LLNA data and not by performing human sensitization tests (QRA expert group, 2006). It should be considered that the threshold for induction of sensitization for some compounds might be lower than the EC3 value, due to certain characteristics, e.g. the strong capacity of formaldehyde donors to cross-link with proteins in the skin resulting in prolonged persistence in the skin to proteins (De Jong et al., 2007).

Table 15 Overview of human and murine thresholds for allergens in consumer products

Substance	Human threshold (µg/cm^2)	Murine threshold (µg/cm^2)
CMI/MI	1.25	2.25
Phenylenediamine	10	22.5
Methylisothiazolinone	12.5	475
Formaldehyde	37	162.5
Benzoisothiazolinone	45	575
Potassium dichromate	111	116
Nickel sulfate	154	140
Isoeugenol	250	325
Cobalt sulfate	313	50
Cinnamic aldehyde	591	775
Oakmoss	700	970
Citral	775	3300
Farnesol	2755	1200
Hydroxycitronellal	2953	8250
Anisyl alcohol	3448	1475
Geraniol	3875	6475
Lyral (HMPCC)	4000	4275
Tetramethylthiuram disulphide	4610	785
Benzyl cinnamate	4720	4600
Cinnamic alcohol	4724	5150
Eugenol	5905	3225
Linalool	13793	7500
Benzylbenzoate	20690	4250
Alpha Amyl cinnamic alcohol	23622	2650
Amylcinnamic aldehyde	23622	2750
Hexylcinnamic aldehyde	23622	2750
Lilial®	29525	4675
isoMethylionone	70866	5450

Adapted from Basketter et al., (2008b)

Thresholds determined in the LLNA can then be used to determine a human threshold, which has been called the No Expected Sensitizing Induction Level (NESIL). Human sensitization assays are recommended to be used only to confirm lack of sensitization and should be performed according to the Research Institute for Fragrance Materials, Inc. (RIFM) standard HRIPT protocol (Politano and Api, 2008). This protocol should not be used to determine hazard but only as verification of animal data. At RIFM a historical database is present that contains more than 1000 HRIPTs and more than 1200 HMTs conducted with fragrances.

7 Risk Assessment for sensitizers

Risk assessment for sensitization serves to ensure that dermal exposure to skin sensitizers does not result in the development of allergic skin disease. Skin contact with a potential sensitizer cannot always be completely avoided; however, the fact that a chemical is a contact allergen does not mean that it cannot be formulated into a consumer product. In contrast, it may be well tolerated, e.g. below the threshold dose for most individuals. Skin sensitization risk assessment of new products and their ingredients is critical before introduction into the market place.

7.1 From traditional risk assessment to QRA

In the past, traditional risk assessment methods for skin sensitization aimed at hazard identification only and were used for classifying and labelling chemicals either as sensitizers and non-sensitizers. A main reason for this was the assumption that allergic reactions to chemicals often were regarded as all-or-none responses that lack dose-response relationships and thresholds.
However, since the year 2000, after years of research, it became more and more accepted that skin sensitization as well as allergy elicitation is only occurring above threshold doses and follows predictable dose-response relationships (reviewed in Griem et al., 2003) making skin sensitization in this respect not different from other toxicological effects. Therefore in risk assessment, newly developed test systems for hazard characterization were more focused on delivering dose-response curves and potency information, such as LLNA in mouse and HRIPT in humans (Kimber et al., 2001; Griem et al., 2003) (see also previous chapter). In this way, a more quantitative and adequate risk assessment approach can be conducted. Since 2000, methodologies for quantitative risk assessment (QRA) for sensitizers in general were proposed by e.g. Robinson et al., (2000) Griem et al., (2003) and more recently also by industry for fragrances (QRA expert group, 2006; Api et al., 2007).
For the quantitative hazard characterization, the EC3 value (as surrogate NOEL) obtained from the LLNA can be used as a starting point (Griem et al., 2003). Apart from a more quantitative hazard characterization, one of the main characteristics/ determinants of a QRA methodology is exposure estimation. Incorporation of chemicals into products must be at levels that produce acceptably low incidences of skin sensitization under foreseeable conditions of exposure. The critical exposure determinant for evaluating skin sensitization risk is dose per unit area of skin exposed (Robinson et al., 2000; Kimber et al., 2008). Use of this parameter allows for comparative assessments from different types of skin sensitization tests (including cross-species comparisons) and, at least for known potent allergens, there is a relatively good similarity in threshold dose/ unit area across species (see previous chapter). The dose/unit area calculation enables a judgment of the sensitization risk for different product types (Robinson et al., 2000). Then through the application of general (though commonly product-type specific) safety factors, a conservative determination of maximum product exposure limits can be determined (Robinson et al., 2000).

For fragrances, a ‘dermal sensitization quantitative risk assessment for fragrance ingredients’ has recently been proposed by the QRA reference group (2006) and Api et al. (2007) and provided by the International Fragrance Association (IFRA) to the fragrance industry for the allowance of fragrances that are potential contact allergens in consumer products (Jowsey, 2007). This QRA is based on the same principal as the quantitative risk assessments as described above.
Nevertheless, some differences exist, for instance the use of human data in the hazard characterization and the use of other, more specific assessment factors for product use and matrix. Furthermore in this approach, another nomenclature for NOEL and safety factors has been utilized.

The key steps of the QRA for fragrances are 1) determination of benchmarks (No Expected Sensitization Induction Level = NESIL), 2) application of sensitization assessment factors (SAFs), and 3) consumer exposure (CEL) through product use. Using these parameters, an acceptable exposure level (AEL) can be calculated and compared with the consumer exposure level (CEL). The ratio of AEL to CEL must be favourable to support safe use of the potential skin sensitizer. However, for a general determination of exposure to allergens in consumer products, a calculation of the AEL/CEL ratio has to be made for every ingredient in each product type which is very time-consuming (Api et al., 2007). The methodology has been developed for fragrance ingredients, but with sufficient data and knowledge, it can be extrapolated to other potential allergenic substances as has been done recently by Basketter et al (2008a) retrospectively for four common preservatives (formaldehyde, CMI/MI, imidazolidinylurea (IU) and 3-iodo-2-propynyl butyl carbamate (IPBC)).

7.2 Threshold of Toxicological Concern (TTC) concept

An alternative approach to assess safe levels is the Threshold of Toxicological Concern (TTC) concept, which was initially proposed for substances to which humans are exposed orally, such as food additives and flavors (Kroes et al., 2005). The concept is applicable for chemicals of which human exposure is low and toxicity data are not available. Advantages of this approach are the saving of time, money and experimental animals. The TTC concept is based on a probabilistic analysis of available toxicity data of structurally related chemicals. For each chemical the maximum oral dose which is considered to be safe to human health after daily lifetime exposure is calculated. If the average daily intake is below this dose, toxicological safety testing is not necessary (Kroes et al., 2005).
The TTC concept has been proposed for cosmetic ingredients (Kroes et al., 2007). For these substances exposure is predominantly topical, and to a lesser extent inhalatory. Hence, in the TTC approach, factors such as skin absorption should be taken into account. Exposure estimation is of critical importance in the TTC approach, and for cosmetic ingredients several factors should be considered. First, for exposure assessment it should be taken into account that the allergen can be present in several different products; hence aggregate exposure has to be assessed. In addition, exposure will be different for rinse-off products than for leave-on products, and for rinse-off products a retention factor should be applied. Furthermore, the use pattern should be established, e.g. not all products will be used on a daily basis, for instance hair dyes, and adjustment factors are proposed for this (Kroes et al., 2007). The TTC concept for cosmetic ingredients focused on systemic toxic effects and not on sensitization. Recently, this approach has also been proposed for skin sensitizers (Safford, 2008).
For skin sensitizers it has been suggested that the TTC concept can be used to assess a Dermal Sensitization Threshold (DST). The main steps to calculate this will be described in short. First, the proportion of sensitizers among all chemicals was estimated and it was shown that 20% of all chemicals listed in the European List of Notified Chemical Substances (ELINCs) database were classified as skin and/or respiratory sensitizers. Second, the potency distribution for known skin sensitizers was established. The potencies were calculated by using published EC3 values and the categorization proposed by ECETOC (2003). It was shown that most substances fall in the categories weak (66) and moderate (69), whereas 21 were strong and 13 were extreme sensitizers. Third, EC3 values were converted into thresholds, by expressing them as dose per unit area. The NESIL was then calculated by applying a correlation factor for interspecies differences and was used to calculate the AEL by dividing the NESIL with the appropriate SAFs, similar to the QRA approach described above (Api et al., 2007). To establish an acceptable risk for chemicals that are not tested it is necessary to assess the probability that the AEL for a chemical will be exceeded. For shampoo and deodorant a DST

of 1.64 and 0.55 μg/cm^2 would give a 95% probability that the AEL will not be exceeded (Safford, 2008).
This proposal is the first attempt to use the TTC concept for skin sensitizers and several remarks on uncertainties were made by the authors. These uncertainties are on the one hand the same as for the QRA, and include for instance the reliability of the NESIL. On the other hand, uncertainty factors specific for the TTC concept were mentioned. It was estimated that 20% of all chemicals in the ELINCs database were sensitizers but not all of these chemicals will be used in cosmetic products. It is important to note that when this probabilistic approach is used, the threshold will not be protective for all chemicals, since there is a 5% probability that an untested chemical will give a risk. It was demonstrated that most of the known sensitizers that would exceed the AEL are not present in cosmetic products, with the exception of CMI, formaldehyde, PPD and some other oxidative hair dyes. In conclusion, the TTC concept could be useful to set a pragmatic DST for cosmetic substances, with the exception of reactive chemicals, such as preservatives and oxidative dyes. Further refinement of this method, by for instance using information on quantitative structure activity relationships (QSARs), for instance sensitization alerts in molecules.

8 Discussion

In the current document information has been reported on the incidence and prevalence of skin contact allergy related to exposure to sensitizers due to the use of consumer products. Various inventories have been made to see what types of consumer products are relevant. It was shown that the ranking of the various allergenic substances is different with respect to prevalence of contact dermatitis (chapter 4, Appendix 3), sensitization potency of the substances (chapter 6, Appendix 6) and frequency of allergens in products (chapter 5, Appendix 4). Furthermore, the prevalence of contact dermatitis compared to other allergic diseases was found to be relatively high (section 4.6) and in a large number of consumer products important allergens are present (chapter 3). Our document underlines the need for better control of the exposure to sensitizers in consumer products. Until now, a quantitative risk assessment (QRA) on these substances in consumer products has not been performed. Recently, Industry has proposed a QRA method for the introduction of new products and ingredients on the market place (chapter 7). Only a small number of limit values are available (e.g. for preservatives in cosmetics), however, the justification for the limit values with regard to protection against sensitization is unclear (if present at all). Furthermore, the declaration limits of sensitizers in preparations (and fragrances in cosmetic products) are valuable for already sensitized consumers because the product is labelled with the specific fragrance, but do not protect to sensitization.
Therefore, the recent Industry initiatives towards the development of a quantitative risk assessment for sensitizers are highly welcomed.
The different aspects that contribute to the safety assessment of sensitizer in consumer products are discussed below.

8.1 Prevalence as result of potency and frequency

One of the main conclusions of this report is that the prevalence of contact dermatitis compared to other allergic diseases is relatively high. When the Dutch prevalence data are used, which vary between 3.7 and 5.4%, the prevalence of contact dermatitis is comparable to the common allergic disease asthma. However, the prevalence as assessed in European epidemiological studies is higher and are in the range of 12.5-40.6% in the general population from 1966-2007 (Thyssen et al., 2007b). The Dutch prevalence data are originating from general practitioners and are probably an underestimation because not everyone with symptoms is visiting a doctor. Furthermore, it is not clear to what extent the contribution of sensitization in consumer products is included in this prevalence, since sensitization at the workplace is also very plausible. Occupational skin disorders such as contact dermatitis are one of the most work-related diseases in Western Europe (Meding et al., 2005). The prevalence of contact dermatitis based on data from general practitioners is lower than those measured in epidemiological studies. The latter refer to ingredients in consumer products and are based on data of epidemiological studies, patch tests using different allergens, sometimes combined with clinical epidemiology. For patients with contact dermatitis that consult a specialist, it is possible that sensitization has taken place at the workplace, but health problems become apparent as a consequence of the use of consumer products.

The contribution of nickel and cosmetic ingredients to the European prevalence of contact dermatitis was estimated to be 7-19% and 3-4%, respectively. Indeed, when all data are put together, the most prevalent allergens in consumer products such as metallic accessories are metals like nickel (up to 17.9% in allergic patients and 10% in the general population), cobalt (6% in patients and 2% in general population) and potassium dichromate (4.6% in patients). Also various fragrances present in cosmetic and household products, result in high prevalence of contact dermatitis. Prevalence of contact

dermatitis after the use of fragrance mix I is varying from 10% in patients and 1-11% in the general population, for Peru Balsam this is 6% in patients and 1% in the general population. Also the use of the hair dye para-phenylene diamine results in a high prevalence of contact dermatitis in patients (3.9%).

Remarkably, the prevalence of contact dermatitis due to the use of preservatives, also recognized as common causes of skin sensitization, is currently not recognized as one of the major allergenic substances. Only Thiomersal and MDBGN have been shown to result in a high prevalence of contact dermatitis in the past, but these preservatives are now banned in vaccines and cosmetic products respectively, leading to a recent decrease in prevalence (Thyssen et al., 2007a;b). Another reason may be the difference in legislation for fragrances and preservatives; for potent preservatives a maximum limit value is derived, while for allergenic fragrances there's only a limit for declaration (see also next section).

From the inventories in the current report, it has become clear that prevalence of sensitization is a result of both sensitization potency of the substance and exposure to consumer products (e.g wide-spread presence in consumer products, and frequency of use). Nickel for instance has a moderate sensitizing potential, but through the extensive use in jewellery, piercings and clothing accessories, it has become the most common contact allergen since many years. Fragrances that are most frequently found in consumer products are D-limonene, linalool, Lilial® and geraniol and are all classified as (extremely) weak sensitizers. From these frequently used fragrances, Lilial® and geraniol are classified as less important sensitizers and D-limonene and linalool as rare sensitizers (Table 4; Schnuch et al., 2007). In contrast, fragrances that are seldom found in products, e.g. oak moss, tree moss and isoeugenol are classified as important sensitizers in patients. Isoeugenol is a strong sensitizer, whereas tree moss and oak moss are classified as moderate sensitizers in humans.
In general, allergenic fragrances that are present in high amount of consumer products but low in the ranking of prevalent substances are not a problem for most consumers. This is also the case for preservatives, since the mildest sensitizers - parabens- are the most frequently used preservatives, at least in cosmetics and induce problem in only a small minority of the patients. On the other hand, fragrances and preservatives that are more potent sensitizers are or can become a problem and should probably be regulated more strictly.

Apart from the wide-spread use of the sensitizers, increasing the probability for the consumer to come in contact with the specific substance, also the concentration of the sensitizer in the products is important. The fragrances with the lowest sensitizing potential, D-limonene, linalool, Lilial® and geraniol, were found in relatively high concentrations in cosmetics. Also in detergents and toys, although the concentrations are far lower than in cosmetics, a relatively high concentration of D-limonene has been found, when this is compared to the concentration of other fragrances (Table 21, Appendix 4).
However, it has to be realized that a potential problem can also arise when frequently used compounds with a low sensitizing potential can be metabolized (by air or on the skin), leading to a more potent sensitizing compound. This has already been described for D-limonene, which can be oxidized to limonene oxides (Karlberg et al., 1992; 1994) and derivates of isoeugenol, used as alternatives for isoeugenol because of the lower sensitizing potency, that can be converted into isoeugenol again (Rastogi and Johansen, 2008).

In order to have an idea of the impact of allergy caused by consumer products, a search was performed to find information on the associated costs of allergy for society. It was found that the information available on costs regarding allergies is very general and not specific for contact dermatitis resulting from chemicals in consumer products. In addition, for calculating a reliable cost estimate, not enough

data (on prevalence and source proportionement) are present for which assumptions have to be made, making the outcome too uncertain.

8.2 Effects of legislation on prevalence of contact dermatitis

Despite several types of regulations that are in force in the EU to reduce exposure to sensitizers (described in section 2.2), prevalence data show that a significant proportion of the population still suffers from contact dermatitis. Apparently, the legislation is not sufficient to prevent the occurrence of contact dermatitis. To achieve this, all allergenic substances should be restricted below threshold levels or completely banned, which is not feasible for all chemicals, e.g. preservatives.
In the current legislation some allergens are prohibited to be used or present in cosmetics (Cosmetics Directive) or toys (draft Toy Directive). Furthermore two different types of limits are used for sensitizers:

1) Maximum limit values.
Examples are nickel (Nickel directive, 1994) and preservatives in cosmetics (Annex VI part 1&2 of Cosmetic Directive). The concentration may not exceed the maximum limit value.
2) Limits of declaration.
In the Preparations Directive there is a limit for declaration of sensitizers of 0.1%. In the Cosmetics Directive, the limit for sensitizing fragrances is 0.001% and 0.01% for leave on and rinse off products, respectively (Annex III). This limit indicates a minimal concentration for labeling, not a maximum. The concentration used may exceed the limit, even up to 100%, when the ingredient is declared on the label. The limit may be useful for already sensitized people to prevent elicitation.

For the majority of the allergens the maximum limit values are, not based on quantitative risk assessment. Exceptions are nickel and Lyral, where clinical epidemiological data in patients were used to set the maximum limit value. For the limits without a quantitative basis, it is unknown if these limits represent safe levels that are sufficient to protect consumers for sensitization. For already sensitized patients, the limits of declaration are useful, because they can avoid products that contain the chemicals to which they are sensitized. However, at this moment it is unclear whether products which contain sensitizers below the limit for declaration (so below 0.1%) also protect already sensitized consumers since for an elicitation reaction, a low(er) concentration is sufficient to provoke the allergic reaction.
It is recommended that for certain substances maximum limit values should be set that protect consumers for sensitization (and preferable also for elicitation). For instance, fragrances such as isoeugenol, oak moss, tree moss and balsam of Peru are important sensitizers and in order to reduce contact dermatitis for these fragrances, it would be advisable to set maximum limit values. Before doing so, more insight in thresholds should be gained, for instance by using quantitative risk assessment approaches.
In the next section, two approaches, recently developed by Industry and still under development, are discussed.

8.3 Methods for determination of risk for sensitization

Two recently developed methods for derivation of safe limits (QRA and TTC) have been described in chapter 7 of this document. In general, these approaches with a quantitative outcome have certainly been improved compared to the traditional methods resulting in a yes/no answer.

One promising approach is quantitative risk assessment (QRA) method for the method of the dermal sensitization of fragrances as proposed by Api et al. (2007).
There are, however, a number of remarks to be made:
First, the dose-response for induction of skin sensitization is determined using animal assays (LLNA). A human repeated insult patch test (HRIPT) is used to confirm the lack of sensitization at an exposure level which was identified as an NOEL in the animal model.
In Table 15 of this document it has been shown that, although the correlation between murine and human threshold levels is relatively good, there are substances for which threshold levels vary substantially between man and mouse. Furthermore, HRIPT is not a validated test system and it is therefore not included in a regulatory test guideline. At present no clear guidance is available for the choice of test concentrations. In addition, predictive sensitization testing in humans is considered unethical. Only healthy volunteers (not previously sensitized) are tested in this HRIPT test but by participating to the test they are put at risk for being sensitized.
Second, with respect to the sensitization assessment factors (SAFs), a factor of 10 is always assigned in this method for the inter-individual variability in sensitivity, however, it can be imagined that a larger variability exists and that a factor 10 is not always sufficient. More information is needed on how to deal with susceptible persons, for instance people with an impaired skin barrier that also use cosmetics on a daily basis. Furthermore, it is unknown if children are more susceptible. It is not clear what the basis is for the SAF for product matrix. It is remarkable that a lot of different product types have the same matrix SAF. The QRA is designed to set safe levels for sensitizers in products. It should be noted, however, that it is not meant as a tool to assess the safety of the whole product. As a result, the presence of more structurally similar substances in the finished product is not considered. Furthermore, a factor for exposure duration is missing (see also below).
A major deficiency of the method as proposed is that aggregated exposures are not considered; the risk is calculated per allergen per product. However, in practice, consumers are exposed to a combination of products with the same fragrances. Although the risk after using one product might be low, the risk may increase with the use of more products containing the allergen. In the QRA example on the preservative CMI/MI (Kathon) that is included in Appendix 7 of this report, it is shown that exposure to one substance in various products can be complex, and a lot of data is needed for a reliable exposure assessment.
In short, the QRA method as described above looks promising, is not yet fully developed, and is a time consuming and costly exercise. Furthermore, it requires test data from animals and in some cases humans which raises ethical issues that need to be weighed against the potential risk of sensitization in consumers.

Another recent approach that can be used for the quantitative risk assessment of sensitizers is based on the Threshold of Toxicological Concern (TTC). In this method, a probabilistic analysis of available sensitization data is performed, that may also be useful for determining the risk of sensitization due to allergens in consumer products. In this method the no expected sensitization level (NESIL) is set without further testing requirements. The acceptable exposure level for each chemical in a product is then determined by applying the same assessment factor (SAFs) as used in the QRA. So the comments given above on the SAFs are valid here as well. Also in this case, aggregate exposure is not taken into account. The data set that has been analysed for this purpose is relatively small and not generally

representative for the world of chemicals or for chemicals used in cosmetic and personal care products (Safford, 2008).
The proposal implies that there is a 5% probability that an untested chemical would give an undue risk. The TTC approach is welcomed, because this would in theory reduce the use of animal testing. However, the proposal as such is not ready for use, since it is based on the QRA for sensitizers, a method that is still under improvement. Further refinement and validation of the QRA but also on the database used for the TTC is urgently needed before further consideration.

Finally, a general remark should be made with respect to the use of the LLNA test system that is used in both approaches as a starting point. It should be noted that although the test is able to generate information on potency and thresholds, the exposure situation in the test does not mimic the exposure conditions in real life, with respect to e.g. exposure duration. Furthermore, the endpoint in the LLNA is not sensitization, since the applied protocol does not intend to sensitize mice, but rather uses proliferation as an endpoint which correlates relatively well with skin sensitizing potential in humans. It would be worthwhile to take this into account by introducing an additional SAF.

8.4 Exposure to allergens via different routes

The two above mentioned approaches only try to quantify the risk of sensitization during dermal exposure. However, from the inventory of exposure to allergens in consumer products it can be concluded that exposure to allergens can occur via different routes. Sensitization through the dermal route has been studied most extensively and only limited information exists on the occurrence of sensitization after inhalation of or oral exposure to chemical allergens.
In the diet several chemical allergens are present, for instance fragrances, nickel, and preservatives which may lead to sensitization via the oral exposure route. For nickel it has been demonstrated that the oral route of exposure also plays an important role in the sensitization of an individual. When oral exposure occurs before skin exposure, oral tolerance is induced, e.g. induction of systemic hypo-responsiveness to this allergen. In mice orally exposed to nickel it was not possible to induce skin sensitization (Van Hoogstraten et al., 1993) and in humans it has been demonstrated that oral nickel contact via orthodontic braces resulted in reduced frequency of nickel allergy (Van Hoogstraten et al., 1991). In contrast, in patients with nickel contact dermatitis, oral exposure can lead to exacerbation of eczema. However, the effects of oral exposure to other contact allergens, e.g. fragrances and preservatives, are unknown (White et al., 2007).

Recently, an epidemiological study conducted in ten countries has found an association between the frequent use of household cleaning sprays at home and the occurrence of asthma. The association was predominantly found for air fresheners, glass cleaners and furniture cleaning sprays (Zock et al., 2007). In addition, in a birth cohort study, it was demonstrated that high domestic chemical exposure during pregnancy was associated with persistent wheeze and lung function abnormalities in infants (Henderson et al., 2008). Although, these epidemiological studies were not designed to study effector mechanisms and it is unknown which chemicals were involved in the development of asthma or wheeze, these studies do suggest that inhalation of household products can induce adverse respiratory effects. Further research is needed to elucidate how these effects are induced.
In addition, patients with contact dermatitis might also be exposed to allergens via the respiratory tractus, when they use scented or household products. If this leads to allergic reactions in the lungs in humans is unknown. In animal studies it has been demonstrated that elicitation reactions can be induced after inhalation exposure of animals that were sensitized topically to known skin and

respiratory sensitizers (Arts et al., 1998; Van der Kleij et al., 2004). In addition, patients with contact dermatitis to fragrances reported more often airway symptoms elicited by scented products (Elberling et al., 2004; Elberling et al., 2005). It is unknown which fragrance chemicals were involved and whether these respiratory symptoms are the consequence of an allergen-specific elicitation reaction or of non-specific irritation of the airways. It is often difficult to distinguish specific and non-specific airway responses in patients with asthma, because their airways are known to respond non-specifically to several external stimuli, e.g. fragrances, cigarette smoke, and cold can lead to symptoms as shortness of breath. In addition, individuals whose symptoms are linked to multiple chemicals sensitivity are known to react with respiratory symptoms to fragrances, which are probably caused by a non-specific irritation of the airways (Carlsen et al., 2008).

Currently there is only limited information on the adverse effects of respiratory exposure to dermal sensitizers. It is obvious that the use of chemical allergens in for instance scented products or household sprays will lead to respiratory exposure. It is, however, unknown whether this will induce or elicit allergic symptoms in the respiratory tract. In theory this is possible, but if it will occur depends on several factors, e.g. exposure dose, exposure time and potency of the allergen. In terms of risk assessment, it is recommended to consider all possible routes of exposure, although for this more data are needed. The impact of respiratory allergy compared to contact dermatitis is higher, since respiratory allergies can induce potential life-threatening symptoms. It can be concluded that a knowledge gap exists on the occurrence of respiratory problems induced by contact sensitizers in consumer products.

8.5 Labeling en communication to the consumer

Sensitized patients, which are allergic to a specific allergen, are advised to avoid exposure to that allergen. For this, avoidance strategies can be successfully employed to diminish the impact and reduce the risk for an elicitation reaction to that specific compound. This can be performed with help of legislation, i.e. limit of declaration on the labels of preparations and cosmetics. In this way, consumers can make an informed choice for a product, and avoid the products on which a specific allergen is declared. However, thresholds for elicitation are unknown. This implies that although an allergen does not need to be declared (since its concentration is below the limit of declaration), it still might induce an elicitation reaction. Furthermore, declaration limits are not based on a quantitative risk assessment, but in most cases practical values. Next to that, limits for declaration are no maximum limit values implying that in theory the levels of the sensitizer in the product may be highly present. Therefore, also the risk for induction of sensitization in consumers is not excluded. In addition, for the majority of the consumers the (usually) complex name of the chemical substances might hinder the effectiveness of declaration of sensitizers (Noiesen et al., 2007).
The range of allergens found at home and at the workplace is increasingly diverse and it can be difficult for people with allergies to avoid exposure completely. Polysensitized people can experience the symptoms all year round, being unable to seek any respite indoors, as this is principally where they are exposed to allergens such as house dust mite, nor outdoors, where pollen and environmental pollution may also trigger reactions. While fortunately not all the symptoms of allergic diseases are life-threatening, the day-to-day life of people with allergies can severely be impaired as the constant nature of allergic reactions to modern life takes its toll. Over a third of patients feel that their symptoms make them tired and irritable all the time (Position paper, EEAACI 2006; Valovirta et al., 2008).

From the market studies presented in this document, it can be concluded that manufacturers are not always in compliance with the legal requirements. Allergenic compounds in consumer products are sometimes present without declaration on the label, which is an alarming situation. For instance in

cleaning products, it was found by the Dutch VWA that in 7 out of 21 products the level of one or more fragrances was above 0.01 weight percent and not declared on the label (Bouma and Van Peursem, 2006). Also the preservatives BIT (forbidden in consumer products) and CMI/MI (maximum level of 0.0015%) were found in children cosmetics and toys without being declared (VWA, 2005; 2007). These incidents indicate that information on the label is not always correct. Therefore, it is very important to monitor the presence and concentrations of sensitizing substances in consumer products.

9 Conclusions and recommendations

– Inventory

- Data evaluated in this report show that the prevalence of contact dermatitis compared to other allergic diseases is relatively high.
- The most frequently found chemicals used in consumer products and causing allergies are nickel, fragrance mix I, Peru Balsam, cobalt chloride, and potassium dichromate.
- The product groups of cosmetics, detergents, textiles, but also some DIY products are of importance in causing allergies.
- The inventory on market studies showed that the most frequently allergens found in consumer products are the fragrances d-limonene, linalool, Lilial® and geraniol and the preservative group of the parabens.

– Potency and Exposure

For substances with a strong potency, exposure is a less predominant factor for the risk of sensitization than the intrinsic sensitizing potency of the chemical, as for strong sensitizers even at low exposure levels there may be a considerable risk. For moderate sensitizers exposure is the major determinant in the risk for sensitization, whereas for very weak sensitizers even at relatively high concentrations (very) low prevalences of contact dermatitis are observed.
Recommendation:
For moderate and weak sensitizers exposure information (concentration and frequency of use in products) is needed for determination of risk to ensure safe use of these substances. For substances with strong and moderate potency maximum (safe) limit values need to be derived or updated according to the last information.

– Legislation and limit values

At present, different types of regulations are used to protect the consumer from an allergic reaction. First there is total prohibition of allergens. Furthermore, two different types of limit values are used for sensitizers:
1) Maximum limit values, e.g. for nickel and preservatives, and
2) Limits of declaration, for fragrances in cosmetics and for all sensitizers in preparations.
For most allergens, these limits are not based on a quantitative risk assessment (QRA), although for the maximum limit values some exceptions are known. Declaration limits might prevent already sensitized people from elicitation (and thus complaints) by avoiding products with the specific sensitizer on the label, but they do not necessarily protect new sensitization cases.
Current legislation is not sufficient to prevent the occurrence of contact dermatitis and a better control of the exposure to sensitizers in consumer products is needed.
Recommendations:
1) For sensitizers that need to be declared, also a maximum limit value needs to be derived. For example, since fragrances vary in potency, for those that are classified as strong or moderate sensitizers not only a limit of declaration should be used, but also specific maximum limit values should be derived.
2) An approach for quantitative risk assessment of sensitizers should be established.

3) Preferably this quantitative risk assessment takes also elicitation into account. Currently there is a lack of information on thresholds for elicitation. Further research is needed on the development of an animal model for elicitation that can be used to assess both potency and thresholds for elicitation

– Quantitative Risk Assessment (QRA)

Industry has developed a method for QRA of sensitizers that can be used to derive safe limits for sensitizers. This method looks very promising, but needs to be further refined.
Recommendations:
1) An indepth analysis of this method is needed, with special focus on
- exposure. The method needs to be expanded to aggregate exposure, since safe limit values cannot be set for one product only. To perform aggregate exposure assessment, information on concentrations of sensitizers in products and frequency of use should be gathered.
- assessment factors. A scientific basis should be formed on specific extrapolation factors for sensitization on duration, intra- and interspecies and matrix effects.

2) To monitor the effectiveness of the QRA approach a reliable cosmetovigilance system should be established.

Industry has recently proposed an approach based on the Threshold of Toxicological Concern (TTC) principle. The TTC for sensitizers identifies a threshold below which the vast majority of sensitizers, including the stronger ones, can be safely used. This approach is promising and also reduces the number of animal experiments. It is based on the QRA method as described above.
Recommendation:
The data base on which the currently proposed TTC is based should be further extended, and the principle should be validated for sensitizers.

– Routes of exposure

This report focused on dermal sensitization, since most information available on sensitization refers to the dermal route. This focus does not imply that respiratory sensitization is not important and does not occur.
Recommendation:
Further research is needed to develop animal models to assess the respiratory sensitizing potency of chemicals. These animal models should be used to investigate the potency of dermal sensitizers to induce respiratory sensitization.

– Labelling and communication to the consumer

Although the limit of declaration of sensitizers (0.1%) is useful for consumers with a known contact allergy to a certain sensitizer, it is clear from surveillance studies that not all consumer products complied. Sensitizers have been found in concentrations above the limit of declaration or above maximum limit values.
Recommendation:
Independent market surveillance studies will remain essential for safe use of consumer products, even when limit values are in place to ensure proper labelling. The results on concentrations of sensitizers and insight in frequency of use in consumer products should be publicly available. This will facilitate aggregate exposure assessments and are essential for interpretation of the results in a cosmetovigilance system.

Especially for moderate sensitizers, exposure determines the risk for sensitization. Exposure to sensitizers can change in time due to change in product use and due to change in composition of products.

Recommendation:

The frequency of contact sensitization for specific ingredients should be monitored on a regular basis in patients with contact dermatitis in order to assess trends and to interfere when necessary.

Further recommendations:

The current method that is used to asses whether a patient is allergic is the patch test. This test is invasive for patients and furthermore it does not allow discrimination between patients with and without clinical symptoms. Development of an alternative less invasive method is therefore recommended, e.g. an antigen specific lymphocyte proliferation test in human blood.

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Appendix 1: Legislative aspects

Information regarding sensitisation from the regulation on classification and labelling implementing the Globally Harmonized System.

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on classification, labelling and packaging of substances and mixtures, and amending Directive 67/548/EEC and Regulation (EC) No 1907/2006

Table 16 Generic concentration limits of ingredients of a mixture classified as either skin sensitisers or respiratory sensitisers that trigger classification of the mixture

Ingredient Classified as:	Skin Sensitiser	Respiratory Sensitiser	
	All physical states	Solid/Liquid	Gas
Skin sensitiser	≥ 0.1% (Note 1) ≥ 1.0% (Note 2)		
Respiratory Sensitiser		≥ 0.1% (Note 1) ≥ 0.1% (Note 1)	≥ 1.0% (Note 3) ≥ 0.2% (Note 3)

Note 1: This concentration limit is generally used for the application of the special labelling requirements of Annex II 2.10 to protect already sensitised individuals. A SDS is required for the mixture containing an ingredient above this cut off limit.
Note 2: This concentration limit is used to trigger classification of a mixture as a skin sensitizer.
Note 3: This concentration limit is used to trigger classification of a mixture as a respiratory sensitizer.

Table 17 Respiratory or skin sensitisation label elements

Classification	Respiratory sensitisation Category 1	Skin sensitisation Category 1
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H334: May cause allergy or asthma symptoms or breathing difficulties when inhaled	H317: May cause an allergic skin reaction
Precautionary statement prevention	P261 P285	P261 P272 P280
Precautionary statement response	P304 + P341 P342+ P311	P302 + P352 P333 + P313 P321 P363
Precautionary statement storage		
Precautionary statement disposal	P501	P501

Source: http://ec.europa.eu/enterprise/reach/docs/ghs/ghs_prop_vol_ii_en.pdf (assessed at April 3 2008)

Appendix 2: Inventory on allergens in consumer products

Table 18 Important substance groups of allergens in consumer products

Allergic substance	Subgroup	Present in	Group members (components)	Cross reactivity
Nickel	metals	Jewelry, piercings, clothing accesoires, (dish)washing powders and liquids		cobalt, palladium
Chromium and potassium dichromate	metals	Cement, glazings, paints, leather clothing, gloves, shoes, (dish)washing powders and liquids inks, paints, paper, rubber floor coverings, treated/preserved timber products, toner powder		
Cobalt	metals	Jewelry, clothing accesoires, household appliances, cutlery, pieces of equipment, musical instruments, (dish)washing powders and liquids		nickel
Fragrances	fragrances	Cosmetics, household products, textiles, shoes, toys	list of 26 fragrances of SCCP, see text section 3.1.2	perubalsam, colophonium
Peru balsam (Myroxylon Pereirae resin)	fragrances	Cosmetics, shoes, tobacco	benzyl cinnamate, benzyl benzoate	colophonium, fragrances, turpentine
Isothiazolinones	preservatives	Glues, waxes, paints, varnishes, leather clothing, wood preservatives, mixed water dyes, cosmetics	1,2-benzisothiazolin-3-one (BIT), 5-chloro-2-methyl-4-isothialzolin-3-one (CMI), 2-methyl-4-isothiazolin-3-one	

			(MI)**	
Methyl dibromoglutaronitrile (MDBGN)	preservatives	Cosmetics (now banned), detergents, ultrasound gel		
Formaldehyde (or formaldehyde liberators)	preservatives	Cosmetics, wash- and wear textiles, paint, varnishes, chipboard	formaldehyde, diazolinidinyl urea, dmdm hydantoin, dehydroacetic acid, quaternium-15, benzylhemiformal, metheamine, sodium hydroxymethylglycinate[a]	
Thiurames	preservatives	Rubber gloves, sprays, adhesive plasters, insect repellant	tetramethylthiuram monosulphide, tetramethylthiuram disulphide, tetraethylthiuram disulphide en dipentamethylenethiuram disulphide	other carbamates
Di-isocyanates[b]	preservatives	Polyurethane foams, paints, varnishes, elastomers, and coatings	1,6-hexamethylene diisocyanate (HDI), toluene-2,6-diisocyanate (2,6-TDI), toluene-2,4-diisocyanate (2,4-TDI), methylene biphenyl isocyanante (MDI)	
Thiromersal[c]	preservatives	Vaccines, cosmetics, tattoo inks, eye drops and contact lens solutions		
Parabens	preservatives	Cosmetics, toiletries	methyl-, ethyl-, propyl- en butyl parahydroxybenzoate.	

p-Phenylene diamine	(hair) dyes	Hair dyes, disperse dyes in textiles, anti-oxidants in rubber, paint, varnishes, plastics and henna additive		
Other hair dye substances	(hair) dyes	Hair dyes	p-aminophenol, toluene-2,5-diamine, 1-hydroxyethyl-4,5-diaminopyrazole (precursors), m-aminophenol, resorcinol, 4-amino-2-hydroxytoluene, 2,4-diaminophenoxyethanol, 2-methylresorcinol (couplers)	
Other dye substances	(hair) dyes	Clothing and non-clothing textiles		
Colophonium (resin from conifers)	resins/solvents	Glues, paints, printing inks		
Formaldehyde resins	resins/solvents	Plywood, carpeting, paper, pulp, plastic, textile finishing, sanitary paper products	p-tert.-butylphenol-formaldehyde resin, (ethylene urea) melamine formaldehyde, urea formaldehyde	various fragrances, tea tree oil
Turpentine oil	resins/solvents	Varnishes, paints, shoe polish, resins, building materials		

a All formaldehyde liberators

b Main exposure route leading to sensitization is occupational. However, di-isocyanates are also present in do it yourself products

c Thiromersal is a preservative, often contaminated with mercury to which the allergic reactions can also be attributed to.

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Appendix 3: Prevalences of contact dermatitis in Europe

Table 19 Overview of recently conducted epidemiological studies in the general population in Europe

Reference	Country	Study design	Population and age	n	Allergens used for patch testing	Frequency of positive reactions
Nielsen, 1992	Denmark	Cross-sectional	Healthy volunteers; 15-69 years	365	TRUE test [3]	total: 14% nickel: 7% cosmetic ingredients: 3% fragrance mix: 1%
Nielsen, 2002	Denmark	Cross-sectional,	Healthy volunteers; 15-69 years	365	TRUE test [3]	total: 20% nickel: 11% cosmetic ingredients: 4% fragrance mix: 2%
Mortz, 2001	Denmark	Cross-sectional	Adolescents; 12-16 years	1146	TRUE test [3]	total: 15.2% nickel: 8.6%, fragrance mix: 1.8%, colophony: 1% thimerosal: 1%
Thyssen, 2007c	Denmark	CE-DUR[1]	Total Danish population	5.400.000	European standard series (ESS) [2], TRUE test[3] and MDBGN	7.3-12.9% in adults 5.5-9.7% in all ages
Schafer, 2001	Germany	Nested case control	Healthy volunteers; 28-78 years	1141	ESS [2]	total: 28% fragrance mix: 11.4% nickel: 9.9% thimerosal: 3.2%

Dotterud, 2007	Norway	Cross-sectional	Healthy volunteers; 18-69 years	1236	TRUE test[3]	total: 28% nickel: 17.6% cobalt: 2.8% fragrance mix: 1.8% colophonium: 1.2%
Dotterud, 2007	Norway	Cross-sectional	Healthy volunteers; 18-75 years	531	TRUE test[3]	total: 26.3 nickel: 19.2% fragrance mix: 3.4% cobalt: 1.7% Balsam of Peru: 1.1% colophonium: 1.1%
Barros, 1991	Portugal	Cross-sectional	Children; 5-14 years	562	European standard series (ESS) [2]	total: 13.3% fragrance mix: 1.8% nickel: 0.9%

[1] CE-DUR method uses data on annual patch test sales (DUR: drug utilization research) combined with clinical epidemiological (CE) data to estimate the prevalence of contact allergy. [2]ESS for patch testing contains: nickel sulphate, cobalt chloride, potassium dichromate, fragrance mix, Balsam of Peru, colophonium, formaldehyde, quaternium-15, Cl+ Me-isothiazolinone, parabens, thiuram mix, IPPD, mercapto mix, mercaptobenzothiazole, neomycin sulphate, benzocaine, clioquinol, lanolin alcohol, budesonide, tixocortol pivalate, PPD, epoxy resin, PRBP-formaldehyde resin, primin, sesquiterpene lactone mix; [3] TRUE test contains 26 chemicals that are known allergens and includes nickel sulphate, lanolin, neomycin, potassium dichromate, caine mix, fragrance mix, colophony, epoxy resin, quinoline mix, Balsam of Peru, ethylenediamine, cobalt chloride, PTBP resin, paraben mix, carba mix, black rubbe mix, Kathon CG , Quaternium 15, mercaptobenzothiazole, PPD, formaldehyde, mercapto mix, thimerosal, thiuram mix.
Abbreviations: MDBGN: methyldibromo glutaronitrile; CE-DUR: clinical epidemiology-drug utilization research

Appendix 4: Market surveys on allergens in consumer products

Table 20 Overview of data on fragrances in cosmetics from market surveys

	Cosmetics								
Product type	**Deodorants**			**Children's cosmetics**					
Research Institute	**Danish EPA**			**Danish EPA**			**VWA**		
	% of the products containing fragrance substance	n	Concentration range (ppm)	% of the products containing fragrance substance	n	Concentration range (ppm)	% of the products containing fragrance substance	n	Concentration range (ppm*)
Fragrances	69.9%	88		74.0%	208		78.0%	23	
Anisyl alcohol	2.3%	2	dl*, 50.5	0.0%	0		4.3%	1	22
Amyl cinnamal	10.2%	9	2.3 - 164.7	8.2%	17	5 - 230	4.3%	1	23
Amylcinnamyl alcohol	ND			2.9%	6	-	4.3%	1	30
Benzyl alcohol	17.1%	15	31.6 - 166.2	9.6%	20	1 - 790	0.0%		-
Benzyl benzoate	25.0%	22	3.2 – 4,054.2	9.1%	19	4 - 210	13.0%	3	50 – 2,654
Benzyl cinnamate	3.4%	3	74.1, 143.2	2.9%	6	-	4.3%	1	21
Benzyl salicylate	39.8%	35	136.3 – 5,279.0	9.6%	20	3 - 82	26.1%	6	28 – 2,123
Butylphenyl methylpropional (Lilial®)	48.9%	43	dl* - 5,455.0	7.7%	16	12.0 – 3,400	21.7%	5	210 – 5,254
Cinnamal	1.1%	1	5.0	1.0%	2	2	0.0%		-
Cinnamyl alcohol	12.5%	11	1.7 - 503.0	6.7%	14	37 - 42	0.0%		-
Citral	26.1%	23	38.8 - 553.9	8.2%	17	4.0 - 73	8.7%	2	109 - 168
Citronellol	65.9%	58	dl* - 5,847.5	10.5%	22	4 - 300	21.7%	5	59 – 1,158
Coumarin	33.0%	29	3.8 – 1,254.9	4.8%	10	21 - 23	26.1%	6	77 - 384
Eugenol	27.3%	24	dl*- 514.0	7.2%	15	6.0 - 42	4.3%	1	23
Farnesol	14.8%	13	9.0 -1,791.0	2.9%	6	7	4.3%	1	524
Geraniol	48.9%	43	dl* - 399.0	12.0%	25	2 - 180	52.2%	12	50 - 492
Hexyl cinnamal	33.0%	29	dl* - 4,434.0	10.1%	21	5 - 170	43.5%	10	29 -4,124
Hydroxycitronellal	27.3%	24	dl* - 1,746.5	6.3%	13	2.0 - 33	43.5%	10	21 - 873

Hydroxyisohexyl-3-cyclohexene carboxaldehyde (HICC = Lyral)	33.0%	29	dl* - 4431.0	5.8%	12	7.0 - 2700	52.2%	12	44 – 2,790
α-Isomethylionon	46.6%	41	5.8 - 2588.0	5.8%	12	3.0 - 530	43.4%	10	71 – 5,395
D-limonene	53.4%	47	1022.8 - 11386.5	23.1%	48	6.0 - 2200	78.3%	18	129 – 4,096
Linalool	53.4%	47	8.2 - 3447.1	21.6%	45	7.0 - 1100	69.6%	16	63 – 1,534
Isoeugenole	9.1%	8	dl* - 138.4	0.5%	1	-	0.0%		22
Methyl heptine carbonate	1.1%	1		0.0%			4.3%	1	14
Oakmoss	4.6%	4		0.0%		*			
Treemoss	2.3%	2		0.0%		*			

* Undetectable, a detection limit cannot be fixed
dl = detection limit
*dl of the substances: about 1 ppm
*ppm = mg/l

Table 21 Overview of fragrances in cleaning products and detergents and toys

	Cleaning products and detergents						Toys		
Research Institute	**Danish EPA**			**VWA**			**Danish EPA**		
	% of the products containing fragrance substance	n	Content % (m/m)	% of the products containing fragrance substance	n	Concentration range (ppm)	% of the products containing fragrance substance	n	Concentration range (ppm)
Fragrances	93.0%	43		80.9%	52		70.0%	10	
Anisyl alcohol	2.3%	1	0.0014	0.0%			0.0%		
Amyl cinnamal	4.6%	2	0.0092; 0.0284	9.6%	5	31 - 376	20.0%	2	11 - 1500
Amylcinnamyl alcohol	4.6%	2	n.d.	0.0%			0.0%		
Benzyl alcohol	30.2%	13	d.l. - 0.2354	32.7%	17	9.0 - 168	30.0%	3	10.0 - 67
Benzyl benzoate	25.5%	11	0.0030 - 0.0152	11.5%	6	4 - 108	10.0%	1	7
Benzyl cinnamate	0.0%			0.0%			0.0%		
Benzyl salicylate	20.9%	9	0.0069 - 0.0587	26.9%	14	24 - 448	20.0%	2	36 - 87
Butylphenyl methylpropional (Lilial®)	55.8%	24	0.0009 - 0.0500	36.5%	19	8.0 - 795			
Cinnamal	2.3%	1	0.0061	0.0%			10.0%	1	3
Cinnamyl alcohol	9.3%	4	0.0021 - 0.0071	0.0%			20.0%	2	37 - 90
Citral	16.2%	7	d.l. - 0.0501	1.9%	1	8	10.0%	1	27
Citronellol	25.5%	11	d.l. - 0.0763	21.2%	11	13 - 516	20.0%	2	1.0 - 8
Coumarin	30.2%	13	0.0027 - 0.0270	26.9%	14	9.0 - 90	20.0%	2	9 - 280
Eugenol	18.6%	8	d.l. - 0.0119	17.3%	9	12.0 - 83	10.0%	1	14
Farnesol	0.0%			0.0%			0.0%		

Geraniol	20.9%	9	d.l. - 0.1454	42.3%	22	10 - 319	40.0%	4	2.0 - 11
Hexyl cinnamal	39.5%	17	d.l. - 0.0492	55.8%	29	8.0 - 744	10.0%	1	4,000
Hydroxycitronellal	6.9%	3	0.0025; 0.0071; 0.0078	0.0%			20.0%	2	40 - 270
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (HICC = Lyral)	6.9%	3	0.0053; 0.0085; 0.0097	0.0%			10.0%	1	610
α-Isomethylionon	39.5%	17	0.0073 - 0.1586	40.3%	21	10 - 160	10.0%	1	950
D-limonene	67.4%	29	d.l. - 0.7693	40.3%	21	13 - 689	40.0%	4	7 - 800
Linalool	39.5%	17	0.00002 - 0.0270	40.3%	21	6.0 - 335	30.0%	3	5.0 - 63
Isoeugenole	6.9%	3	0.0048; 0.0085; 0.0097	1.9%	1	40	0.0%		
Methyl heptine carbonate	0.0%			0.0%			0.0%		
Oakmoss							0.0%		
Treemoss							0.0%		

Table 22 Overview of all data on fragrances in air fresheners from market surveys

	Air fresheners					
Research Institute	**Danish EPA**			**BEUC**		
	% of the products containing fragrance substance	n	Concentration range (ppm)	% of the products emitting fragrance substance	n	Emissions (µg/m^3)
Fragrances	100.0%	19		(n=76)		
Anisyl alcohol	0.0%					
Amyl cinnamal	26.3%	5	640 – 16,000			
Amylcinnamyl alcohol	5.3%	1	17 - 50			
Benzyl alcohol	52.6%	10	73 – 50,000	1.3%	1	22
Benzyl benzoate	68.4%	13	7.7 – 10,000	1.3%	1	9
Benzyl cinnamate	10.5%	2	170 - 500			
Benzyl salicylate	52.6%	10	4.1 – 13,000			
Butylphenyl methylpropional (Lilial®)	57.9%	11	450 – 12,000	13.2%	10	2 - 310
Cinnamal	15.8%	3	10.0 - 63	6.5%	5	3 - 146
Cinnamyl alcohol	10.5%	2	19 - 320			
Citral	36.8%	7	200 – 26,000	2.6%	2	2.0 - 48
Citronellol	52.6%	10	190 – 18,000			
Coumarin	47.4%	9	15 – 13,000	5.3%	5	4.0 - 22
Eugenol	63.2%	12	11.0 – 9,000	1.3%	1	16
Farnesol	0.0%					
Geraniol	42.1%	8	390 – 8,900	1.3%	1	40
Hexyl cinnamal	68.4%	13	39 – 22,000			
Hydroxycitronellal	26.3%	5	440 – 2,600	1.3%	1	51
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (HICC = Lyral)	47.4%	9	310 – 62,000			
α-Isomethylionon	52.6%	10	220 – 11,000			
D-limonene	78.9%	15	41 – 21,000	88.1%	67	1.0 – 2,003

Linalool	78.9%	15	970 – 39,000	27.6%	21	5 - 750
Isoeugenole	15.8%	3	23 - 120			
Methyl heptine carbonate	15.8%	3	3.5 - 270			
Oakmoss						
Treemoss						

Appendix 5: Examples of exposure calculations

I) Methanamine, an aggregated exposure calculation using rough (screening) assumptions

Within the Framework of Existing Chemicals, a risk assessment report (RAR) was drawn on methenamine (ECB, 2006). The most important area of use of methenamine is the production of powdery or liquid preparations of phenolic resins and phenolic resins moulding compounds to which methenamine is added as a hardening component. These preparations are used as binders, e.g. in brake and clutch linings, abrasive products and non-woven textiles as well as in formed parts produced by moulding processes. Methenamine is a skin and possible respiratory sensitizer, and is currently labelled with R42/43. According to the Cosmetics Directive 76/768/EEC, Annex VI, the maximal allowed concentration of methenamine in a cosmetic product is 0.15%.
The exposure assessment for consumers did take into account exposure via carpets/upholstery cleaners, solid fules, limestone removers, and cosmetics. In the case of cosmetics, dermal exposure might derive by use of lotions, creams and make up. The rough approach of the SCCNFP was used. In the specific case of preservatives the SCCNFP calculated a global daily exposure value for all cosmetic products that one person may daily apply on the skin. In a worst-case scenario, considering the consumer would use a set of cosmetic products containing the same preservative, the SCCNFP-value accounts 17.79 g/day (SCCNFP/0321/00, Final). With consideration of the weight fraction of methenamine of 0.15% and the body weight of 60 kg, the external exposure can be calculated to 445 µg/kg bw/d.

This example shows a fairly simple way of quantifying the exposure estimate, using rough assumptions. In some cases, this can be enough for risk assessment, especially when this worst case exposure estimate is assessed to be safe.

II) AHTN, an aggregated exposure assessment

AHTN (6-Acetyl-1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydronaphtalene) is also assessed in the Existing Chemicals framework. AHTN is a fragrance which is applied in a fragrance mixture used in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products, air fresheners etc. The exposure assessment is taken from the RAR of AHTN (ECB, 2007).
For the dermal route, a consumer exposure assessment was performed including exposure via cosmetics and household detergents. The levels of perfume in the various classes of cosmetics and the 97.5th percentile use level (12%) of AHTN in the perfume were the results of industry surveys (IFRA, survey of use of AHTN in the fragrance industry; private communication via COLIPA, 1996 to the SCCNFP) and are shown in Table 23.

Table 23 Use levels (97.5 percentile use) of AHTN in cosmetic products

Product category	Fragrance oil in product in %	AHTN in fragrance oil (%)	AHTN in product (%)
Body lotion	0.4	12	0.048
Face cream	0.3	12	0.036
Eau de toilette	8.0	12	0.96
Fragrance cream	4.0	12	0.48
Anti-perspirant /deodorant	1.0	12	0.12
Shampoo	0.5	12	0.06
Bath products	2.0	12	0.24
Shower gel	1.2	12	0.144
Toilet soap	1.5	12	0.18
Hair spray	0.5	12	0.06

The resulting exposure to AHTN on the skin from the use of a combination of all classes of consumer products on a daily basis was calculated to result in a 'worst case situation' of 0.34 mg/kg bw/day (see Table 24) and this value will be used for the risk characterization (for more details on the exposure data see the AHTN RAR).

Table 24 Overview of products and uses that can contain AHTN adapted from the SCCNFP

Type of cosmetic product	Application quantity in grams per application	Application frequency per day	Retention factor (%)[5]	AHTN in product (%)	Exposure to AHTN (mg/day)	Exposure to AHTN for 60 kg person (mg/kg/day)
Body lotion[1]	8	0.71	100	0.048	2.7	0.045
Face cream[2]	0.8	2	100	0.036	0.576	0.0096
Eau de toilette[3]	0.75	1	100	0.96	7.2	0.12
Fragrance	5	0.29	100	0.48	7.0	0.116

cream[1]						
Anti-perspirant /deodorant	0.5	1	100	0.12	0.60	0.010
Shampoo	8	1	1	0.06	0.048	0.0008
Bath products[4]	17	0.29	1	0.24	0.12	0.002
Shower gel[4]	5	1.07	10	0.144	0.77	0.013
Toilet soap	0.8	6	10	0.18	0.86	0.014
Hair spray	5	2	10	0.06	0.6	0.010
				Total	**20.5**	**0.34**

SCCNFP, 24 OCTOBER 2000, taken from the AHTN RAR, 2007

1. Assumes use of conventional body lotion 5 times a week and a fragranced cream twice a week.
2. Including make up and foundation.
3. Including perfume and after shave, but these three products are not used concurrently. The quantity used is inversely proportional to the fragrance concentration so these values include all hydroalcoholic products.
4. Assumes use of bath products twice a week and an average use of shower gel 1.5 times a day, 5 times a week.
5 Proportion of product remaining on the skin.

AHTN is also used in household and laundry cleaning products (Balk and Ford, 1999). Both the fragrance manufacturing industry and the consumer product industry were surveyed by the International Fragrance Association (IFRA, 2002) to determine the use levels of fragrance oils in product types and the levels of AHTN that are used to formulate these oils. (Table 25)

Table 25 Use levels of AHTN in household cleaning products. Results of a survey including data from manufacturers of fragrances as well as household cleaning products

Product category	Median use level of fragrance oil in product in %	97.5 percentile use level of AHTN [a]	Level of AHTN in product
Laundry regular powder	0.33	8.7%	0.03%
Laundry liquid	0.80	8.7%	0.07%
Laundry compact (tabs)	0.33	8.7%	0.03%
Laundry compact (powder and other)	0.28	8.7%	0.02%
Laundry liquid concentrate	0.85	8.7%	0.07%
Fabric softener (conditioner)	0.43	8.7%	0.04%
Fabric softener concentrate	0.80	8.7%	0.07%
Laundry additive, powder bleach	0.20	8.7%	0.02%
Laundry additive, liquid bleach	0.20	8.7%	0.02%
Laundry additive, tablet	0.30	8.7%	0.03%
Hand dishwashing liquid	0.23	8.7%	0.02%

Hand dishwashing liquid concentrate	0.45	8.7%	0.04%
Machine dishwashing powder	0.15	8.7%	0.01%
Machine dishwashing liquid	0.15	8.7%	0.01%
Machine dishwashing tablet	0.15	8.7%	0.01%
Surface cleaner liquid	0.60	8.7%	0.05%
Surface cleaner powder	0.25	8.7%	0.02%
Surface cleaner gel	0.75	8.7%	0.07%
Surface cleaner spray	0.13	8.7%	0.01%
Toilet cleaner powder	0.30	8.7%	0.03%
Toilet cleaner liquid	0.35	8.7%	0.03%
Toilet cleaner gel (concentrate)	0.38	8.7%	0.03%
Toilet cleaner tablet	0.30	8.7%	0.03%
Toilet rim block or gel	6.0	8.7%	0.52%

97.5 percentile use level of AHTN in fragrance oils used in household and detergent products
For the products in Table 25, exposure calculations have shown that because of the low contents of AHTN and the use patterns of these products, exposure to AHTN is considered negligible in comparison to the exposure from cosmetic use (HERA draft risk assessment, 2003). Only exposures from laundry detergents and dish washing liquid are shown here. For the estimates of consumer exposure to laundry detergents and dish washing liquids, the consumer exposure models developed by the Association Internationale de la Savonnerie, de la Détergence et des Produits d'Éntretien (International Association for Soaps, Detergents & Maintenance Products) (A.I.S.E) and the European Chemical Industry Council (CEFIC) as part of their program on Human & Environmental Risk Assessment (HERA) of ingredients of household cleaning products and presented in the HERA guidance document are used along with the data presented in the Table of Habits and Practices for Consumer Products in Western Europe, an appendix to that document. This table presents use data for cleaning products in grams/task, use frequency, duration of task and other intended uses. While minimum, maximum and typical use frequencies and amounts are given; only the maximum figures are used for the exposure estimations with the understanding that further refinement will be possible if necessary.

Direct skin contact from hand-washed laundry
Hand-washed laundry is a common consumer habit. During this procedure, the AHTN-containing laundry solution with an estimated product concentration of 10 mg/ml comes in direct contact with the skin of hands and forearms. A hand-washing task typically takes 10 minutes (Table of Habits and Practices - HERA, 2002). This table also reports a maximum frequency of 18 times per week (3 times/day) when using laundry powder, which seems highly exaggerated but nevertheless is used here as a worst case scenario. The table gives a lower frequency of hand washing with laundry liquid of 10 times per week (1.43 times/day), which still seems exaggerated. Because the use level of AHTN is different in powder (0.03%) from that in liquid (0.07%) both scenarios are calculated here.
The exposure to AHTN is estimated according to the following algorithm from the HERA guidance document.

$$\mathbf{Exp_{sys} = F_1 \times C \times Kp \times t \times S_{der} \times n / BW}$$

For this exposure estimate, the terms are defined with following values for the calculation considering a worst-case scenario:

F_1	percentage weight fraction of substance in product	**0.03%** (0.0003) or **0.07%** (0.0007) **Table 4.1.1.3.B**
C	product concentration in mg/ml:	**10 mg/ml** (HERA, 2002)
Kp	dermal penetration coefficient	**3.4 x 10^{-5} cm/h***
t	duration of exposure or contact	**10 min (0.167h)** (HERA, 2002)
S_{der}	surface area of exposed skin	**1980cm^2** (TGD, 1996)
n	product use frequency (tasks per day)	**3** or **1.43** (HERA, 2002)
BW	body weight	**60 kg**

* The dermal penetration coefficient was calculated from the dermal flux (10.3 ìg/cm^2) which was determined in an *in vitro* dermal penetration (Green and Brain, 2001) according to the following algorithm: Kp = dermal flux/(exposure time x concentration of test solution); Kp = (0.00815 mg/cm^2)/(24h x 10 mg/cm^3) = 3.4 x 10^{-5} cm/h

For powder use:

Exp_{sys} = [0.0003 x (10 mg/ml) x (3.4 x 10^{-5} cm/h) x (0.167h) x 3 x (1980 cm²)] / 60 kg= **0.0017 µg/kg bw/day**

For liquid use:

Exp_{sys} = [0.0007 x (10 mg/ml) x (3.4 x 10^{-5} cm/h) x (0.167h) x 1.43 x (1980 cm²)] / 60 kg= **0.0019 µg/kg bw/day**

Direct skin contact from pre-treatment of clothes

Consumers typically spot-treat clothing stains by hand using either a detergent paste (i.e. water/laundry powder = 1:1) or a laundry liquid, which is applied undiluted (i.e. concentration = 1000 mg/ml) directly on the garment. In this exposure scenario, only the skin surface of the hand (~ 840 cm^2) is exposed.

The exposure to AHTN is estimated according to the same algorithm from the HERA guidance document as is used above using 100% liquid detergent since this contains the highest concentration of AHTN.

F_1	percentage weight fraction of substance in product	0.0007 (laundry liquid) (**Table 4.1.1.3.B**)
C	product concentration in mg/ml:	**1000 mg/ml** (100%)
Kp	dermal penetration coefficient	**3.4 x 10^{-5} cm/h** (Green and Brain, 2001)
t	duration of exposure or contact	**10 min (0.167h)** (HERA, 2002)
S_{der}	surface area of exposed skin	**840cm^2** (TGD, 1996)
n	product use frequency (tasks per day)	**0.5** (HERA, 2002)
BW	body weight	**60 kg**

$$\mathbf{Exp_{sys}} = [0.0007 \times (1000\ mg/ml) \times (3.4 \times 10^{-5}\ cm/h) \times (0.167h) \times (840\ cm^2) \times 0.5]/\ 60\ kg =$$
0.028 µg/kg bw/day

This exposure estimate is very conservative in that it does not recognize use of water to dilute the detergent, a common practice and the fact that only a fraction of the two hands' surface skin will actually be exposed.

Direct skin contact from hand dishwashing
The determination of AHTN exposure from hand dishwashing also uses the same algorithm to calculate the dermal exposure to AHTN from hand dishwashing. The following assumptions have been made to address a reasonable worst-case scenario:

F_1	percentage weight fraction of substance in product	**0.02%** (0.0002) (Table 4.1.1.3.B)
C	product concentration in mg/ml:	**2 mg/ml** (HERA, 2002)
Kp	dermal penetration coefficient	**3.4 x 10^{-5} cm/h** (Green and Brain, 2001)
t	duration of exposure or contact	**45 min** (0.75h) (HERA, 2002)
S_{der}	surface area of exposed skin	**1980 cm^2** (TGD, 1996)
n	product use frequency (tasks per day)	**3** (HERA, 2002)
BW	body weight	**60 kg**

$$\mathbf{Exp_{sys}} = [0.0002 \times (2\ mg/ml) \times (3.4 \times 10^{-5}\ cm/h) \times (0.75h) \times (1980\ cm^2) \times 3] / 60\ kg =$$
0.001 µg/kg bw/day

Summarizing, the total dermal exposure of consumers to products containing AHTN can mainly be attributed to cosmetics (worst-case estimate 0.34 mg/kg bw/day). Compared to this exposure the dermal exposure of consumers to household products is negligible.

The exposure data derived from the RAR exposure assessment only includes the dermal route, in the RAR also the inhalation route was taken into account. It shows many figures for this specific substance in different products. These values are often not available to risk assessors. Furthermore, in the RAR the modeled data were compared with measured data from two different sources, concluding that the exposure estimates are fairly conservative. This example shows the amount of data necessary when an exposure assessment is to be performed on a more aggregate and realistic basis. Furthermore, it is shown that choices made (e.g. using the 97th percentile) might be important for the outcome of the assessment.

III) Kathon in children's cosmetics

The Danish Environmental Protection Agency is engaged in identifying chemical substances in a large number of consumer products. One of their surveys was aimed at cosmetic products for children on the Danish market (Poulsen and Smidt, 2007). One of the substances that studied in detail was Kathon or CMI/MI. From this report, the exposure assessment is described here, illustrating the need for measured data.
In total 11 products are analyzed for a quantitative content of Kathon. The table below states the intervals of the measured concentrations of Kathon in the different product types being studied. Furthermore, it is an overview of the product types in which Kathon is found via the study. The maximum permissible concentration of Kathon in cosmetic products is 15 mg/kg.

Table 26 Products containing Kathon. The measured concentrations are stated for the analyzed products

Product type	Products analyzed	Products in total with Kathon	Measured concentrations I mg/kg (ppm)
Body shampoo/bath gel	6	9	< 2 – 7.7
Liquid soap	1	1	10 – 12
Bobble bath	2	4	3.0 – 11
Body lotion/cream	1	1	< 2
Shampoo	1	2	4.4 – 6.7
Eau de toilette	0	1	No analyses conducted

taken from Poulsen and Schmidt, 2007. The detection limit is 2 mg/kg

The calculated exposure scenarios for Kathon are worst case scenarios, calculated according to the guidelines and default values in TGD and retention factors from SCCNFP 0690 (2003). The retention factor is introduced by SCCNFP to consider products being diluted when they are used and cleansed off after use, i.e. for shampoo products, body shampoo and similar 'rinse-off' products. For calculating the exposure estimates, the following factors are part of the calculation and are seen in Table 27.

Table 27 Applied factors in the exposure assessment

Product type	Number of appplications	Applied quantity per application	Concentra-tion of Kathon	Uptake through the skin	Retention factor	The child's weight
Body shampoo/ Bath gel	1-2 per day	5.0 g	7.7 mg/kg	100%	0.01	15 kg

Fluid soap	6 per day	1.0 g	12 mg/kg	0.01
Bobble bath	1-2 per week	17.0 g	11 mg/kg	0.01
Body lotion/cream	1-2 per day	7.5 g	2 mg/kg	1
Shampoo	2-7 per week	12.0 g	6.7 mg/kg	0.01
Eau de toilette	1-2 per day[1]	3.0 g[2]	15 mg/kg[3]	1

1 – assumption as no data in TGD or SCCNFP guidelines.
2 – the value for deodorant spray is applied. This value will be significantly higher than for eau de toilette (but there is no available value for eau de toilette in TGD).
3 – no eau de toilette products have been analyzed. Therefore, the maximum permissible concentration of 15 mg/kg is applied.

The daily exposure is calculated by use of the formula below where SED (Systemic Exposure Dosage) is the daily exposure, A is the quantity being applied daily, C is the concentration of the substance in the cosmetics product, DA (Dermal Absorption) is the absorption through the skin indicated in %, Rf is the retention factor (introduced by SCCNFP to consider "rinse-off" products) and bw (body weight) is the body weight of the child.

SED = (A x C x DA x Rf)/ bw

The daily exposure of Kathon when using body lotion on a three-year-old child can be calculated to:

SED = (0.0075 kg/ application x 2 times/day x 2 mg/kg x 1 x 1) / 15 kg = 0.002 mg/kg/day

Table 28 Daily exposure (SED) for Kathon for the different product types

	Applied quantity per application (in kg)	Number of daily applications	Concentration (mg/kg)	R_f	SED (mg/kg/day)
Body shampoo/bath gel	0.005	2	7.7	0.01	0.000051
Liquid soap	0.001	6	12	0.01	0.000048
Bobble bath	0.017	0.33	11	0.01	0.000041
Body lotion/cream	0.0075	2	2	1	0.0020
Shampoo	0.012	1	6.7	0.01	0.000054
Eau de toilette	0.003	2	15	1	0.0060

The highest daily exposures occur when using eau de toilette and body lotion. It must be noted that the application of eau de toilette is overestimated since as the same exposure values as for normal deodorant are used.

This exposure estimation is specifically for children, via cosmetics. Other sources such as paints (in the past at least) and detergents were not taken into account. This specific example shows the amount of data necessary, and also the need of agreement on assumptions on frequency and amounts used. Similarly to the above mentioned examples, these exposure estimates can be compared with a NOAEL for a certain endpoint. For sensitization it would be better to have exposure estimates in $\mu g/cm^2$ to compare with possible threshold levels.

Appendix 6: Potencies of allergens in consumer products

Table 29 Potency of allergens present in consumer products: fragrances

	LLNA[1]		Human category[2]	References
	EC3 value	Category		
Amyl cinnamal	10.6	+	extremely weak	(Elahi et al., 2004; Api et al., 2006)
Amylcinnamyl alcohol	25	+	weak	(Bhatia et al., 2007a)
Anisyl alcohol	5.9	+	weak	(Api et al., 2006)
Benzyl alcohol	>50	+	weak	(Api et al., 2006)
Benzyl benzoate	>50	+	extremely weak	(Api et al., 2006; Patlewicz et al., 2008)
Benzyl cinnamate	18.4	+	weak	(Bhatia et al., 2007b)
Benzyl salicylate	1.5	++	weak	(Lapczynski et al., 2007b)
Cinnamyl alcohol	20.1	+	weak	(Elahi et al., 2004; Patlewicz et al., 2008)
Cinnamal	2.0	++	moderate	(Elahi et al., 2004; Api et al., 2006; Arts and Kuper, 2006)
Citral	5.6	+	weak	(Api et al., 2006)
Citronellol	43.5	+	extremely weak	(Api et al., 2006)
Coumarin	negative	non-sensitizer	non-sensitizer	(Vocanson et al., 2006; Vocanson et al., 2007; Patlewicz et al., 2008)
Eugenol	10.1	+	weak	(Gerberick et al., 2001; Basketter et al., 2005; Basketter et al., 2007)
Farnesol	4.8	+	weak	(Skold et al., 2008)
Geraniol	22.4	+	weak	(Hagvall et al., 2007; Patlewicz et al., 2008)
Hexyl cinnamaldehyde	9.9	+	moderate	(Basketter et al., 2005; Basketter et al., 2007)
Hydroxycitronellal	33	+	weak	(Basketter et al., 2001; Gerberick et al., 2001; Patlewicz et al., 2008)
Hydroxymethylpentyl-cyclohexenecarboxyaldehyde (Lyral)	17.1	+	weak	(Api et al., 2006; Patlewicz et al., 2008)
Isoeugenol	1.5	++	strong	(Basketter and Cadby, 2004; Arts and Kuper, 2006)
Lilial®	18.7	+	weak	(Basketter et al., 2001)
d-Limonene	69	+	weak	(Patlewicz et al., 2008)
Linalool	46.2	+	extremely weak	(Gerberick et al., 2001; Skold et al., 2004)
Methyl heptine carbonate	0.5	++	strong	(Api et al., 2006)
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	21.8	+	weak	(Lapczynski et al., 2007a)
Oak moss	3.9	+	moderate	(Api et al., 2006)

Tree moss	>20	+	moderate	(Api et al., 2006)
Peru balsam	NA	--	NA	

[1] EC3 values determined in the LLNA were used to categorize potency of allergens: EC3 ≤ 2%: stronger sensitizer (++) and EC3 > 2%: other sensitizer (+) (OECD expert group on sensitization hazards, 2008)

[2] Chemicals are classified into five categories: strong, moderate, weak, extremely weak, nonsensitizing. These data are based on human data and expert judgment (Basketter *et al.*, 2000). Abbreviations: LLNA: local lymph node assay; NA: not available

Table 30 Potency of allergens in consumer products: hair dye substances

	LLNA[1] EC3 value	LLNA Category	GPMT[2]	Buehler test[3]
p-Phenylenediamine	0.06	++	NA	NA
N-Phenyl-p-phenylenediamine	0.02	++	NA	NA
1,2,4-Trihydroxybenzene	0.08	++	NA	NA
Dihydroxyindole	0.17	++	not classifiable	NA
6-Hydroxyindole	<0.2[a]; 0.2	++	+	+
Isatin	<1[a]; 2.5	++, +	++	not classifiable
Basic Brown 17	NA	--	++	NA
4-Nitro-o-phenylenediamine	≤0.05	++	NA	NA
HC Red n° 1	<2[b]	++	++	NA
3-Nitro-p-hydroxyethylaminophenol	0.07	++	NA	NA
m-Aminophenol	0.24	++	NA	NA
4-Amino-2-hydroxytoluene	0.44	++	NA	NA
Phenyl methyl pyrazolone	≤1	++	NA	NA
N,N-bis(2-hydroxyethyl)-pphenylenediamine Sulfate	<0.25[a]; 1.04	++	NA	NA
4-Amino-m-cresol	1.45	++	NA	NA
Hydroxyethyl-3,4-methylenedioxyaniline HCl	<0.5[a]	++	NA	NA
2,6-Dimethoxy-3,5-pyridinedieamine HCl	1.25	++	not classifiable	NA
Hydroxypropyl bis(N-hydroxyethyl-phenylenediamine) HCl	NA	--	++	NA
1-Hydroxyethyl-4,5-Diamino Pyrazole Sulfate	NA	--	++	+
Violet n° 1	0.9	++	not classifiable	NA
2-Amino-6-chloro-4-nitrophenol	0.68	++	NA	NA
Hydroxyanthraquinone-aminopropyl Methyl Morpholinium Methosulfate	NA	--	++	+

Lawsone	NA	--	++	NA
p-Methylaminophenol sulphate	2.2	+	NA	NA
Diaminophenoxyethanol and its salts	3.2	+	NA	not classifiable
2-Methylresorcinol	50	+	NA	NA
Dihydroxyindoline HBr	NA	--	+	NA

§ Data are derived from SSCP memorandum on hair dye substances and their skin sensitizing properties, 2006 and are based on submissions by the industry

1 EC3 values determined in the LLNA were used to categorize potency of allergens: EC3 ≤ 2%: stronger sensitizer and EC3>2% other sensitizers

2 Potency categorization assessed in GPMT is based on the intradermal concentration employed during induction and on the incidence of sensitization: stronger sensitizers (++) intradermal concentration ≤ 0.1%: incidence of sensitization ≥30% or intradermal concentration >0.1% to ≤ 1%: incidence of sensitization ≥30%. Other sensitizers (+): intradermal concentration > 0.1% to ≤ 1 : incidence of sensitization ≥30% to <60% or intradermal concentration >1%: incidence of sensitization ≥30%.

3 Potency categorization assessed in Buehler test is based on the concentration employed during induction and on the incidence of sensitization: stronger sensitizers (++) concentration ≤ 0.2%: incidence of sensitization ≥15% or concentration >0.2% to ≤ 20%: incidence of sensitization ≥60%. Other sensitizers (+) : concentration >0.2% to ≤ 20%, incidence of ≥30% to <60% or concentration >20% and incidence of sensitization ≥15%.

b EC3 value was not calculated; Abbreviations: LLNA: local lymph node assay; GPMT: guinea pig maximization test; NA: not available

Table 31 Potency of allergens in consumer products: metals, preservatives and other

	LLNA[1] EC3 value	Category	Human category[2]	References
Nickel	NA	+*		(Basketter and Scholes, 1992)
Cobalt	NA	++*		(Basketter and Scholes, 1992)
Chromium dichromate	NA	--		
Potassium dichromate	0.09	++		(Basketter et al., 2007)
Colophonium	NA	--	NA	
Methyl dibromoglutaronitrile (MDBGN)	1.3	++	strong	(Basketter et al., 2005b; Basketter et al., 2007)
Thiurams				
Tetramethylthiuram disulfide	0.7	++	moderate	(De Jong et al., 2002)
Tetraethylthiuramdisulfide	1.4	++		(De Jong et al., 2002)
Dipentamethylenethiuramdisulfide	5.2	+		(De Jong et al., 2002)
Tetramethylthiurammonosulfide	5.4	+		(De Jong et al., 2002)
Dipentamethylenethiuramtetrasulfide	20.5	+		(De Jong et al., 2002)
Tetrabutylthiuramdisulfide	34.8	+		(De Jong et al., 2002)
(Chloro)methyl isothiazolinone (isothiazolinone mixture CMI/MI)	0.01	++	Strong	(Basketter et al., 1999; Gerberick et al., 2001)
Methyl trimethylene isothiazolinone (MTI)	2.0	++	Strong	(Basketter et al., 1999; Basketter et al., 2000; Gerberick et al., 2001)
Benzisothiazolinone (BIT)	10.4	+		(Basketter et al., 1999)
Turpentine oil	NA			
Formaldehyde (or formaldehyde liberators/resins)		--	NA	
Formaldehyde	0.96			(De Jong et al., 2007)
Paraformaldehyde	3.2	+	Moderate	(De Jong et al., 2007)
2-chloro-N-acetamide	16.0	+		(De Jong et al., 2007)
Quartenium-15	20.8	+		(De Jong et al., 2007)
Hexamethylenetetramine	30.6	+		(De Jong et al., 2007)
Propylparaben	negative			(Basketter and Scholes, 1992)
Di-isocyanates				
Toluene 2.4-diisocyanate (TDI)	0.11	++		(Van Och *et al.*, 2005)

[1] EC3 values determined in the LLNA were used to categorize potency of allergens: EC3 ≤ 2%: stronger sensitizer (++) and EC3 > 2%: other sensitizer (+) (OECD expert group on sensitization hazards, 2008)

[2] Chemicals are classified into five categories: strong, moderate, weak, extremely weak, nonsensitizing. These data are based on human data and expert judgment (Basketter *et al.*, 2000). Abbreviations: LLNA: local lymph node assay; NA: not available

* Classification based on experiments in GPMT

Appendix 7: Quantitative risk assessment of Kathon

To provide some insight in performing a quantitative risk assessment, the information from CMI/MI (Kathon) present in cosmetic products for children, gathered by The Danish Environmental Protection Agency, is used as a start. Exposure estimates were calculated for in mg/kg bw/day for a child of 15 kg. For performing a QRA as laid out by Api et al. (2007) it is necessary to calculate exposures in dose per square cm. However, Api et al. (2007) collected a lot of information, but not specific on children. Therefore, the measured data from this study were used to perform the QRA for adults.
Firstly, the daily exposures are recalculated using a body weight of 60 kg. Using the information on surface areas for different products, exposure estimates are calculated per square cm.
In the table below the daily exposure (SED) for Kathon is stated for the different product types.

Table 32 Daily exposure (SED) for a child (15kg) to Kathon for the different product types

	SED (mg/kg bw/day) child	**SED (mg/kg bw/day) female**	**surface area (cm2)**	**Kathon exposure (µg/cm2/day)****
Body shampoo/bath gel	0.000051	0.0000127	16900 (body area, female)	0.000045
Liquid soap	0.000048	0.000012	840 (area hands)	0.00086
Bobble bath	0.000041	0.000010	16900 (body area, female)	0.000036
Body lotion/cream	0.0020	0.0005	12895 (area body – head and ½ trunk, female)	0.0023
Shampoo	0.000054	0.0000135	1430 (area hands + ½ head)	0.00057
Eau de toilette	0.0060	0.0015	100	0.9

* taken from Poulsen and Schmidt, 2007, recalculated for a female (60 kg). Information on surface area and used product amount, taken from Api et al. (2007). In the final column, the exposure to Kathon per square cm is given.
**Kathon exposure (mg/cm2 per day) = SED female (mg/kg bw/day) x bw of 60 kg/ surface area

It must be noted that the application of eau de toilette is assessed to be much overestimated as the same exposure values as for normal deodorant are applied. As a start the exposure estimated from Poulsen & Schmidt were used, however recalculated for a (female) adult. Furthermore, the surface areas are taken from Api et al. (2007) without judgment. Retention factors used by Poulsen and Schmidt (2007) are similar to those of Api et al. (2007) for the products considered here, where the mg product per application is about similar.

As a threshold for Kathon (CMI/MI), the human threshold derived from a patch test (the NESIL, No Expected Sensitizing Induction Level as given in Table 15 is taken (1.25 µg/cm^2).
Sensitization Assessment Factors as introduced by Api et al. (2007) are used. The overall SAF consists of a factor for interindividual variation (always 10), a factor for the matrix, and a use factor. The factor for the matrix is dependent on the product type, in which the presence of irritants or skin penetration enhancers, different from the vehicle in the sensitization test, should be taken into account. The use factor considers that in the experimental situation the use is defined and controlled, whereas in real life, the site of contact, skin integrity, duration, way of operating might be different. For performing the QRA, the Acceptable Exposure Level (AEL) can be established.

AEL = NESIL/ SAF

When the Consumer Exposure Level (CEL) is available (which is already estimated using the Danish data), the AEL/CEL ratio can be determined. The present concentration would be acceptable when the AEL exceeds the CEL.

Table 33 QRA of CMI/MI for different product types

	Kathon exposure µg/cm^2/day CEL	**SAF**	**AEL µg/cm2**	**ratio AEL/CEL**
Body shampoo/bath gel	0.000045	100	0.0125	278
Liquid soap	0.00086	100	0.0125	14.5
Bobble bath	0.000036	100	0.0125	347
Body lotion/cream	0.0023	300	0.0042	1.8
Shampoo	0.00057	100	0.0125	21.9
Eau de toilette	0.9	300	0.0042	0.005

For all products separately the AEL/CEL ratio is above 1, and thus there is no concern, except for the eau de toilette. It was already mentioned that product use data and surface area for this product are missing, and that data for a normal deodorant were used which overestimates the exposure. Furthermore, when assuming that a person uses a body gel, shampoo and body lotion at (almost) the same time, the aggregate exposure estimate would be 0.0029 µg/cm2/day, which results in a AEL/CEL ratio of 1.4 (even taking into account the lowest AEL).

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