

Review Article

Contact allergy epidemics and their controls*

JACOB PONTOPPIDAN THYSSSEN, JEANNE DUUS JOHANSEN AND TORKIL MENNÉ

Department of Dermato-venerology, National Allergy Research Centre, Gentofte University Hospital, Ledreborg Allé 40, 1, 2820 Gentofte, Denmark

Contact dermatitis can be severe and lead to sick leave as well as significant healthcare expenses. The aim of this review is to present the published knowledge on 6 historical epidemics of contact allergy to apply this knowledge on the prevention and control of future contact allergy epidemics. A historical review is performed on nickel, chromium, methylchloroisothiazolinone/methylisothiazolinone, methyldibromo glutaronitrile, formaldehyde, and para-phenylenediamine. The first cases of contact dermatitis are mostly occupational, whereas consumer cases appear later. There is often a latency period from the first cases are observed until an epidemic occurs, and the problem is recognized. Finally, no one seems to take responsibility of dealing with the situation, and there are no attempts of regulation until an epidemic is consolidated among consumers for many years. Steps should be taken to prevent contact allergy epidemics. It is essential that dermatologist, scientists, administrators, and consumers organize and structure known methods to accelerate the control of emerging contact allergens.

Key words: chromium; contact allergy; contact dermatitis; epidemic; formaldehyde; isothiazolinone; methyldibromo glutaronitrile; nickel; para-phenylenediamine; risk assessment. © Blackwell Munksgaard 2007.

Accepted for publication 19 November 2006

Contact allergy affects nearly 15–20% of the general population (1). Sensitization is caused by skin contact with low-molecular-weight haptens. Risk factors include the inherent sensitizing potential of an allergen, elevated allergen concentration (dose per unit area), high frequency of exposure, occlusion, long exposure time, the presence of penetration-enhancing factors, and an altered skin barrier function (2). Genetic predisposition seems to play a minor role (3–5). A sensitized person who becomes exposed to an allergen concentration that exceeds the individual threshold will develop allergic contact dermatitis. Furthermore, elicitation depends on the duration and frequency of exposure, region of application, and the presence of irritants (6).

Certain allergens are ubiquitous in our environment. This can make total allergen avoidance impossible. Consequently, some patients develop chronic dermatitis leading to sick leave as well as increased healthcare expenses.

The aim of this review is to present the published knowledge on 6 historical epidemics of contact allergy. The chosen allergens have all caused high

incidences of allergic contact dermatitis among consumers and workers (7). Furthermore, there have been attempts to regulate all 6 allergens.

The description of each allergen includes its origin, use, and exposure as well as a chronological overview of the first publication of contact dermatitis, its epidemic, and finally control.

The review will provide an insight to some historical setbacks and achievements in contact dermatitis. It is our intention that past contact allergy epidemics will teach us important and decisive measures, when it comes to the prevention, detection, and control of future epidemics.

Material and Methods

A historical review is performed on nickel, chromium, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), methyldibromo glutaronitrile (MDBGN), formaldehyde, and para-phenylenediamine (PPD). Fragrance mix has been considered unsuitable for this review because of its heterogeneity.

The literature search has been performed both manually and by the use of Pubmed Medline and Google™ internet search engine. As Pubmed Medline does not cover all published data, a

*The content has not been published previously and is not otherwise submitted for publication.

historical search in our library has also been carried out. It is possible that the authors have not been able to isolate the first published cases of contact dermatitis to specific allergens, as part of the literature is old and not easily accessible.

In the selection of references, priority has been given to initial descriptions, original larger clinical materials, exposure assessments, experimental clinical exposure studies, and eventual regulations.

With the term epidemic, the authors mean the occurrence of cases of an illness in a community or region, which is in excess of the number of cases normally expected for that disease in that area at that time (8).

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 Fredrik Cronstedt as he was attempting to extract copper from niccolite (kupfernickel) (9). Nickel is used in many industrial and consumer products, including stainless steel, magnets, metal plating, coinage, and special alloys.

The first report of contact dermatitis caused by nickel exposure appeared in the late 1880s as Blascho described the 'galvanization eczema' (10). At the time, nickel dermatitis was typically observed on the hands and forearms of miners and workers in the plating industry (10, 11). Nickel dermatitis often led to severe eczematous disease, as nickel exposure was high and treatment absent. In 1925 in Kiel, nickel was proven, by patch testing, to be the aetiological factor for the development of dermatitis in the electroplating industry (11). Further reports about occupational nickel dermatitis were released through the 1920 and 1930s (12–14).

In 1931, the first case of nickel dermatitis among consumers of nickel-plated objects worn in direct skin contact was observed (15). For the next 6 decades, an accumulation of cases especially among female consumers took place: in the 1930–1960s, the most frequent sensitizing object was nickel-plated suspenders (16). In the 1970s, nickel dermatitis was most frequently caused by metal buttons and zippers in blue jeans (17), and in the 1980s, nickel dermatitis was most frequently caused by jewelry (18).

As a result, the frequency of positive patch test to nickel increased in most countries, e.g. in Malmö, Sweden, an increase among female patients was observed from 7% to 29% in the period 1962–1997 (19). Consumer nickel dermatitis often proved severe and could evolve to hand eczema and, in rare cases, systemic contact dermatitis.

Investigations showed that the induction and elicitation of nickel contact allergy depended on the amount of nickel per skin unit area present in the epidermis and on the fact that free nickel ion could be leached out as a response to the corrosion caused by human sweat on nickel-plated surfaces and alloys (20–22). Based on this research, a limit of $0.5 \mu\text{g}/\text{cm}^2$ per week of nickel release was suggested and acknowledged as a safe limit for nickel exposure (21). In 1990, a legislation was passed in Denmark to diminish nickel release in consumer products (23). In 1994, a similar legislation was passed in the European Union (EU) prohibiting trade with products that released more than $0.5 \mu\text{g}/\text{cm}^2$ per week of nickel (24). The theoretical basis for these regulations was supported by a meta-analysis of the dose–response relationship for nickel based on scientific articles published between 1971 and 1999 (25). The Nickel Directive was recently revised so that the requirement concerning nickel content in piercing posts is changed to a new requirement concerning nickel release (26).

It is generally acknowledged that nickel contact allergy and dermatitis is decreasing because of these regulatory interventions. Among Danish children aged 0–18 years, nickel allergy decreased significantly from 24.8% to 9.2% over a 12-year period (27). Furthermore, ear piercing performed after 1992 led to a decreased risk of nickel sensitization (28). In Germany, nickel sensitization decreased significantly from 36.7% to 25.8% among women younger than 30 years over a 9-year period (29). Despite these regulations, nickel remains the most common allergen in patch test clinics all over Europe (30). In the USA, where no nickel regulation has been introduced, nickel continues to be responsible for clinical disease among youngsters (31).

Chromium

Chromium is a steel grey, lustrous, hard metal that takes a high polish. It was first identified in 1797 when French chemist Nicolas-Louis Vauquelin produced chromium oxide (CrO_3) from samples of crocoite ore (PbCrO_4) (9). It is primarily used not only in metal alloys and plating but also in leather tanning, paint, anticorrosives, ceramics, and chemicals.

Historically, the most important cause of contact allergy from chromium has been occupational exposure to cement. Only trivalent Cr (III) and hexavalent Cr (VI) oxidation states of chromium act as haptens. Their existence depends on various factors such as pH and temperature. In cement, Cr (VI) is produced when the trivalent compound, Cr_2O_3 , is heated to 1400–1500°C.

The first cases of contact dermatitis to cement were reported in 1908 and 1925 during the construction of the Metro in Paris and the Underground in London, respectively (32, 33). Patch testing with potassium dichromate 0.5% petrolatum was performed in 1931 and is still used today in the European standard patch test series (34). In 1966, Kligman showed using the maximization test that potassium dichromate was an extreme hapten (35).

In 1950, the hexavalent chromium content in cement was associated with the development of contact allergy in workers with cement eczema (36). During the 1970s, an accumulation of patients with occupational chromium dermatitis led to an increasing number of persons with permanent disability in Denmark (37). In 1979, it was suggested that the addition of iron sulfate to cement could reduce the amount of water soluble hexavalent chromium (38). In 1981, iron sulfate was added to cement manufactured by Aalborg Portland[®], Denmark, reducing the water soluble chromate content to not more than 2 parts per million (p.p.m.). In 1983, legislation made this addition compulsory in Denmark. Since then, the prevalence of chromium allergy among construction workers in Denmark has decreased (39).

In countries that did not pass similar legislations, chromate allergy continued to cause occupational chromium dermatitis (40). Hence an EU Directive restricting the marketing and use of cement containing more than 2 p.p.m. hexavalent chromium came into effect on January 17, 2005 (41).

The epidemiology and clinical picture of chromium allergy in Denmark has changed from an occupational problem to a consumer problem. Leather products are now responsible for the main chromium exposure (42). The prevalence of chromium allergy in the background population is between 0.5% and 1.7% but considerably higher among consecutive eczema patients (1, 42–44). A suggestion on threshold levels for Cr (III) release and Cr (VI) content in leather products has been raised, as modifications in the leather manufacturing process can limit the content of Cr (III) and Cr (VI). Hansen et al. determined the threshold concentration that will elicit contact dermatitis in chromium-allergic subjects based on scientific work performed between 1954 and 1998 (45). Further exposure studies are warranted.

Formaldehyde

Formaldehyde is a colourless flammable gas with a strong pungent odour. It was first synthesized in 1859 by Russian chemist Alexandr Butlerov

but was conclusively identified by German chemist August Wilhelm von Hofmann in 1867 (9). In 1888, the disinfectant properties of formaldehyde were discovered, but it was not until 1897 that the production of formaldehyde grew significantly (46). Formaldehyde appears as free formaldehyde, formaldehyde donated from formaldehyde-releasing preservatives, and finally as formaldehyde resins. Free formaldehyde and formaldehyde-releasing preservatives are used not only as preservatives in household products, such as detergents, topical medications, and cosmetics but also in industrial products such as paints, cutting fluids, lacquers, and disinfectants.

Today, formaldehyde-releasing preservatives have replaced formaldehyde in most cosmetics and industrial products, as they are less frequent sensitizers (47). However, the majority of formaldehyde is combined with phenol, urea, or melamine in the production of formaldehyde resins. These resins are commonly used as adhesives and binders in plywood, carpeting, paper, pulp, plastic, textile finishing, and as the wet-strength resin added to sanitary paper products.

Occupational sensitization to formaldehyde is widespread and has been reported among hairdressers, medical personnel, paper manufacturers, shoe manufacturers, embalmers, and especially among industrial workers exposed to metalworking fluids (47). In 1905, the first case of occupational contact dermatitis to formaldehyde was published when Galewsky described eczema among physicians and medical personnel in Dresden, Germany (48).

Historically, consumer sensitization to formaldehyde has mainly been observed for clothing and cosmetics, but contact dermatitis to formaldehyde was already well described at the turn of the century among patients suffering from hyperhidrosis (48). In 1934, textile dermatitis was reported for the first time at the Finsen Institute in Denmark (49). An accumulation of cases was seen in the 1950s and 1960s, whereas the 1970s saw fewer cases (47). This change was mostly because of the development of new textile finishes that released less formaldehyde.

Contact allergy to nail varnish was described for the first time in 1925 (50). Preservation of cosmetics with formaldehyde increased in the 1940s and 1950s because it was cheap and effective. Between 1963 and 1986, a 3.9% incidence of formaldehyde sensitivity was estimated in 119,505 patients from mainly Western Europe and North America (47). In 1979, Jordan et al. showed the dose–response relationship to provocative axillary use testing and patch testing in 16 formaldehyde-sensitive patients (51). The authors concluded that

a usage concentration of 30 p.p.m. or less could decrease contact allergy to formaldehyde (51). This finding was supported by Flyvholm et al. who showed that formaldehyde may elicit an allergic reaction during repeated occlusive exposure down to 30 p.p.m. (52–54).

As part of the European Cosmetic Directive, the content of formaldehyde was limited to 0.2% in cosmetic products and 0.1% in oral hygiene products and 5% in nail hardeners (55). Cosmetics containing more than 0.05% formaldehyde must be labeled as 'contains formaldehyde'. In 2006, Zachariae et al. showed a non-eliciting concentration of diazolidinyl urea of 0.05% (130 p.p.m. formaldehyde) applied in a cream on the arm, neck, and face in formaldehyde-sensitive individuals (56). Furthermore, effective microbial preservation was achieved using 1/6 of diazolidinyl urea concentration typically found in facial moisturizers (56).

It has been suggested that the combination of increasing incidences of formaldehyde sensitization, the EU directive and increasing preservation with MCI/MI, led to a decline in the use of formaldehyde in leave-on cosmetics during the 1980s (47). However, Wilkinson et al. reported that formaldehyde sensitivity remains high as result of continuous product preservation with formaldehyde and formaldehyde-releasing preservatives (57). In support, Gruvberger et al. showed that out of 100 moisturizers examined on the Swedish market, 10 (10%) contained formaldehyde (58). Furthermore, a considerable increase in the use of formaldehyde especially in paints and lacquers was observed between 2002 and 2005 in Denmark (59). The risk of sensitization to formaldehyde remains present among European consumers and workers.

Methylchloroisothiazolinone/ methylisothiazolinone

Preservatives containing MCI/MI have been widely used since the late 1970s in Europe and early 1980s in the USA (60). They quickly gained popularity and have mostly been applied in industrial products as well as toiletries and cosmetics. In 1980–1982, the first cases of allergic contact dermatitis to MCI/MI were discovered among workers, and later in consumers, in Malmö, Sweden (61, 62). Consequently, the MCI/MI-containing preservatives Kathon[®] CG and Kathon[®] 886 were added to the routine patch test series and cutting oil patch test series, respectively, in Malmö and Lund (61). In 1983, Chan et al. supported these findings when they showed that MCI/MI was a contact allergen in guinea-pigs (63).

In the 1980s, several reports of allergic contact dermatitis to MCI/MI among workers and con-

sumers were published (64–66), and at the same time, the prevalence of positive allergic patch test reactions increased markedly in unselected eczema patients, reaching prevalence rates between 3% and 8% (61, 67, 68). This increase was primarily attributed to cosmetic leave-on products, despite the products contained a concentration of MCI/MI that was within the recommended levels of that time (30 p.p.m.) (69).

Since the 1990s, the content of MCI/MI in the EU is limited to a concentration of 15–55 p.p.m. in industrial products and 15 p.p.m. in cosmetic products (70). However, the Cosmetics, Toiletries and Fragrance Association recommends a use concentration of no more than 7.5 p.p.m. in cosmetic leave-on products and 15 p.p.m. for cosmetic rinse-off products (71).

It has been suggested that these efforts have not only diminished the risk of primary sensitization but also the elicitation of contact dermatitis in MCI/MI-sensitized individuals from the use of rinse-off products (69). However, the levels of patch test sensitivity to MCI/MI from a 10-year multicentre analysis remain high at 2–2.5% (57). Furthermore, Zachariae et al. showed that the elicitation threshold for a MCI/MI-containing solution is less than 2 p.p.m. in sensitized individuals (72). Further monitoring is therefore necessary.

Recently, a new preservative containing only MI and not MCI has been introduced in the EU for use in cosmetics and industrial products. So far, 2 industrial reports indicate that MI holds a potential for eliciting and probably inducing contact allergy in humans (73, 74).

Methyldibromo glutaronitrile

Euxyl[®] K 400 (Schülke & Mayr, Hamburg, Germany) was marketed in Europe for the preservation of industrial and cosmetic products in 1983 and 1985, respectively. The product is a combination of 2 preservatives, MDBGN and 2-phenoxyethanol (PE), in a 1:4 ratio. Euxyl[®] K 400 was introduced as a potent alternative to other sensitizing preservatives, in particular MCI/MI.

In 1983, the first case of allergic contact dermatitis to MDBGN was reported, when a worker developed eczema on the hands and forearms after exposure to glue preserved with Tektamer 38 (75). Allergic contact dermatitis to Euxyl[®] K 400 is almost exclusively because of sensitization with MDBGN and only rarely because of PE (76). In 1986, the EU scientific Committee on Cosmetology authorized the content of MDBGN in cosmetics products at a maximum concentration of 0.1% in both leave-on and rinse-off products (77). However, in 1989, the first of many reports of

allergic contact dermatitis among consumers was published in Germany (78). Since then, allergic contact dermatitis has been reported from MDBGN in different products such as soap, cleansing milk, shampoos, moisturizers, ultrasonic gel, moistened toilet paper, sunscreen lotion, detergents, and eye gel. de Groot et al. showed an increase in the frequency of positive test reactions to MDBGN in the Netherlands from 0.5% in 1991 to 4% in 1994 (79). Similarly, the levels of patch test sensitivity to MDBGN increased from 0.7% in 1991 to 3.5% in 2000 in a European multi-centre analysis (57). Concurrently with the continuous reports of increasing incidence rates of MDBGN contact allergy, several studies concerning the sensitizing capacity of MDBGN were carried out (80–82). Data from the manufacturer of Tektamer 38[®] showed that the preservative was a moderate skin irritant and that a human repeat insult patch test procedure did not sensitize any of 52 individuals undergoing 12 daily applications of 3000 p.p.m. Tektamer 38[®] over a 3-week period (75). However, in 1993, Hausen showed that Euxyl[®] K 400 and MDBGN had a distinct but weak sensitizing potency when using a modified Freund's complete adjuvant procedure (81). In 1999, Wahlkvist et al. supported these findings and concluded that to detect the allergenic potential of possible contact allergens, it is necessary to apply various predictive test models (82). The differing results may be because of the limited number of applications in the tests and that multiple applications of MDBGN may be necessary for sensitization. A rinse-off exposure study with MDBGN showed that none of 11 pre-sensitized individuals using a 0.02% MDBGN-containing shampoo, 3 days weekly for a 9- to 13-week period, developed contact dermatitis (83). However, Jensen et al. showed that the use of 0.1% MDBGN soap elicited contact dermatitis in 7/19 individuals after 6–34 days (84).

It is generally acknowledged that there has been a risk assessment failure concerning MDBGN. In the light of these findings, an amendment to the EU Cosmetic Directive has been added, restricting the use of MDBGN to rinse-off products only, in a concentration of 0.1% since 2005. Furthermore, in a recent Scientific Committee on Consumer Products (SCCP/0863/05) opinion on MDBGN, it was recommended that MDBGN should not be present in any cosmetic product.

Para-phenylenediamine

PPD is 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, but today it is mainly used for permanent hair dyeing and is an ingredient in almost every permanent hair colour product on the market, regardless of brand.

During the 19th century, hair dying with henna became increasingly popular in the Middle East and soon spread to daring women in Europe. The introduction of PPD gradually replaced henna as the preferred hair dye among European hairdressers. In 1898, Cathelineau reported 18 cases of occupational dermatitis to PPD among female hairdressers in France (85). Sensitization by PPD was considered a significant health risk and was therefore prohibited in Germany in 1906 (86). In 1907, French chemist Eugene Schueller, later founder of l'Oreal, developed a hair colour formula based on PPD that he sold to Parisian hairdressers (9). In 1910, imported French hair dyes caused contact dermatitis among hairdressers in Spain (87). During the next decades, the cosmetic industry transferred the PPD technology mainly from the textile and fur industry to hair dyeing. Hence, in the 1930s, accumulating cases of contact dermatitis to synthetic hair and fur dyes made Bonnevie suggest that PPD became a part of the patch test standard series (16). In 1943 and 1951, respectively, Sweden and France prohibited the use of PPD (86).

In the 1960s, hair dyeing became a popular home cosmetic procedure in the USA. Shirley Polykoff certainly made a contribution to increasing sales when she in 1956 advertised for Clairol hair dying product with lines such as 'Does she ... or doesn't she? Only her hairdresser knows for sure,' and 'Is it true blondes have more fun?' In only 6 years, Clairol sales increased by 413%, as more than 50% of US adult women began using hair colour, up from 7% (88). Today, hair dyeing is widely applied, with 75% of American and Danish women reportedly dyeing their hair and an increasing number of men following their lead (89, 90).

Under the EU Cosmetic Directive, PPD is allowed in hair dye products with a concentration limit of 6%. Even though many hair care manufacturers apply PPD in smaller concentrations, sensitization to PPD is high among hairdressers and patients. Between 1980 and 1993, 45.9% of 379 hairdressers patch tested in Madrid had a positive reaction to PPD (91). Conde-Salazar et al. found a comparable mean value of positive patch test reactions to PPD among hairdressers in 12 earlier publications (91). In 1992, Guerra et al. showed that 24% of 302 Italian hairdressers were sensitized to PPD (92). Furthermore, 9 European centres reported that 15% (range 0–45.5%) of 809

patch tested hairdressers had a positive reaction to PPD (93). In St John's, London, the prevalence of positive patch tests to PPD was 3.2% among 26 706 patients suspected of contact dermatitis between 1982 and 1998 (94). Reports from Germany and the USA have showed slightly higher frequencies, 4.6% and 6.4%, respectively (95, 96). When Sweden entered the EU in 1992, the national prohibition on the use of PPD was lifted. However, no increase in PPD sensitization has been observed (97), probably because PPD was also used before 1992 because of import of PPD-containing hair dye products by hairdressers (98) but also because chemically related substances have been applied instead.

Contact dermatitis to PPD can be severe for hairdressers and consumers. Hairdressers and barbers rate among the 3 most prevalent groups suffering from occupational dermatitis in England (99). In Germany, an increase in the frequency of sensitization to PPD among clients using hair dye was noted between 1995 and 2002 (100). Since the use of hair dye is becoming increasingly popular, the permitted PPD use concentration in hair products clearly calls for a review.

Discussion

Experience from past contact allergy epidemics

This review suggests that contact allergy epidemics have certain similarities (Table 1). Most often, the first cases of contact dermatitis are occupational, whereas consumer cases seem to appear later. Therefore, recent observations of occupational contact dermatitis to MI may be the beginning of an emerging epidemic and should be followed closely (73, 74). Furthermore, there is a latency period from the first cases are described until the contact allergy epidemic is recognized. Among other things, this transition phase should be used to identify patch test concentrations (101). Past contact allergy epidemics also show that there are no attempts of regulation until an epidemic is consolidated among consumers, and thus allergens persist in consumer products for a long time. The regulations are most often based on public research.

Table 1. Common trends of contact allergy epidemics

Primary cases are often occupational
Consumer cases predict major problems
The epidemic is not fully recognized until a high number of consumers are sensitized
Epidemics are long lasting as allergens tend to persist in consumer products
Generally, there is no public or industrial interference
Regulations are most often based on public-financed research

Finally, past experience shows that neither manufacturers nor administrators seem to take clear responsibility of dealing with emerging contact allergy epidemics.

Pre-marketing risk assessment and its limitations

Traditionally, risk assessment of new contact allergens has focused on pre-marketing safety tests. This step is critical, as it can prevent new substances with strong allergenic potentials from reaching consumers. The risk assessment process generally follows a stepwise approach: hazard identification, dose–response assessment, exposure assessment, and risk characterization (102). Prior to product marketing, a maximum allowable exposure limit for the ingredient is determined from exposure calculations and skin sensitization tests. However, the main problem with current test methods such as chemical and cellular *in vitro* tests, the guinea-pig maximization test, the local lymph node assay, and the human repeat insult patch test is the sensitivity of the test systems, the correct interpretation of test data, and their incorporation into the final risk assessment.

It is critical to risk assessment that an understanding of exposure, allergenic potency, and dose–response is achieved. Certain sensitizing chemicals can be applied in various products without inducing contact allergy, as long as the concentration is low. However, if the concentration of a sensitizing chemical is too high, the risk of sensitization is increased. The purpose of preservation is to eliminate microbial growth, but often a higher concentration than necessary is applied (56). This increases the risk of sensitization.

Safety evaluation failures are sometimes encountered. Alternating preservative contact allergy epidemics have been replacing one another with noticeable delays in effective attempts of regulation (103): in the 1970s, formaldehyde was widely replaced by MCI/MI in cosmetic products (47). As an epidemic of contact dermatitis to MCI/MI was observed, MDBGN was marketed, but unfortunately, it induced and elicited contact dermatitis in millions of patients.

Early detection and communication of contact allergy epidemics

Early detection can be achieved through the use of comprehensive data networks. The European Surveillance System on Contact Allergies carries out surveillance of contact allergy in clinical populations, and this enables European dermatologists to detect general trends and associations as well as local trends and subgroups at risk.

Manufacturers perform risk assessment prior to product marketing, and often, risk assessment continues after the product has been marketed. Regrettably, safety data do not always reach scientific journals and meetings. Furthermore, public research funding is often scarce. This combination makes post-marketing risk assessment difficult. Data from industries as well as public research institutions should be easily accessible to investigators to enhance future risk assessment.

Scientific contributions to the solution of contact allergy epidemics

Research that will lead to the regulation of a specific contact allergen is often funded by public institutions. It is therefore important that the limited resources are clearly targeted (Table 2). Early investigations largely depend on clinical descriptions in case reports as well as epidemiological studies that define the extent of a contact allergy epidemic. However, experimental clinical exposure studies are of critical importance as they form the basis for future regulations of allergen exposure. A thorough investigation of an allergen includes determination of its potency, the dose that induces and elicits contact dermatitis, the number of repeated applications necessary to elicit contact dermatitis, time relationship, and eventually a confirmatory repeated open application test.

In the past, contact dermatitis research has only been organized to a certain extent. However, several workgroups continuously discuss current problems in contact dermatitis. Today, there is an understandable delay in scientific production because there seem to be a shortage of human as well as financial resources. The solution for future contact allergy epidemics could ideally be accelerated by enhanced international planning.

Administrative contribution to the solution of contact allergy epidemics

A substance that has proven capable of inducing and eliciting contact dermatitis can be managed

with different regulatory measures: the strongest regulating measure is prohibition, e.g. MDBGN in stay-on cosmetic products. This is applied when safety data have proven a clear correlation between low concentration allergen exposure and clinical disease, often in conjunction with a large epidemic. As observed with MDBGN, administrative decisiveness can take many years and should ideally be shortened. Another regulatory measure is limitation of an allergenic ingredient in a product, e.g. nickel release from metals and jewelry. Such regulations may also prove effective and change epidemiological patterns, as observed for nickel (27–29).

Historically, regulations have most often been implemented in individual European countries prior to the establishment of EU directives, e.g. the Danish nickel and chromium regulations. It is generally acknowledged that these regulations have been effective, but nevertheless, it took another 22 years before chromium in cement was regulated in the EU in comparison with Denmark. It is possible that future regulations will have a similar chronology, as the 25 EU countries have divergent national interest and opinions, which to a certain extent depends on their home industries.

Other contributions to the solution of a contact allergy epidemic

Industrial willingness to limit allergen exposure to consumers and workers post-marketing is also a way to prevent contact allergy epidemics. In 1981, Aalborg Portland® added iron sulfate to their cement before it became compulsory by law in Denmark in 1983. Likewise, in the 1990s, hair-dressing products containing acid perms with glyceryl monothioglycolate (GMT) were withdrawn from the German market. GMT had been responsible for contact dermatitis among hairdressers and consumers in Germany (104, 105), but after GMT-containing perm solutions were withdrawn by major German manufacturers, the incidence of sensitization decreased (106). Such initiatives can be costly for the manufacturers because they may involve changes in several steps of the production. However, the liability of a product is vital to all companies and a decrease will most often lead to removal of the product.

Other initiatives to avoid contact allergens have also undoubtedly been important for the development of consumer safety. An EU requirement on mandatory labelling of cosmetic products has eased consumer access to the ingredient list on personal products (55).

Members of the North American Contact Dermatitis Society (ACDS) have access to the Contact

Table 2. Enhanced data collection for the prevention of contact allergy epidemics

Better description of clinical cases
Accurate exposure descriptions
Dose–response data from patch testing (multiple patch test concentrations)
Open testing with repeated applications
Qualitative and quantitative exposure assessment
Surveillance systems should be established to accelerate data availability
Retrospective epidemiological studies determine the effect of regulations

Table 3. Contact allergy risk assessment – necessary data for the prevention of contact allergy

Pre-marketing
Quantitative structure–activity relationship data
Chemical and cellular <i>in vitro</i> data
Outcome of animal testing
Determination of no expected sensitization induction level from historical experimental human sensitization tests
Identification of safety assessment factors
Calculation of consumer exposure from exposure scenarios
Post-marketing
Descriptions of clinical cases
Causative exposure assessment
Dose–response elicitation data, patch test data, and repeat open application test
Epidemiological data from local and international networks
Application of previous exposure regulation outcomes with the current problem allergen

Allergy Replacement Database, which contains the ingredient list of more than 2000 topical skin care products (107). This database developed at Mayo clinic facilitates patient allergen avoidance when they consult dermatologists, pharmacists, and other members of ACDS. There are several other useful databases; however, most of them are of national interest (108).

Future perspectives

Past risk assessment failures teach us that regulatory steps should be enhanced to prevent long-term contact allergy epidemics. As previously proposed, contact sensitizing chemicals in cosmetic products should not be permanently approved until a final risk assessment and risk management has been established (109). A combination of pre- and post-marketing risk assessment and the discussed regulatory measures and initiatives may be sufficient to prevent major future contact allergy epidemics (Table 3).

It is essential that dermatologist, scientists, and administrators organize and structure known regulatory methods to accelerate the control of emerging contact allergens.

Acknowledgement

The study was supported by the funding from The Copenhagen County Research Foundation.

References

- Nielsen N H, Linneberg A, Menne T, Madsen F, Frolund L, Dirksen A, Jorgensen T. Allergic contact sensitization in an adult Danish population: two cross-sectional surveys eight years apart (the Copenhagen Allergy Study). *Acta Derm Venereol* 2001; 81: 31–34.
- Robinson M K, Gerberick G F, Ryan C A, McNamee P, White I R, Basketter D A. The importance of exposure

- estimation in the assessment of skin sensitization risk. *Contact Dermatitis* 2000; 42: 251–259.
- Agner T, Menne T. Individual predisposition to irritant and allergic contact dermatitis. In: *Contact Dermatitis*, 4th edition, Frosch P J, Menné T, Lepoittevin P-J (eds): Berlin-Heidelberg-New York, Springer, 2006: 127–134.
- Bryld L E, Hindsberger C, Kyvik K O, Agner T, Menne T. Genetic factors in nickel allergy evaluated in a population-based female twin sample. *J Invest Dermatol* 2004; 123: 1025–1029.
- Westphal G A, Schnuch A, Moessner R, König I R, Kranke B, Hallier E, Ziegler A, Reich K. Cytokine gene polymorphisms in allergic contact dermatitis. *Contact Dermatitis* 2003; 48: 93–98.
- Johansen J D, Frosch P J, Menne T. Allergic contact dermatitis in humans – experimental and quantitative aspects. In: *Contact Dermatitis*, 4th edition, Frosch P J, Menne T, Lepoittevin J-P (eds): Berlin-Heidelberg-New York, Springer, 2006: 189–198.
- Frosch P J, Menne T, Lepoittevin J-P. *Contact Dermatitis*, 4th edition. Berlin-Heidelberg-New York, Springer, 2006.
- CDC (Centers for Disease Control and Prevention). *Glossary of terms* (available from <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/glossary.htm>). 2006.
- Wikipedia. *The Free Encyclopedia* (available from <http://www.en.wikipedia.org>). 2006.
- Blascho A. Die berufsdermatosen der arbeiter. Das galvanisierkzem. *Dtsch Med Wschr* 1889; 15: 925–927.
- Schittenhelm A, Stockinger W. Über die idiosynkrasie gegen nickel (nickel krätze) und ihre beziehung zur anaphylaxie. *Z ges Exp Med* 1925; 45: 58–74.
- Bulmer F M R. Studies in the control and treatment of nickel rash. *J Ind Hyg Toxicol* 1926; 8: 517–527.
- Du bois C. La dermatite du nickel. *Schweiz medizinische wochenschrift* 1931; 12-1: 278–280.
- Jadassohn W S F. Über die häufigkeit des vorkommens von kickelekzem. 1929; 157: 572–577.
- McAlester A W Jr, McAlester Third A W. Nickel sensitization from white gold spectacle frames. *Am J Ophthalmol* 1931; 14: 925–926.
- Bonnevie P. Der linische Wert der ekzempnen, an der nickeldiosynkrasie erläutert. *Acta Dermatovenereol* 1936; 17: 376–388.
- Brandrup F, Larsen F S. Nickel dermatitis provoked by buttons in blue jeans. *Contact Dermatitis* 1979; 5: 148–150.
- Boss A, Menne T. Nickel sensitization from ear piercing. *Contact Dermatitis* 1982; 8: 211–213.
- Hindsen M, Bruze M, Christensen O B. Individual variation in nickel patch test reactivity. *Am J Contact Dermat* 1999; 10: 62–67.
- Flint G N. A metallurgical approach to metal contact dermatitis. *Contact Dermatitis* 1998; 39: 213–221.
- Menne T, Brandrup F, Thestrup-Pedersen K, Veien N K, Andersen J R, Yding F, Valeur G. Patch test reactivity to nickel alloys. *Contact Dermatitis* 1987; 16: 255–259.
- Pedersen N B, Fregert S, Brodelius P, Gruvberger B. Release of nickel from silver coins. *Acta Derm Venereol* 1974; 54: 231–234.
- Menne T, Rasmussen K. Regulation of nickel exposure in Denmark. *Contact Dermatitis* 1990; 23: 57–58.
- European Communities. European Dir. 94/27/EC of 30 June 1994 amending for the 12th time Dir. 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 dangerous substances. *Official J Eur Communities* 1994; 37: 1–2.
- Fischer L A, Menne T, Johansen J D. Experimental nickel elicitation thresholds – a review focusing on occluded nickel exposure. *Contact Dermatitis* 2005; 52: 57–64.
- European Commission. Commission Directive 2004/96/EC of 27 September 2004 amending Council Directive 76/769/

- EEC as regards restrictions on the marketing and use of nickel for piercing post assemblies for the purpose of adapting its Annex I to technical progress. *Official Journal of the European Union* 2004; L301/51–301/52.
27. Johansen J, Menne T, Christophersen J, Kaaber K, Veien N. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985–86 and 1997–98, with a special view to the effect of preventive strategies. *Br J Dermatol* 2000; 142: 490–495.
 28. Jensen C S, Lisby S, Baadsgaard O, Volund A, Menne T. Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Br J Dermatol* 2002; 146: 636–642.
 29. Schnuch A, Uter W. Decrease in nickel allergy in Germany and regulatory interventions. *Contact Dermatitis* 2003; 49: 107–108.
 30. Uter W, Hegewald J, Aberer W, Ayala F, Bircher A J, Brasch J, Coenraads P J, Schuttelaar M L et al. The European standard series in 9 European countries, 2002/2003 – first results of the European Surveillance System on Contact Allergies. *Contact Dermatitis* 2005; 53: 136–145.
 31. Belsito D V. *Speech at the 8th Congress of the European Society of Contact Dermatitis*. Berlin, Germany, 2006.
 32. Martial R. La “Gâle” du ciment. *Presse Med* 1908; 64: 507–508.
 33. O'Donovan W J. Lime dermatitis. *Lancet* 1925; 21: 599–602.
 34. Englehardt W E, Mayer R L. Über Chromeczeme im Graphischen Gewerbe. *Arch Gewerbepath Hyg* 1931; 2: 140–168.
 35. Kligman A M. The identification of contact allergens by human assay. 3. The maximization test: a procedure for screening and rating contact sensitizers. *J Invest Dermatol* 1966; 47: 393–409.
 36. Jäeger H., Pelloni E. test épicutané aux bichromates, positifs dans l'eczéma au ciment. *Dermatologica* 1950; 100: 207–215.
 37. Menne T, Bachmann E. Permanent disability from skin diseases. A study of 564 patients registered over a six year period. *Derm Beruf Umwelt* 1979; 27: 37–42.
 38. Fregert S, Gruvberger B, Sandahl E. Reduction of chromate in cement by iron sulfate. *Contact Dermatitis* 1979; 5: 39–42.
 39. Avnstorp C. Follow-up of workers from the prefabricated concrete industry after the addition of ferrous sulphate to Danish cement. *Contact Dermatitis* 1989; 20: 365–371.
 40. Uter W, Ruhl R, Pfahlberg A, Geier J, Schnuch A, Gefeller O. Contact allergy in construction workers: results of a multi-factorial analysis. *Ann Occup Hyg* 2004; 48: 21–27.
 41. European Commission. Directive 2003/53/EC of the European Parliament and of the Council of 18 June 2003 amending for the 26th time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (nonylphenol, nonylphenol ethoxylate and cement). *Official Journal of the European Union* 2003; 178/24–178/28.
 42. Zachariae C O, Agner T, Menne T. Chromium allergy in consecutive patients in a country where ferrous sulfate has been added to cement since 1981. *Contact Dermatitis* 1996; 35: 83–85.
 43. Geier J, Schnuch A, Frosch P J. Contact allergy to dichromate in women. *Dermatol Beruf Umwelt* 2000; 48: 4–10.
 44. Schafer T, Bohler E, Ruhdorfer S, Weigl L, Wessner D, Filipiak B, Wichmann H E, Ring J. Epidemiology of contact allergy in adults. *Allergy* 2001; 56: 1192–1196.
 45. Hansen M B, Rydin S, Menne T, Duus J J. Quantitative aspects of contact allergy to chromium and exposure to chrome-tanned leather. *Contact Dermatitis* 2002; 47: 127–134.
 46. Museum of Funeral Customs. *Formaldehyde: its development and history since 1986* (available from <http://www.funeralmuseum.org/pdf/formaldehyde.pdf>). Springfield, 2006.
 47. Fransway A F. The problem of preservation in the 1990s: I. Statement of the problem, solution(s) of the industry, and the current use of formaldehyde and formaldehyde-releasing biocides. *Am J Contact Dermatitis* 1991; 2: 6–23.
 48. Galewsky E. Ueber berufliche Formalinonchyrien und -Dermatiden. *Muench Med wochensh* 1905; 52: 164–165.
 49. Marcussen P V. Contact dermatitis due to formaldehyde in textiles 1934–1958. Preliminary report. *Acta Derm Venereol* 1959; 39: 348–356.
 50. Miller H E, Taussig L R. Cosmetics. *J. Am Med Assoc* 1925; 84: 1999–2002.
 51. Jordan W P Jr, Sherman W T, King S E. Threshold responses in formaldehyde-sensitive subjects. *J Am Acad Dermatol* 1979; 1: 44–48.
 52. Flyvholm M A, Hall B M, Agner T, Tiedemann E, Greenhill P, Vanderveken W, Freeberg F E, Menne T. Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. Relationship to repeated open application test with a product containing formaldehyde releaser. *Contact Dermatitis* 1997; 36: 26–33.
 53. Maibach H I. Formaldehyde: effects on animal and human skin. In: *Formaldehyde Toxicity*, Gibson J E. (ed.): Washington, New York, London, Hemisphere, 1983: 166–174.
 54. Marzulli F N, Maibach H I. The use of graded concentrations in studying skin sensitizers: experimental. *Food Cosmet Toxicol* 1974; 12: 219–227.
 55. Anonymous. Council Directive 76/768/EEC of 27 July on the approximation of the laws of Member States relating to cosmetic products. *Official J EEC* 1976; L262: 169.
 56. Zachariae C, Hall B, Cottin M, Cupferman S, Andersen K E, Menne T. Experimental elicitation of contact allergy from a diazolidinyl urea-preserved cream in relation to anatomical region, exposure time and concentration. *Contact Dermatitis* 2005; 53: 268–277.
 57. Wilkinson J D, Shaw S, Andersen K E, Brandao F M, Bruynzeel D P, Bruze M, Camarasa J M, Diepgen T L et al. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002; 46: 207–210.
 58. Gruvberger B, Bruze M, Tammela M. Preservatives in moisturizers on the Swedish market. *Acta Derm Venereol* 1998; 78: 52–56.
 59. Flyvholm M A. Preservatives in registered chemical products. *Contact Dermatitis* 2005; 53: 27–32.
 60. Law A B, Moss J N, Lashen E S. Kathon-CG: a new single component, broad spectrum preservative for cosmetics and toiletries. In: *Cosmetic and Drug Preservation. Principles and Practice*, Karaba J J (ed.): New York, Marcel Dekker, 1984: 129–141.
 61. Bjorkner B, Bruze M, Dahlquist I, Fregert S, Gruvberger B, Persson K. Contact allergy to the preservative Kathon CG. *Contact Dermatitis* 1986; 14: 85–90.
 62. Gruvberger B. *Methylisothiazolinones – Diagnosis and Prevention of Allergic Contact Dermatitis*. Sweden, The Department of Occupational and Environmental Dermatology, Malmö University Hospital, 1997: 9–13.
 63. Chan P K, Baldwin R C, Parsons R D, Moss J N, Stiratelli R, Smith J M, Hayes A W. Kathon biocide: manifestation of delayed contact dermatitis in guinea pigs is dependent on the concentration for induction and challenge. *J Invest Dermatol* 1983; 81: 409–411.
 64. de Groot A C, Liem D H, Weyland J W. Kathon CG: cosmetic allergy and patch test sensitization. *Contact Dermatitis* 1985; 12: 76–80.
 65. Foussereau J. An epidemiological study of contact allergy to 5-chloro-3-methyl isothiazolone/3-methyl isothiazolone in Strasbourg. *Contact Dermatitis* 1990; 22: 68–70.

66. O'Driscoll J B, Beck M H. Occupational allergic contact dermatitis from Kathon WT. *Contact Dermatitis* 1988; 19: 63.
67. Hannuksela M. Rapid increase in contact allergy to Kathon CG in Finland. *Contact Dermatitis* 1986; 15: 211–214.
68. Tosti A. Prevalence and sources of Kathon CG sensitization in Italy. *Contact Dermatitis* 1988; 18: 173–174.
69. Fewings J, Menne T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis* 1999; 41: 1–13.
70. Reinhard E, Waeber R, Niederer M, Maurer T, Maly P, Scherer S. Preservation of products with MCI/MI in Switzerland. *Contact Dermatitis* 2001; 45: 257–264.
71. Cosmetic Ingredient Review Panel of the Cosmetic, Toiletry Fragrance Association. Final report on the safety assessment of methylisothiazolinone and methylchloroisothiazolinone. *J Am Coll Toxicol* 1992; 11: 75–128.
72. Zachariae C, Lerbaek A, McNamee P M, Gray J E, Wooder M, Menne T. An evaluation of dose/unit area and time as key factors influencing the elicitation capacity of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) in MCI/MI-allergic patients. *Contact Dermatitis* 2006; 55: 160–166.
73. Isaksson M, Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis* 2004; 15: 201–205.
74. Thyssen J P, Sederberg-Olsen N, Thomsen J F, Menne T. Contact dermatitis from methylisothiazolinone in a paint factory. *Contact Dermatitis* 2006; 54: 322–324.
75. Mathias C G. Contact dermatitis to a new biocide (Tek-tamer 38) used in a paste glue formulation. *Contact Dermatitis* 1983; 9: 418.
76. Lovell C R, White I R, Boyle J. Contact dermatitis from phenoxyethanol in aqueous cream BP. *Contact Dermatitis* 1984; 11: 187.
77. The Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers. Opinion concerning methylidibromoglutaronitrile, COLIPA no. P77, adopted by the SCCNFP during the 20th plenary meeting of 4 June 2002. European Commission, 2002.
78. Senff H, Exner M, Gortz J, Goos M. Allergic contact dermatitis from Euxyl K 400. *Contact Dermatitis* 1989; 20: 381–382.
79. de Groot A C, de Cock P A, Coenraads P J, van Ginkel C J, Jagtman B A, van Joost T, Joost van der Kley A M, Meinardi M M et al. Methylidibromoglutaronitrile is an important contact allergen in The Netherlands. *Contact Dermatitis* 1996; 34: 118–120.
80. Bruze M, Gruvberger B, Agrup G. Sensitization studies in the guinea pig with the active ingredients of Euxyl K 400. *Contact Dermatitis* 1988; 18: 37–39.
81. Hausen B M. The sensitizing potency of Euxyl K 400 and its components 1,2-dibromo-2,4-dicyanobutane and 2-phenoxyethanol. *Contact Dermatitis* 1993; 28: 149–153.
82. Wahlkvist H, Boman A, Montelius J, Wahlberg J E. Sensitizing potential in mice, guinea pig and man of the preservative Euxyl K 400 and its ingredient methylidibromoglutaronitrile. *Contact Dermatitis* 1999; 41: 330–338.
83. Tosti A, Vincenzi C, Smith K A. Provocative use testing of methylidibromoglutaronitrile in a cosmetic shampoo. *Contact Dermatitis* 2000; 42: 64–67.
84. Jensen C D, Johansen J D, Menne T, Andersen K E. Methylidibromoglutaronitrile in rinse-off products causes allergic contact dermatitis: an experimental study. *Br J Dermatol* 2004; 150: 90–95.
85. Cathelineau H. Note sur 18 cas d'accidents provoques par teinture pour cheveux a base de chlorhydrate de PPD. *Bull Soc Franc Syph* 1898; 9: 28–35.
86. Fregert S. [Chemical demonstration of paraphenylene diamine in hair dyes]. *Hautarzt* 1972; 23: 393–394.
87. Azua J. Dermatitis producida por una tintura de pelo (quinona resultante de la accion del agua oxigenada sobre el clorhidrato de parafenileno-diamina). *Actas Dermo-Sif* 1910; 2: 220–228.
88. Crain Communications Inc. *The Advertising Century* (available from <http://adage.com/century/people024.html>). 2006.
89. Hairproducts.com. *Hair Color* (available from <http://www.hairproducts.com/hair-color-loreal-clairol.html>). Springfield, 2006.
90. Sosted H, Hesse U, Menne T, Andersen K E, Johansen J D. Contact dermatitis to hair dyes in a Danish adult population: an interview-based study. *Br J Dermatol* 2005; 153: 132–135.
91. Conde-Salazar L, Baz M, Guimaraens D, Cannavo A. Contact dermatitis in hairdressers: patch test results in 379 hairdressers (1980–1993). *Am J Contact Dermat* 1995; 6: 19–23.
92. Guerra L, Tosti A, Bardazzi F, Pigatto P, Lisi P, Santucci B, Valsecchi R, Schena D et al. Contact dermatitis in hairdressers: the Italian experience. Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali. *Contact Dermatitis* 1992; 26: 101–107.
93. Frosch P J, Burrows D, Camarasa J G, Doooms-Gossens A, Ducombs G, Lahti A, Menne T, Rycroft R J et al. Allergic reactions to a hairdressers' series: results from 9 European centres. The European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis* 1993; 28: 180–183.
94. Armstrong D K, Jones A B, Smith H R, Ross J S, White I R, Rycroft R J, McFadden J P. Occupational sensitization to p-phenylenediamine: a 17-year review. *Contact Dermatitis* 1999; 41: 348–349.
95. Marks J G, Belsito D V, DeLeo V A, Fowler J F Jr, Fransway A F, Maibach H I, Mathias C G, Nethercott J R et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998; 38: 911–918.
96. Schnuch A, Uter W, Geier J, Gefeller O. Epidemiology of contact allergy: an estimation of morbidity employing the clinical epidemiology and drug-utilization research (CE-DUR) approach. *Contact Dermatitis* 2002; 47: 32–39.
97. Wahlberg J E, Tamella M, Anderson C. Contact allergy to p-phenylenediamine in Sweden. *Occup Environ Dermatol* 2002; 50: 51–54.
98. Lind M L. Dermatitis in hairdressers as a problem in chemical control. *Ann Occup Hyg* 2005; 49: 457–459.
99. Health and Safety Executive. *Health and Executive Statistics: Dermatitis and other Skin Disorders* (available from www.hse.gov.uk/statistics/causdis/skin.htm). London, 2006.
100. Uter W, Lessmann H, Geier J, Schnuch A. Contact allergy to ingredients of hair cosmetics in female hairdressers and clients – an 8-year analysis of IVDK data. *Contact Dermatitis* 2003; 49: 236–240.
101. Gruvberger B, Isaksson M, Dubnika M, Hindsen M, Pontén A, Svedman C, Bruze M. Patch testing with isothiazolinones. 8th Congress of the European Society of Contact Dermatitis. 13–16 September 2006, Berlin, Germany.
102. Felter S P, Ryan C A, Basketter D A, Gilmour N J, Gerberick G F. Application of the risk assessment paradigm to the induction of allergic contact dermatitis. *Regul Toxicol Pharmacol* 2003; 37: 1–10.
103. Dillarstone A. Cosmetic preservatives. *Contact Dermatitis* 1997; 37: 190.
104. Peters K-P, Peters K-P, Frosch P J, Uter W, Schnuch Typ-IV-Allergien auf Friseurberufsstoffe: Ergebnisse einer

- multizentrischen Studie in acht Kliniken der Deutschen Kontaktallergiegruppe und des 'Informationsverbundes Dermatologischer Kliniken' in Deutschland. *Dermatol Beruf Umwelt* 1994; 42: 50–57.
105. Schnuch A, Geier J. Glycerylmonothioglykolat-Sensibilisierung bei Friseurkunden. *Dermatol Beruf Umwelt* 1995; 43: 29.
106. Uter W, Geier J, Schnuch A. Downward trend of sensitization to glyceryl monothioglycolate in German hairdressers. IVDK study group. Information Network of Departments of Dermatology. *Dermatology* 2000; 200: 132–133.
107. Kist J M, el-Azhary R A, Hentz J G, Yiannias J A. The contact allergen replacement database and treatment of allergic contact dermatitis. *Arch Dermatol* 2004; 140: 1448–1450.
108. Uter W, Orton D, Perrenoud D, Schnuch A. Computers in the management of contact dermatitis. In: *Contact Dermatitis*, 4th edition, Frosch P J, Menne T, Lepoittevin J-P (eds): Berlin-Heidelberg-New York, Springer, 2006: 893–901.
109. Menne T, Wahlberg J E. Risk assessment failures of chemicals commonly used in consumer products. *Contact Dermatitis* 2002; 46: 189–190.

Address:

Jacob Pontoppidan Thyssen, MD
Department of Dermato-venerology
National Allergy Research Centre
Gentofte University Hospital
Ledreborg Allé 40, 1
2820 Gentofte
Denmark
Tel: +45 3977 7307
Fax: +45 3977 7118
e-mail: jacpth01@gentoftehosp.kbhamt.dk