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Hamnerius, Nils

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NILS HAMNERIUS
FACULTY OF MEDICINE | LUND UNIVERSITY

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Nils Hamnerius

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Faculty opponent
Professor Kristina Jakobsson
Department of Public Health and Community Medicine
University of Gothenburg, Gothenburg, Sweden

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Abstract

Hand eczema is common in healthcare workers. Besides wet work, healthcare work also implies exposure to contact allergens. Occupational hand exposures have changed in recent years owing to implementation of hand hygiene procedures including an increased use of medical gloves.

An increase of hand eczema caused by contact allergy to surgical gloves, in most cases owing to contact allergy to the rubber additive diphenylguanidine (DPG), was found in surgical theatre personnel (paper I). Most patients had worked with surgical gloves for decades, but their hand eczema was of recent onset. Contact allergy to DPG in medical gloves has previously been disputed, but in this study the presence of DPG in the patients' gloves was confirmed by chemical analysis.

In a questionnaire study distributed to healthcare workers in Southern Sweden (paper II) a 1-year prevalence of hand eczema of 21% was found. After adjustment for confounding factors a dose-dependent association with hand eczema was found for daily number of hand washes with soap at work, and for time working with medical gloves. No association was found between hand eczema and use of alcoholic hand disinfectant.

In a cross-sectional study healthcare workers with hand eczema were investigated (paper III). Occupational hand eczema was found in 62%. Of these 11% had occupational allergic contact dermatitis, in most cases caused by contact allergy to rubber glove additives. Occupational contact allergy to rubber additives was associated with sick-leave related to hand eczema

In an experimental study factors influencing DPG release from a polyisoprene rubber glove was investigated (paper IV). Alcoholic hand disinfectant prior to glove donning increased the amount of DPG recovered from the hands. Within 10 minutes more than 80% of available DPG was released from the glove into artificial sweat. Compared to a nitrile glove, proportionally more DPG was released into artificial sweat from the polyisoprene glove

Key words occupational dermatitis, healthcare worker, hand eczema, allergic contact dermatitis, rubber additives, diphenylguanidine, medical gloves

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Nils Hamnerius

LUND
UNIVERSITY

Faculty
Department

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Mieux vaut tard que jamais

Thesis at a glance

Paper	Objective	Method	Main findings/conclusion
I. Occupational allergic contact dermatitis caused by sterile non-latex protective gloves: clinical investigation and chemical analyses.	To investigate healthcare workers with occupational contact dermatitis caused by their rubber surgical gloves, and to describe a method for analysing the content of the allergens in the glove.	A case series of 16 healthcare workers patch tested with the baseline series, a rubber chemical series, and the patients' own gloves. A modified method for chemical analysis of the rubber additive diphenylguanidine (DPG) in the gloves was developed.	Contact allergy to DPG was a common cause of glove-related occupational contact dermatitis. Most patients had worked with surgical gloves for decades, but their hand eczema was of recent onset. DPG were detected at higher concentrations on the inside than on the outside of the culprit gloves.
II. Wet work exposure and hand eczema among healthcare workers - a cross-sectional study.	To assess the occurrence of hand eczema in healthcare workers. To assess skin exposures related to the mandatory hygiene procedures in healthcare work. To investigate relationships between wet work exposure and hand eczema.	An electronic questionnaire was distributed to hospital employees in southern Sweden. Questions included occurrence of hand eczema, occupational wet work exposures and a number of confounding factors. Relationship between hand eczema and wet work exposures was analysed with multivariate regression analysis.	The 1-year prevalence for hand eczema in healthcare workers was 21%. Working with non-sterile gloves and number of hand washings with soap was associated with hand eczema. No association was found between hand eczema and use alcoholic disinfectants.
III. Hand eczema and occupational contact allergies in healthcare workers with a focus on rubber additives.	To investigate the occurrence of occupational allergic contact dermatitis. To correlate identified contact allergies with the occupational exposures and with hand eczema	Healthcare workers were clinically investigated and patch tested with a special test series with allergens present in the gloves, soaps, alcoholic hand disinfectants, and hand creams provided at the hospitals.	Contact allergy to rubber additives in medical gloves was the most common cause of occupational allergic contact dermatitis. Contact allergy to DPG was as common as contact allergy to thiurams.
IV. Skin exposure to the rubber accelerator diphenylguanidine in medical gloves - an experimental study.	To assess if skin exposure to DPG released from medical gloves is influenced by alcoholic hand disinfectants, time and pH	DPG deposited on the hands was measured. Comparison was made between the hand exposed versus the hand unexposed to alcoholic hand disinfectant prior to glove donning. Assessment of DPG release from polyisoprene gloves to artificial sweat in relation to time and pH. Comparison of DPG release to artificial sweat from polyisoprene gloves versus nitrile gloves.	Alcoholic disinfectant prior to donning of polyisoprene gloves increased the amount of DPG recovered from hands. Within 10 minutes more than 80% of available DPG was released from polyisoprene gloves into artificial sweat. Proportionally more DPG was released into artificial sweat from the polyisoprene gloves than from the nitrile gloves.

List of publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Occupational allergic contact dermatitis caused by sterile non-latex protective gloves: clinical investigation and chemical analyses**
Pontén A, Hamnerius N, Bruze M, Hansson C, Persson C, Svedman C, Thörneby Andersson K, Bergendorff O. Contact Dermatitis. 2013 Feb;68(2):103-10

II. **Wet work exposure and hand eczema among healthcare workers - a cross-sectional study**
Hamnerius N, Svedman C, Bergendorff O, Björk J, Bruze M, Pontén A. Br J Dermatol. 2018 Feb;178(2):452-461

III. **Hand eczema and occupational contact allergies in healthcare workers with a focus on rubber additives.**
Hamnerius N, Svedman C, Bergendorff O, Björk J, Bruze M, Engfeldt M, Pontén A. Contact Dermatitis. 2018 Sep;79(3):149-156

IV. **Skin exposure to the rubber accelerator diphenylguanidine in medical gloves - an experimental study**
Hamnerius N, Pontén A, Björk J, Persson C, Bergendorff O. Contact Dermatitis 2019 Feb 6. doi: 10.1111/cod.13238. [Epub ahead of print]

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Abbreviations

CI	Confidence interval
D	Day
DPG	Diphenylguanidine
HPLC	High-performance liquid chromatography
IDRG	International Contact Dermatitis Research group
PPD	Paraphenylenediamine
UV	Ultraviolet light
wt	Weight

Background

Introduction

A prerequisite for the present project is the long tradition and the capacity at the departments of Occupational and environmental Dermatology, Malmö, and of Dermatology, Lund, of investigating occupational allergic contact dermatitis, performing advanced chemical rubber analyses, and the capacity to undertake extensive workplace investigations. The accumulation of healthcare workers with glove-related hand eczema, and the unexpected profile of contact allergies among the patients that are presented in paper I became an impetus for the present project. Were we actually witnessing a new epidemic of allergic contact dermatitis among healthcare workers? Could it be that a rubber accelerator regarded as obsolete in medical gloves now was of significance? We also had a hypothesis of changed chemical exposures in healthcare workers. Use of rubber gloves and alcoholic hand disinfectants had increased substantially in the last decades. Still, there was a lack of data regarding levels of exposures, on the occurrence of occupational hand eczema, and occupational allergic contact dermatitis in Swedish healthcare workers.

Terminology

Eczema and dermatitis

Scientific terminology should ideally be descriptive, stringent, and consequent. However, the emergence of terms, and especially diagnoses, has usually been a step-wise and changing evolution owing to changing conceptions of disease mechanism, cultural context, and traditions. Dermatitis literarily means inflammation of the dermis. Examples of inflammatory conditions engaging the skin are non-infectious conditions like eczema, psoriasis, lichen planus, but also infectious disease like impetigo or tinea represents dermatitis. However, in certain diseases the term dermatitis is used synonymously with eczema, like in irritant contact dermatitis, allergic contact dermatitis, atopic dermatitis. In these examples the denotation of dermatitis is unambiguous and stands for an eczematous dermatitis. In the literature these terms have become commonly used to denote these skin diseases. As for hand eczema, or hand dermatitis the situation is somewhat different. Hand eczema and hand dermatitis are often used synonymously, but occasionally hand dermatitis have

a wider meaning encompassing not only eczema but also psoriasis, pustulosis palmoplantaris, lichen planus, etc. Searches in PubMed and Embase databases (accessed 7 February 2019) indicates that "hand eczema" is about 1.5–2 times more frequent than "hand dermatitis".

Disinfection

Disinfection of hand has been discussed since the advent of asepsis and sterilization in the second half of 19th century (1, 2). However, WHO and Centers for Disease Control and Prevention (CDC), USA restrict the term disinfection to the elimination of pathogenic microorganisms on inanimate objects. and instead use the terms hand antisepsis, hand sanitizers, antiseptic hand rub and alcohol-based hand rub (3, 4). Still, in the medical literature the term hand disinfection and hand disinfectants are commonly used

Allergen

Allergens are substances that can induce an allergic reaction. A hapten is a small substance that by itself cannot induce an allergic reaction. Combined to a protein it will constitute a complete allergen that is capable to induce an allergic reaction (5). In the literature on contact allergy, substances that can cause an allergic contact reaction are often referred to as contact allergens irrespective of if they are a complete allergen or a hapten.

Rubber and elastomers

A number of terms are used for the denomination of rubber. Some of them were first picked up by the Spanish and Portuguese invaders in the Americas. *Caucho* (Spanish, *cautcho* in Portuguese) and *hule* (Spanish) derives from indigenous words for rubber encountered in the Americas of present Peru and Mexico respectively. *Kawchu* in Quechua language is said to stand for tears of the tree (6). In German and French *Kautchuk* and *cautchouc*, respectively are used for rubber. Gum (*goma* in Spanish and Portuguese, *gomme* in French), *Gummi* (in German and Swedish) derives from the ancient Greek *κόμμι* which probably has Egyptian origin (7, 8). It stands for any viscous exudate from plants, e.g. gummi arabicum, but is today usually used in the more restricted sense of rubber. Latex comes from Latin *latex* (running, water, liquid), possibly a loan from ancient Greek *λάταξ* (drop of wine) (9). Latex stands for milky sap of trees that coagulates in air or a water based emulsion, e.g. water-based paint (9, 10). Today latex is often used to denominate natural (vegetal) rubber in contrast to synthetic rubber. Originally, the word *rubber* stands for a cautchouc item used for rubbing out, or erasing, pencil marks (11). Equally *borracha* in Portuguese can signify both the rubber material and a rubber eraser (12). A polymer is a large molecule composed of many repeated subunits. Elastomers are defined as polymers that display rubber-like elasticity (13).

Donning

To don means to put on at piece of clothing, e.g. gloves. It is a contraction of the archaic expression "do on"(14).

In the present manuscript the terms contact dermatitis and atopic dermatitis, hand eczema, and hand disinfection/disinfectant are used. Latex is used in the restricted sense of natural (vegetal) rubber.

Detour into elastic matters and hygiene

Rubber

Rubber is an elastic material made of elastomers, either of plant origin or artificially made. By vulcanization the elastomers are cross-linked to improve performances and maintain the performances over a greater range of temperatures (15). In most instances the vulcanisation is brought about by addition of sulfur, and vulcanization accelerators and retarders are added to control the process. To reduce degradation by oxygen and ozone exposure antioxidants are added, and fillers, colouring agents etc. can be added to create the product wanted. Rubber gloves are produced by dipping hand shaped formers in liquid rubber solutions that are vulcanized to form the finished product (16). For surgical gloves, a coating can be added on the inside of the glove to facilitate glove donning.

Natural rubber is produced by at least 2500 species of plants (17). For industrial production of natural rubber, the sap (latex) from *Hevea brasiliensis* is the predominant source, although some rubber is produced from *Parthenium argentatum* (guayole rubber) (18). Natural rubber is almost completely composed of cis-1,4-polyisoprene, while gutta percha stands for plant-derived trans 1,4-polyisoprene. The polymers of synthetic rubber are based on raw materials of petroleum or natural gas origin. Examples are polychloroprene, polyisoprene and nitrile rubber. In contrast to natural polyisoprene rubber, synthetic polyisoprene rubber contains a small percentage of trans-polyisoprene (19), but is free from plant-derived so called latex proteins.

Rubber has been used for more than 3500 years in the Americas (20). Use of rubber products in other parts of the world started in late 18th century (21). One of the first medical applications was flexible catheters made of rubber (22). During the 19th century the main source of rubber was the Amazonas. Since the beginning of the 20th century large *Hevea* plantations in equatorial Asia and Africa have become the predominant producers of natural rubber (21). Around 1930 nitrile rubber, (acrylonitrile butadiene rubber) and polychloroprene were developed (23, 24). Although artificial polyisoprene was synthesised in laboratory already in 1880s (25), it was not until the 1960s that methods for production of polyisoprene with a

high level of the cis isomer were developed (24). Accelerators like metallic dithiocarbamates and their oxidation products, thiuram disulphides, and mercapotobenzothiazole have been used since the 1920s (26). Diphenylguanidine, synthesised in 1874, has also been used as an accelerator since the 1920s (26, 27).

Hand hygiene, disinfection and gloves

Hand washing has ancient traditions, not only for personal hygiene, but also for ritual purposes (3, 28-30). Although the concept of transmission of disease to the patient by the means of the caregiver's hands was described earlier (31-33), Semmelweis, in 1847, was the first to prove that hand disinfection could reduce morbidity and mortality in puerperal sepsis (34). The works of Pasteur and Koch laid ground for the aseptic technique with emphasis on preventing germs to be introduced in the surgical wound (2). In the last 2 decades of the 19th century sterilising of surgical instruments and dressings, clean or sterile gowns on the personnel, hand washing with soap, and use of antiseptic solutions including alcoholic solutions before surgery came into use (35-37).

The rationale for employing gloves in medical practice was primarily to protect the physician against contamination. In 1758 Walbaum used a partial glove (leaving the thumb and the second finger uncovered) made from ovine caecum when performing obstetrical procedures (38). In the end of the 18th century rubber gloves were recommended for gynaecological examination in patients with vaginal disease (38) and they were later recommended in dissections and post-mortem examinations to protect the surgeon from infections (39). However, the concept of gloves to prevent transmission of infection for benefit of the patient was proposed already in 1844 (40). In 1878 a patent was received for a method of producing rubber gloves for surgical use by dipping a former in a rubber solution (41). Anecdotal reports indicate use of rubber gloves in operating theatres round 1880 with object to protect the surgeon's hands in septic cases or against corrosive effect of disinfectants (38). The use of sterile surgical gloves began at some clinics in the late 1890s, but was subject to much debate (42-49). General use of sterile gloves in non-septic surgery was not the rule till after World War I (50). Until the 1960–1970 surgical gloves were sterilised and reused, but since then disposable, single-use gloves have become the standard. Non-latex examination gloves made from nitrile rubber were introduced in the beginning of the 1990s.

The preventive effect of rubber gloves on hand eczema was recognized early (51), while hand eczema caused by gloves was rarely reported during the first half of the 20th century. In 1933 Downing reported on 7 cases of dermatitis due to a particular type of rubber glove. Patch testing with a piece of glove for 24 hours was performed in 1 patient and 3 controls, and all 3 responded with dermatitis, which could indicate an irritant reaction. However, in 1 test the dermatitis developed 48 hours after the patch was removed, which is likely to indicate a delayed hypersensitivity reaction.

Neoprene (polychlorprene) gloves were recommended for surgeons with dermatitis caused by the surgical gloves in a report from 1943 (52).The first reports on contact allergy to specific accelerators, mercaptobenzothiazols, and thiurams were published in the middle of the 20th century (53 ,54).

Medical gloves made of natural rubber as well as of synthetic rubber are mainly produced in Southeast Asia, with Malaysia as the number one producer (55). From the beginning large-scale production of natural rubber has been associated with colonial economy, forced labour, poor conditions and human sufferings, including the atrocities of the Congo Free State (6, 21, 56-58). Even today the labour conditions in medical rubber glove production are controversial (59).

Hand eczema

By definition hand eczema engages the hands, but spread to wrists and distal arms is not uncommon. It is an inflammatory skin disease with varied clinical picture and in many cases with a chronic and relapsing course. In adults, the 1-year prevalence is about 10% (60-62). Hand eczema is more common in women and in young adults (61). In Scandinavia, the incidence of hand eczema has been estimated at 5.5–11.6 per 1000 person-years (63-65). Hand eczema can have considerable impact on the quality of life, and can result in high costs, both for the patient and the society (66-75).

Hand eczema can be caused by endogenous mechanisms or exogenous contacts. In the latter case this is due to either an allergic mechanism, or to irritant or toxic effects by the exogenous exposure itself (irritant contact dermatitis) that does not involve any hypersensitisation. In many instances there is a combination of mechanisms leading to and maintaining the hand eczema. Risk factors for hand eczema (Table 1) includes a history of atopic dermatitis, exposure to wet work, especially soap and water, as well as lifestyle factors. There are no universally accepted criteria for wet work, but a commonly used definition is based on German regulatory classification set by occupational dermatologists. It defines wet work as work more than 2 hours per day with the hands in a wet environment or frequent or intensive hand washing or wearing gloves with occlusive effect for a corresponding period (76). It has been proposed that frequent hand washing corresponds to > 20 times daily (77).

It is not possible to identify the causes of hand eczema by clinical picture only. For instance, rubber glove allergy typically causes eczema on the dorsal aspects of hands and wrists or lower arms (78), thus on locations often associated with irritant eczema (79). This emphasises the need to rule out possible component of allergic contact dermatitis in patients with suspected irritant or endogenous hand eczema.

Table 1 - Risk factors for hand eczema

Risk factor	Comment	Reference
Age	Decreasing hand eczema prevalence with increasing age	(60, 61)
Gender	Hand eczema is more common in women, but this gender difference is attributable to differences in wet work exposure.	(61, 62, 80) (62, 80, 81)
	Experimental data does not support any increased susceptibility to skin irritants in women	(82-84)
Atopic dermatitis	The odds ratio for hand eczema is aproximately 3–4 in individuals with a history of atopic dermatitis	(85-87)
Alergic asthma and/or rhinoconjuntivitis	If no concomitant history of atopic dermatitis, low or no increased risk for hand eczema	(63, 65, 88, 89)
Genetic factors other than atopy	Filaggrin gene loss-of-function mutations confer increased risk for irritant dermatits when there is a concomitant atopic dermatitis, but is probably not an independent risk factor for irritant dermatitis	(90-94)
	TNF-alfa gene polymorphisms are possibly associated with an increased susceptibility to irritant dermatitis	(95-98)
Wet work	Water, detergents, and metal working fluids are well-documented risk factors.	(64, 99-110)
	Occlusive gloves are possible risk factor, but data are ambigous	(104, 111, 112)
Mechanical friction	Mostly anecdotal reports. Could be a modifying factor in metalworking-associated irritant dermatitis.	(109, 110, 113)
Climate	Cold and low humidity	(114-116)
Exposure to contact allergens	In the sensitised individual, hand exposure to contact allergens confers a risk for hand eczema	
	Certain allergens carries a high risk for sensitisation: epoxy, (meth)acrylates, isothiazolinone group of preservatives, paraphenylenediamine, etc	(117-124)
Smoking	Possible risk factor, but data are ambiguous	(61,125-128)
Obesity	Possible risk factor, but data are ambiguous	(127, 129)
Physical exercise	In 1 study, hand eczema was less common in individuals reporting high physical exercise	(127, 130)
Stress	Possible risk factor, but data are ambiguous	(127, 129-131)

Atopic dermatitis

Atopic dermatitis is a genetically determined skin disease characterized by a dry skin and itchy dermatitis. In the Western world, the prevalence of atopic dermatitis has increased during the last 50 years. At present the lifetime prevalence is approximately 20% (132). It typically begins in childhood, but persistency into adulthood is common (132-135). In adult patients hand engagement is common (134, 136).

Irritant contact dermatitis

Irritant contact dermatitis is a non-allergic inflammatory condition, where the innate immune responses are primarily induced by the intrinsic toxicity of the causative chemical or by physical/mechanical irritation of the skin (137). It is often triggered by repetitive exposure to weak irritants such as water, detergents and solvents. The repeated insults lead to a disturbed epidermal barrier function and subsequent inflammation (138, 139). There is individual variability of the susceptibility to irritant exposure, which is at least in part genetically determined (Table 1). In experimental studies on irritant dermatitis, sodium lauryl sulfate, a common detergent in soaps, is frequently used to induce irritant dermatitis (140, 141).

Delayed contact allergy and allergic contact dermatitis

In contrast to irritant contact dermatitis, allergic contact dermatitis is dependent on prior sensitisation to the offending contact allergen. The most common immune mechanism is delayed hypersensitivity, or type IV-allergy. It is a T-cell mediated inflammatory reaction caused by low molecular weight (<500 Dalton) chemicals that can penetrate the stratum corneum (142). They are too small to provoke an immune response by themselves and are referred to as haptens (incomplete allergens). In the epidermis they combine with endogenous epidermal proteins, provoke an inflammatory response via innate immune system mechanisms and become recognisable by the epidermal antigen-presenting cells, i.e. Langerhans cells. An inflammatory response in the skin is essential to enable the Langerhans cells to mature and emigrate (143). The activated Langerhans cells then process and transport the allergen to the draining lymph node where they activate naive T-cells, leading to differentiation and clonal expansion of allergen-specific T-cells that are released into to the blood circulation (137). This induction of sensitisation, the sensitisation phase, usually lasts about 10–14 days, but sometimes longer. Once sensitised, new exposure to the allergen will elicit an inflammatory reaction. In the elicitation phase the Langerhans cells present the antigen to the antigen-specific T-cells. The activated T-cells trigger a cytokine-induce inflammatory process that results in a localized eczematous reaction, usually within 2–7 days, but sometimes later (144, 145).

Patch testing

Patch testing is the standard procedure to diagnose contact allergy caused by type IV-allergy. The patch tests are applied at the back of the patient on day (D) 0 and removed after 48 hours. Two patch test readings are recommended, usually D3 or D4, and D7 (146). Patch test results are scored according to the criteria of the International Contact Dermatitis Research group (ICDRG) (146,147). Much effort has been made to define the best test vehicle, test concentration and test volume for the test substances used, as well as exposure time and number and timing of the readings of tests, and this is an ongoing work as new allergens emerge (148-153). Apart from testing with defined test substances, based on the history of exposure, testing with ingredients in the patient's products, or with the products *per se* are commonly needed in the investigations of suspected allergic contact dermatitis.

Immediate contact allergy

Contact allergy caused by immediate IgE mediated allergy (type 1-allergy), is probably less frequent in healthcare workers than delayed type of contact allergy. In IgE-mediated allergy antigens usually are proteins. The antigens are recognised by the adaptive immune system which by subsequent events leads to production of specific IgE antibodies by B-cells. Upon re-exposure the allergen reacts with IgE on the surface of mast cells and basophils and provokes release of mediators like histamine within minutes to hours (154). The clinical manifestation is usually urticarial (immunologic contact urticaria), A more eczematous dermatitis can develop, so called protein contact dermatitis, often in settings with combined irritant exposure like food processing work (154, 155). The allergens are most commonly animal or vegetal proteins, including natural latex proteins in rubber gloves. IgE-mediated allergy is diagnosed by a positive skin prick test or/and identification of serum specific IgE antibodies.

Occupational hand eczema

Occupational disease is a disease caused or worsened by the working environment. Occurrence data on occupational diseases are dependent on regulations, which differ across countries. Conclusive Swedish data are lacking. In countries with more comprehensive reporting and registration of occupational diseases, occupational skin disease is among the most frequent occupational diseases and contact dermatitis constitutes about 90–95% of the cases (156-159). In Denmark contact dermatitis is the most frequently recognised occupational disorder, and around 70% are caused by irritant exposures (158). Occupations with frequent wet work and exposures to contact allergens entail an increased risk for occupational hand eczema.

Healthcare work and hand eczema

Healthcare work is regarded as a risk factor for hand eczema. A 1-year prevalence between 16% and 32% in healthcare workers has been reported in earlier Scandinavian studies (160-162), but there are no recent data in Swedish healthcare personnel. In part this variation of prevalence can be due to different study population selections and possibly different exposures. Healthcare work implies wet work and possible allergen exposures to the healthcare personnel. The chemical exposures in healthcare work have undergone considerable changes in the past decades. Apart from hand washing with soap, implementation of mandatory and more efficient hygiene procedures (163) has led to increased use of alcoholic hand disinfectants and disposable gloves. Based on purchase data there is a more than 10-fold increase of use of non-sterile nitrile gloves during the last decade (164). Allergic contact dermatitis in healthcare workers has been most commonly caused by contact allergy to medical gloves (165-167) and disinfectants including aldehydes (166, 168, 169). There are also reports on occupational allergic contact to chlorohexidine (170), and isopropyl alcohol (171). Preservatives and fragrances in soaps and emollients can also be the cause of allergic contact dermatitis (168).

Hand eczema in healthcare is problematic, not only because the impairment of the diseased and costs owing to treatment and sick leave. Of great concern is increased risk for increased carriage of potentially hazardous microorganisms including methicillin-resistant Staphylococcus aureus on eczematous skin of the hand, and the potential for infection transmission (172-176).

Medical gloves and glove additives

Medical gloves include non-sterile examination gloves and sterile surgical gloves, and are made of different polymeric materials (Table 2). Medical gloves are used to protect patients against spread of infection, thus medical devices, but also to protect healthcare personnel from microbiological agents and chemicals, thus personal protective equipment. The demands on gloves are various (177). Medical gloves shall be a barrier for microorganisms. The gloves shall be free from holes, and shall not break easily. For surgical gloves it is imperative that they are well fitting and do not interfere with dexterity. The elasticity of the material is thus more important for surgical gloves than for examination gloves. In laboratory work and when handling cytostatic drugs, the chemical resistance of the material is important. Ideally the glove shall not cause any adverse reactions. Examination gloves are by number the most used medical gloves. Not only has the use of examination gloves increased during the last decades, but in Swedish hospitals polyvinyl chloride examination

gloves have largely been replaced by nitrile rubber gloves which contributes to the great increase of exposure to nitrile rubber in healthcare work (178). There has only been a modest increase in the use of surgical gloves, but natural latex gloves have to a large extent been replaced by synthetic rubber (178).

Table 2 - Materials used for medical gloves

Material name	Chemical composition	Reference
Surgical gloves		
Natural rubber		
Natural (latex) rubber	Isoprene [a)]	(177)
Synthetic rubber		
Isoprene rubber	Isoprene [a)]	(177)
Chloroprene (trade name Neoprene)	Chloroprene	(177)
Styrenic block copolymers	Styrene-butadiene-styrene	(179)
	Styrene-isoprene-styrene	(179)
Examination gloves		
Natural rubber		
Natural (latex) rubber		(177)
Synthetic rubber		
Nitrile rubber	Acrylonitrile/butadiene	(177)
Plastic materials		
Polyvinyl chloride (PVC)	Vinyl chloride	(177)
Polyethylene (PE)	Polyethylene	(177)
Ethylene vinyl acetate (EVA)	Ethylene vinyl acetate	(177)

a) Natural latex rubber consists of almost 100% cis isomer, while synthetic polyisoprene rubber usually contains a small percentage of trans isomer.

Cutaneous side effects of medical gloves

Irritant contact dermatitis

Medical gloves exert an occlusive effect on the skin. The use of occlusive gloves more than 2 hours per day is included in the German wet work criteria described above (76). Skin occlusion leads to transient increase of the skin hydration, but if this perpetuates skin barrier function is disputed (180).

Physical urticaria

Tight fitting gloves can in disposed individuals elicit physical urticaria from pressure/friction (181-184).

Latex allergy

During the 1980s and 1990s an epidemic of IgE-mediated hypersensitivity to latex proteins in healthcare workers was seen. Not only contact urticaria and, eczematous protein dermatitis, but also rhinoconjunctival symptoms and asthma were seen (185, 186). Factors contributing to this were an increased use of disposable gloves as part of virus infection control programmes, use of gloves with high latex protein content, and a switch from talcum powder to starch powder in gloves (187). Starch powder stays in the air longer, and releases more easily adhered latex proteins than talcum powder. The powder was used to facilitate glove donning. After preventive measures were instituted, such as switching to non-powdered gloves made of non-latex materials or improved latex materials (188). IgE-mediated allergy to latex protein declined in the western world (186, 189-194). However, there are no recent data on the occurrence of IgE-mediated latex allergy in Swedish healthcare workers.

Allergic contact dermatitis

Glove-induced allergic contact dermatitis is caused by contact allergy to glove-related additives. During the manufacturing of rubber gloves the rubber polymer is blended with various additives, like vulcanizing agents, accelerators and retarders, antioxidants, pigments, biocides. Vulcanization is needed irrespective of the gloves are manufactured from natural latex rubber or synthetic rubber.

A number of glove additives can cause contact allergy (Table 3). Rubber glove contact allergy in general has most commonly been attributed to rubber accelerators like thiurams, dithiocarbamates, mercapto compounds, and to antioxidants derived from paraphenylenediamine (PPD) (195, 196). In medical gloves non-staining oxidants are usually used instead of the pigmented PPD derivatives (197). Accelerators of thioureas type, used in chloroprene manufacturing, and guanidines have been considered rare in medical gloves (196, 198). Rubber gloves are a major cause of rubber allergy, and especially thiuram allergy is associated with occupational contact dermatitis (199). In a Danish study the majority of cases with recognised occupational allergic contact dermatitis was related to rubber additives and epoxy. Of those with contact allergy to rubber additives (most commonly thiurams), 87% was related to glove exposure (158). In a study on reusable gloves 5 of the 6 patients with a positive test to rubber gloves tested as is had also a positive test to thiuram mix (200).

Thiuram disulfides and dithiocarbamates constitute a redox pair — dithiocarbamates are oxidised to the corresponding thiuram disuldfide and thiuram disulfides are reduced to the corresponding dithiocarbamates, and the real hapten remains unknown (201). Based on the chemical analyses and information from glove manufacturers, it appears that thiurams have to a great extent been replaced by dithiocarbamates in medical gloves (198, 202-204). However, in healthcare workers contact allergy to thiurams remains more common than contact allergy to

dithiocarbamates (165,169, 205, 206), although a downward trend of thiuram allergy has been reported by some authors (207-209). This supports studies that indicate that patch testing with thiurams are more likely to identify contact allergy to dithiocarbamates than are patch testing with dithiocarbamates themselves (201, 210).

Table 3 - Medical glove-related contact allergens

Glove additive	Reference
Rubber gloves	
Accelerators	
Thiurams	(211)
Dithiocarbamates	(202, 203, 211-213)
Mercapto compounds	(202, 203, 211)
Guanidines	(214, 215)
Thioureas	(197, 204)
Retarders	
Cyclohexylthiophtalimide	(216)
Pigments	
Pigment Blue 15	(217)
Donning agents	
Cetylpyridin chloride	(218, 219)
Plastic gloves	
Biocides	
Benzisothiazolinone	(220)
Antioxidant	
Triphenyl phosphite	(221)
Bisphenol A (vinyl glove)	(222)
Pigments	
Pigment Blue 15	(223)

Diphenylguanidine (DPG) is a well-known accelerator, but for a long time mostly reported as a contact allergen in non-glove rubber products, and regarded to play a minor role in medical glove allergy (198). Although not chemically related to dithiocarbamates DPG is part of the patch test mixture carba mix. Carba mix was formerly included in the Swedish and European standard series. In 1988 carba mix was removed from the European standard series as data had shown that many concomitant reactions with thiurams were frequent and very few cases of rubber allergy would be missed without carba mix testing (224). Furthermore, patch testing with DPG, as well as with carba mix has been considered problematic with a high risk for irritant patch test reactions (198, 210).

Starch or talcum powder is no longer used in order to facilitate glove donning. Cetylpyridinium chloride, a quaternary ammonium compound, has a lubricating

effect which can facilitate glove donning and is used in certain surgical gloves. There have been occasional reports on contact allergy to cetylpyridinium chloride in connection with surgical glove use (218,219).

Contact allergy to vinyl glove additives is rare, and only a few case reports can be found in the literature (Table 3).

In recent years accelerator-free gloves have been developed utilizing techniques without traditional sulfur-dependent cross-linking, e.g. ultraviolet (UV)-induced cross-linking. Furthermore, styrenic block copolymers can organize themselves in the form of elastic films without the use of any 'chemical crosslinking', and therefore do not need the use of any accelerators (179).

Pitfalls in diagnosis of rubber glove allergy

To investigate hand eczema in healthcare workers who uses disposable gloves, it is recommended to supplement the baseline series with test with the patient's own gloves *as is* (78, 225). However, a number of pitfalls need to be considered:

- Rubber additive or glove patch tests negative: true? - false?
- Rubber additive or glove patch tests positive: true? - false?
- If rubber additive patch test positive: present exposure?
- Labelling/information from manufacturer: missing? - correct? - incorrect?
- Chemical analyses of the glove do not confirm presence of suspected allergen: correct method of analysis? - sensitivity of method? - cross-reactivity?
- Chemical analyses of the glove confirm presence of suspected allergen: is the allergen released from the glove to the skin?

A negative patch test of gloves tested *as is* does not rule out the possibility of contact allergy, and test with extracts can possibly increase the sensitivity of testing (226). Extraction from an object, e.g. by ultrasound bath method, aims at obtaining a concentration of a possible sensitiser that allows for a positive patch test reaction to be elicited in a hypersensitive individual (227). A positive test to the patient's own glove *as is* or extract of the glove, usually confirms the glove allergy, and can be supported by a positive patch test of a rubber additive possibly present in the glove. However, it can occasionally represent a false positive reaction, e.g. an irritant reaction, and retesting and control tests on unexposed individuals may be needed (78). Furthermore, to be able to recommend gloves for the allergic patient, one must know which substance(s) in the glove that are the culprit. The number of possible glove additives in the baselines series is limited and extended testing with rubber additives or other substances is often needed. A positive test to a rubber additive might indicate the culprit allergen, but to verify

the relevance of the found allergy one must ascertain the presence of the chemical in the gloves. However, it is often hard to establish the presence of a certain accelerator in the glove. According to European regulation (228) labelling should include information on natural latex rubber, while information on remaining accelerators in the gloves are not required, but shall be disclosed on request. Furthermore, information is sometimes incomplete or inaccurate (229). Thus, chemical analysis is the most certain way to identify additives in gloves, but requires laboratory resources. Unfortunately, manufacturing procedures often changes, including use of accelerators etc, and older analyses data for a specific brand can be obsolete. Finally, if the suspected allergen is found in the glove, we must consider to what extent the skin is exposed. How long exposure to glove is needed to reach the threshold level of allergen exposure to elicit an allergic contact dermatitis? Are there other factors that can influence the allergen exposure from the glove? For instance, when clinically investigating healthcare workers with hand eczema the possibility of an interaction between alcoholic hand disinfectants and disposable glove is often brought up.

Aims

The aims of this study of hand eczema in healthcare workers are:

- To identify possible contact allergens in current occupational skin exposures with a focus on rubber glove allergens.
- To assess the prevalence of hand eczema.
- To assess the skin exposures related to the mandatory hand hygiene procedures.
- To investigate the relationships between wet work exposures and hand eczema.
- To investigate the frequency of rubber allergy.
- To investigate possible factors that could influence the skin exposure of the rubber accelerator DPG from commonly used medical gloves

Methods

Study I

Study participants

Case series of 16 patients investigated at the Department of Occupational and Environmental Dermatology, Malmö and at the Department of Dermatology, Kristianstad.

Patch testing

Patch test preparations

Patients were investigated according to the departments' routines for establishing allergic contact dermatitis with patch test with the Swedish baseline series, and based on the patient's history, aimed testing with additional series including rubber glove additives and their own gloves.

Patch test procedures

Patch tests were applied with Finn Chambers (Epitest OY, Tuusula, Finland) with an area of 50 mm^2, 20 mg of petrolatum test preparations and 15 µL of liquid test preparations were used (149, 151). Test reading was performed on D 3 or 4 and on D 7, and scored according to ICDRG recommendations (146, 147).

Chemical analyses

The medical rubber gloves were analysed by high-performance liquid chromatography (HPLC) with an UV diod array detector. For thiurams, dithiocarbamates and mercaptobenzothiazole derivatives analyses were performed with HPLC on a polyether ether ketone-lined C18 column eluted with a gradient containing acetonitrile aqueous zinc sulphate as previously described (203). Analyses of DPG and cetylpyridinium chloride were performed with HPLC on a cyano column eluted with a gradient consisting of a mixture of acetonitrile, methanol, and sodium acetate buffer, for details see Paper I. This method allowed

simultaneous identification of DPG and cetylpyridinium chloride. Different extraction media, including water, acetone and ethanol, were compared for the extraction of DPG and cetylpyridinium chloride.

Proportions of thiuram mix and DPG contact allergy

Patch test data on thiurams and DPG in consecutive dermatitis patients investigated because of a suspected rubber contact allergy were retrieved from the the patch test database of the Department of Occupational and Environmental Dermatology, Malmö. The proportions of thiuram mix and DPG contact allergy was calculated.

Study II

Study participants

E-mail addresses to all employees were obtained from the hospital administrations in the Southern Health Care Region of Sweden. An electronic questionnaire was distributed to 28762 hospital employees in 2014.

Questionnaire

An electronic questionnaire was constructed using a web-based application (Relationwise Survey Solution, Kundkoll Sverige, Siljansnäs, Sweden). Questions included hand eczema occurrence, occupational wet work exposures (use of soap, alcoholic hand disinfectants and medical gloves), wet work exposures outside work, gender, age, history of atopic dermatitis, life style factors, and perceived causes of hand eczema with regard to hygiene procedures. Questionnaires were distributed electronically, and non-responders received 2 reminders.

Statistical analyses

Possible associations between hand eczema and exposures were analysed with χ^2-test. For the multivariate analyses the exposures to non-sterile gloves, alcoholic hand disinfectants and hand washing with soap were each grouped into 3 levels, low, medium and high. Adjustments were made successively for occupational wet work exposure, age and gender, wet work exposures outside work, lifestyle factors and atopic dermatitis. Possible interactions between wet work exposures and atopic dermatitis were analysed by including a cross-product term in the fully adjusted

model. Statistical analyses were performed with IBM SPSS Statistics 22 (IBM Corp.).

Ethical approval

The study was approved by the Regional Ethical Review Board, Lund, Sweden (2013/151, 2014/339).

Study III

Study participants

Participants were recruited from the questionnaire study (Study II). In all 502 hospital employees investigated, including 311 healthcare workers with hand eczema within the past 12 months, and 114 healthcare workers with no history of hand eczema. The investigations were carried out in 11 hospitals by a mobile team from the Department of Occupational and Environmental Dermatology, Malmö during the autumn and winter 2014–2015. Biomedical scientists and assistant nurses performed patch testing, occupational dermatologists performed clinical examination and patch test readings, and logistics were the responsibility of a study coordinator.

Clinical examination

At the first visit patch tests were applied, blood samples were collected and the participants were asked to fill in a form on hand eczema history, if present hand eczema, and if the hand eczema influenced the performance of hygiene procedures (soap, alcoholic hand disinfectant or disposable gloves). At the second visit this form served as base for the medical history documented at the consultation.

At the second visit D3/D4, a defined order for the consultation was used. First the patch test was read, then clinical signs and extent of hand skin disease was recorded in a form, and only thereafter the history was discussed. The participants were informed not to discuss their history before the physician had finished the patch test reading and the clinical examination. If contact allergy was detected, participants received written information on the allergen(s).

At the third visit (D7) information on the result of the patch test was given, prescriptions were given when needed and the participant received a structured summary of the investigations including the cause(s) of the hand eczema, and an

information sheet on hand care and hand eczema treatment. If additional contact allergy was detected, participants received written information on the allergen(s). When necessary participants were referred to supplementary investigation and/or for further treatment.

Patch testing

Patch test preparations

A special aimed patch test series, based on a survey of potential allergens related to the present hygiene procedures, was established. All procured medical rubber gloves were analysed for rubber additives with HPLC. Rubber additives were included in the series based on previous and present analyses at the Department of Occupational and Environmental Dermatology, Malmö, as well as on literature data. Information on procured soaps and moisturizers were based on ingredient labelling. For the alcoholic hand disinfectants information was supplied by the manufacturers. Furthermore, all participants were patch tested with Swedish baseline series. For practical reasons test with the participants own gloves were not feasible in the study setting.

Patch test with DPG

In order to evaluate if a higher test concentration of DPG would identify more contact allergic reactions, participants were tested with both DPG 1.0% (Chemotechnique Diagnostiques, Vellinge, Sweden) and 2.0% pet (wt/wt) (prepared at the department). Control tests performed prior to the study did not indicate an increased risk of irritant reactions, for details see Paper III.

Patch test procedures

Patch tests were applied with IQ Ultra Chambers (Chemotechnique Diagnostics, Vellinge, Sweden) with an area of 64 mm^2, and 25 mg of petrolatum test preparations and 20 µL of liquid test preparations were used. Test reading was performed on D3 or D4 and on D7, and scored according to ICDRG recommendations (146, 147). The petrolatum test preparations, except for fragrance mixes I and II, were preloaded before testing and kept in a refrigerator. As many fragrance compounds are volatile (230), fragrance mixes I and II , as well as all the liquid preparations, were loaded into test chambers immediately before testing.

Specific IgE

Blood samples were collected and analysed for IgE specific for latex and chlorhexidine at the immunological laboratory at Labmedicin Skåne, Lund,

Sweden, with ImmunoCAP® (Phadia, Uppsala, Sweden) being used for analysis. IgE levels ≥ 0.35 kU/L were considered a positive test. If positive for specific IgE, the participant was recommended further investigation with skin prick test.

Statistical analyses

Two-sided Fisher's exact test was used for analyses of associations between contact allergies and hand eczema diagnosis, and hand eczema-related sick leave. Multivariate analyses were performed with adjustments for sex, age, and history of atopic dermatitis. Statistical analyses were performed with IBM SPSS Statistics 24 (IBM Corp.).

Ethical approval

The study was approved by the Regional Ethical Review Board, Lund, Sweden (2013/151, 2014/339).

Study IV

Study participants

The in vivo investigations were performed between 2014 and 2017 in the months of October till May with the participation of volunteers without hand eczema, recruited from Departments of Occupational and Environmental Dermatology, and of Dermatology, Malmö. The in vitro investigations were carried out from 2013 till 2018.

Comparison of DPG-release from gloves to hands exposed versus unexposed to alcoholic hand disinfectants

Alcoholic hand disinfectants with and without humectants were applied to one hand but not the other before glove donning (Fig 1A). After 60 minutes the gloves were removed and the hands inserted in a 1 L polyethylene bag and washed with 50 mL ethanol 50% in water (wt/wt) for 60 seconds (231, 232) (Fig 1C). The ethanol-water wash liquid was analysed for DPG and comparisons between hands exposed to alcoholic hand disinfectants and unexposed hands were made. Two brands of gloves, 1 surgical polyisoprene rubber glove and 1 nitrile rubber examination glove, and 2 different alcoholic disinfectants procured by Skåne University Hospital, were used for the investigations. Previous HPLC analyses at our laboratory had shown

that both gloves contained DPG. There was about 8 times more DPG per gram of glove in the polyisoprene gloves. The glove time of 60 minutes was arbitrarily chosen. However, for surgical nurses use of sterile gloves for 1 hour or more is common and it is recommended to change surgical gloves after 90–150 minutes (233,234).

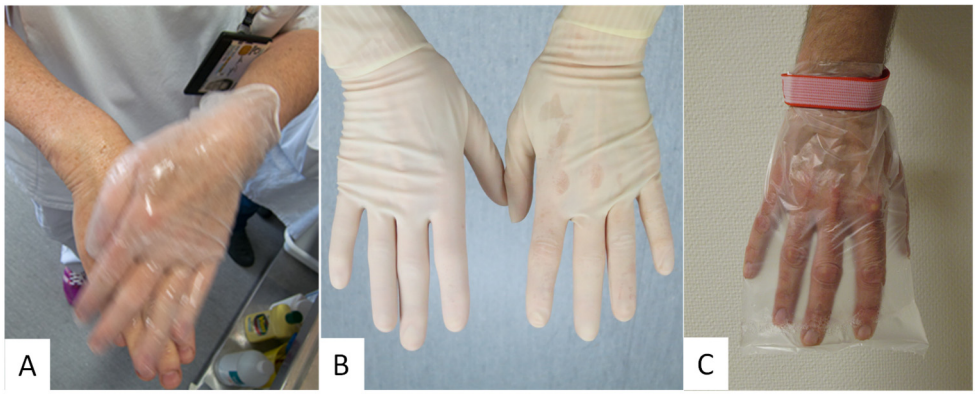

Figure 1 Comparison of DPG-release from gloves to hands exposed versus unexposed to alcoholic hand disinfectants prior to glove donning
A) Rubbing alcoholic hand disinfectant prior to glove donning. The hand unexposed to disinfecant is covered with a vinyl glove - B) Rubber gloves during 60 minutes - C) Ethanol-water hand wash in polyethylen bag.

Influence of time and pH on DPG release from the inside of gloves.

Polyisoprene gloves were filled with artificial sweat and samples were drawn after 10, 30, 60, and 180 minutes. The skin pH can vary between individuals in the range of 4 - 6 (235, 236). To assess a possible influence of pH the investigations were performed with artificial sweat buffered to pH 4, 5, and 6.

Proportion of DPG released from the gloves into artificial sweat

DPG was extracted from the gloves, first with artificial sweat for 180 minutes, then with 4 subsequent extraction cycles with ethanol 95%. The sum of DPG in artificial sweat and ethanol extractions was used to calculate the proportion of the DPG extracted from the gloves by artificial sweat.

Chemical analyses

Analyses of DPG were made by HPLC with a UV diod array detection on a C18 column eluted with a gradient consisting of a mixture of methanol and sodium

phosphate buffer, as previously described (215). The advantage of this method was a higher sensitivity for DPG than the method employed in study I

Statistical analyses

Comparisons between DPG recovered from exposed and unexposed hands were analysed with Wilcoxon signed rank test. Analyses were made both on recorded and on log-transformed data in order to investigate the robustness of the results. For correlation between pH of artificial sweat (3 ordered groups with pH 4, 5 or 6) and DPG extracted from gloves, Jonckheere-Terpstra test was used. Statistical analyses were performed with IBM SPSS Statistics 25 (IBM Corp.).

Ethical approval

The study was approved by the Regional Ethical Review Board, Lund, Sweden (2013/366).

Results

Study I

Contact allergy in healthcare workers

Of the 16 healthcare workers with contact allergy to their surgical gloves, 11 had worked more than 20 years in their present occupation, and in 13 the history of hand eczema was 1 year or less. Contact allergy to rubber accelerators was found in 15/16 (DPG in 12, thiuram mix in 8). Contact allergy to cetylpyridinium chloride was found in 7/8 tested, including 1 healthcare worker who did not react to any rubber accelerator. All cases with contact allergy to both DPG and cetylpyridinium chloride had been exposed to sterile rubber gloves containing these substances. Patch tests with gloves *as is* were positive in 10/15, and with extracts of glove in 8/9.

Chemical analyses of surgical gloves

DPG was found in 3 of the 5 investigated gloves. The 2 gloves without DPG contained dithiocarbamates. Mercapto compounds were found in all 5 gloves. No thiurams were detected in any of the gloves. Cetylpyridinium chloride was found in all 3 DPG-containing gloves. The concentration of cetylpyridinium chloride was higher on the inside of the gloves. For 2 of the DPG-containing gloves the concentration of DPG per area found on the inside of the gloves was about 10 times the concentration found on the outside. Extraction with water, and ethanol, respectively, was approximately twice as efficient as extraction with acetone.

Contact allergy to thiurams and DPG in dermatitis patients

Among the patients investigated at the department for suspected rubber-related dermatitis in 1997 to 2010 there was no change in the proportion of patients with a positive test to thiuram mix, whereas there was an increase in contact allergy to DPG between 2008 and 2010 as compared with the preceding years.

Study II

Hand eczema in healthcare workers

Response rate

The overall response rate was 43% (12288 of 28762). The main body of respondents (9313) reported their profession as nurse, assistant nurse or physician, and was selected for the subsequent analyses. Of these 262 had not answered questions on hand eczema and were therefore excluded from the analyses.

Hand eczema occurrence

The 1-year prevalence of self-reported hand eczema in healthcare workers was 21%. Hand eczema at some time in adult life was reported by 35% of healthcare workers.

Occupational wet work exposures related to hygiene procedures

On a daily basis, 30% (2682/9050) reported hand washing with soap >20 times at work, 45% (4053/8987) used alcoholic hand disinfectants >50 times, and 54% (3404/6292) used non-sterile gloves >2 hours.

Associations between hand eczema within the past 12 months and wet work exposures related to hygiene procedures

After logistic regression analysis, a dose-dependent association was found between hand eczema and time spent with non-sterile gloves. Equally, a dose-dependent association was found between hand eczema and the number of daily hand washes with soap at work. No association between hand eczema and use of alcoholic hand disinfectant was found. No association between hand eczema and number of non-sterile gloves was found. Odds ratios for adjusted data are presented in Table 4.

Associations between hand eczema and other risk or confounding factors

Based on logistic regression analysis, an association was found between hand eczema and a history of kitchen work >30 minutes per day, a history of atopic dermatitis, and obesity, respectively. A dose-dependent association was found between stress and hand eczema.

Perceived causes of hand eczema

The questions on perceived causes of hand eczema were answered by 43%-57% of the respondents with hand eczema within the past 12 months. Use of alcoholic hand disinfectant was regarded as a cause of their hand eczema by 47% (373/800), use of disposable gloves by 35% (367/1061), and hand washing with soap at work by 26% (210/810). There was dose-dependent association between exposure to hand

washing with soap and to report alcoholic hand disinfectant as a likely cause of their hand eczema (p for trend <0.001).

Table 4 - Associations between hand eczema and wet work
Comparison between healthcare workers with hand eczema within the past 12 months versus with no history of hand eczema - logistic regression analysis. Results are presented as odds ratios (95% confidence interval). Adjusted for daily number of hand washes at home, kitchen worktime, number of children ≤4 years old, body mass index, daily smoking, and stress.

		n = 3460
Exposure		OR (95% CI)
Disposable non-sterile gloves - time	Low (<1h/d)	1
	Medium (1–3h/d)	1,20 (0,97 - 1,50)
	High (>3h/d)	1,47 (1,14 - 1,88)
Hand washing with soap at work	Low (0–10/d)	1
	Medium (11–20/d)	1,33 (1,08 - 1,64)
	High (>20/d)	1,43 (1,12 - 1,83)
Alcoholic hand disinfectant use	Low (0–20/d)	1
	Medium (21–50/d)	0,82 (0,61 - 1,09)
	High (>50/d)	0,76 (0,56 - 1,03)

n = number ; d = day ; h = hour ; OR = odds ratio ; CI = confidence interval

Atopic dermatitis

A history of atopic dermatitis was reported by 22%. In this group, 34% reported hand eczema within the past 12 months versus 15% ($p < 0.001$) among those with no history of atopic dermatitis. No significant interaction between atopic dermatitis and occupational wet work exposures was found. When the group of healthcare workers were analysed separately, no association between hand eczema and occupational wet work exposures could be ascertained.

Study III

Occupational allergen exposures in healthcare work

Glove related additives

A total of 9 non-sterile examination gloves and 11 sterile surgical gloves supplied by the different hospitals of the Southern Health Care Region of Sweden were chemically analysed. Of the examination gloves, 7 were made of nitrile rubber, and

1 of natural latex rubber and 1 of polyvinyl plastic. Dithiocarbamates were found in all nitrile gloves, mercapto compounds were found in 1 nitrile glove and in the latex glove, and DPG was found in 1 nitrile. Furthermore, benzisothiazolinone was found in 2 nitrile gloves. Of the surgical gloves, 5 were made of natural latex rubber, 5 of synthetic polyisoprene rubber, and 1 of neoprene rubber. Dithiocarbamates were found in 3 latex and 4 synthetic polyisoprene gloves, mercapto compounds were found in 3 latex and 5 synthetic polyisoprene gloves, and DPG was found 3 in synthetic polyisoprene gloves. The polyisoprene gloves with DPG also contained cetylpyridinium chloride. In no glove thiurams were found.

Exposures related to soaps, alcoholic hand disinfectants and hand creams

According to labelling chlorhexidine was included in 1 disinfectant. Apart from monoalcohols, all alcoholic hand disinfectants contained humectants, glycerol or/and propylene glycol. Labelling indicated presence of fragrance in 3 products (2 soaps/wash creams, and 1 hand cream), a formaldehyde-releasing preservative, imidazolidinyl urea, in 1 hand cream, and sodium benzoate was 7 products (2 hand creams and 5 soaps/wash creams).

Contact allergy in healthcare workers

Among the 311 healthcare workers with hand eczema in the past 12 months, contact allergy to any glove-related rubber additives was found in 20, including 9 positive to DPG. All DPG-positive had been exposed to surgical gloves containing DPG. Patch test with DPG 1.0% was positive in 8 of 9. The participant with a positive test only to DPG 2.0% had a doubtful reaction to DPG 1.0%. Of the 9 healthcare workers with thiuram allergy, test with thiuram mix was negative in 3 participants who reacted only to 1 of the thiurams tested separately.

Of the 22 participants with occupational contact allergy, 17 had contact allergy to rubber additives. Contact allergies to any glove-related rubber additive or to fragrance mix I and/or II were significantly more common in healthcare workers with hand eczema in past 12 months compared with healthcare workers with no history of hand eczema (Study III, Table 3). Of the occupational contact allergies, 9 of 22 (41%) were found with the baseline series, whereas 13 of 22 (59%) were detected only by use of the aimed patch test series.

Participants allergic to any glove-related rubber additive were more often allergic to fragrance mix I and/or fragrance mix II and to preservatives than participants without contact allergy to glove-related rubber additives. No association was found between contact allergy to metals and hand eczema or contact allergy to glove-related rubber additives.

Clinical diagnosis of hand eczema in healthcare workers

Occupational hand eczema was found in 193 (62%). Of these, 22 (11%) had an occupational allergic contact dermatitis. More than 1 diagnosis was made in 51% of the participants with hand eczema within the past 12 months. A diagnosis of irritant contact dermatitis was made in 89%, endogenous dermatitis in 56% and allergic contact dermatitis in 8%. No association between a history of atopic dermatitis and a clinical diagnosis of irritant contact dermatitis or an allergic contact dermatitis was found (p (χ^2) 0.25 and 0.28, respectively).

Consequences of hand eczema in healthcare workers

Among the healthcare workers with hand eczema within the past 12 months, sick leave because of hand eczema was reported by 8%, and seeking medical care for hand eczema by 49%. Sick leave due to hand eczema was associated with contact allergy to glove-related allergens (adjusted odds ratio (confidence interval (CI) 95%) 5.6 (1.9–17.0), p 0.002), as well as to a diagnosis of allergic contact dermatitis (adjusted odds ratio (CI 95%) 5.1 (1.7–15.3), p 0.004). No association was found between sick leave and diagnosis of irritant contact dermatitis or endogenous dermatitis. When the hand eczema was most active, 71% found it difficult to use alcoholic hand disinfectant, whereas the majority had no difficulty in using disposable gloves.

Specific IgE

IgE specific for latex was found in 9/360 (2.5%) with hand eczema compared 1/113 (0.9%) of healthcare workers without hand eczema (p 0.46). Corresponding figures for IgE specific to chlorhexidine was 5/360 (1.4%) and 0/113 (p 0.60). All IgE levels found were <1 kU/L. All with positive test for IgE were invited to further investigation with skin prick test. Two participants with positive IgE test for latex were skin prick tested but no latex allergy could be ascertained. (In manuscript)

Study IV

Comparison of DPG-release from gloves to hands exposed versus unexposed to alcoholic hand disinfectants

With the polyisoprene gloves, statistically significantly more DPG was recovered from the hands exposed to versus unexposed to alcoholic hand disinfectants. An example of HPLC chromatogram is shown in Figure 2. DPG exposure from the nitrile gloves was very low and no difference between the hands exposed and unexposed to alcoholic hand disinfectants was found.

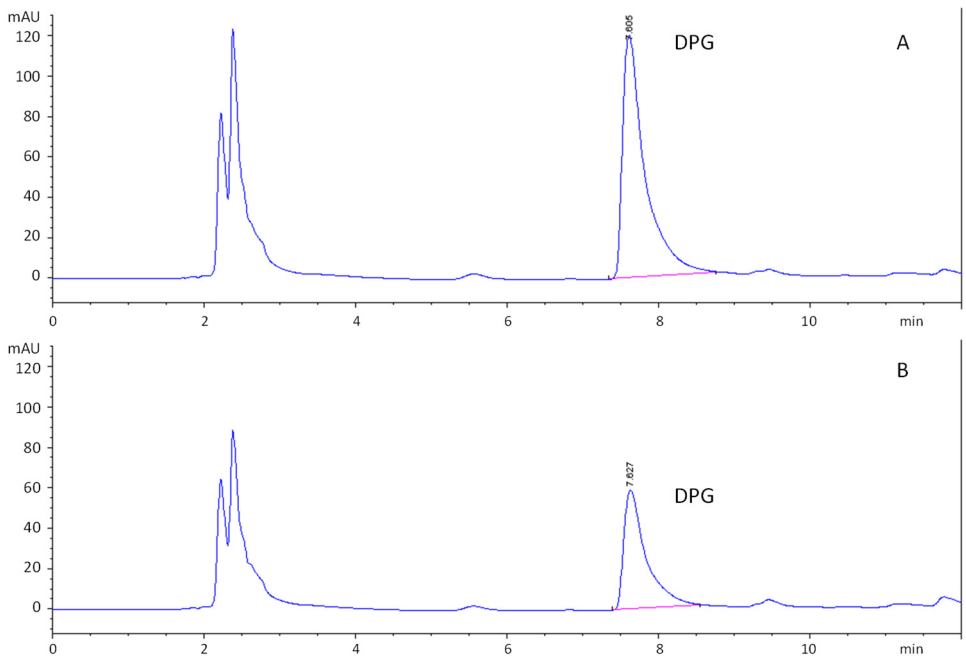

Figure 2 - Example of high-performance liquid chromatography analyses of diphenylguanidine in ethanol hand wash from hands exposed (A) and unexposed (B) to alcoholic hand disinfectant prior to glove donning

Influence of time and pH on DPG release from the inside of gloves

Of the DPG released from polyisoprene gloves into artificial sweat on 180 minutes, more than 80% was released within 10 minutes. pH did not influence the rate of release.

Proportion of DPG released from the gloves into artificial sweat

More than 70% of the total (artificial sweat plus 4 ethanol-water extractions) DPG from the polyisoprene glove was recovered in the artificial sweat fraction. From the nitrile gloves 0.3% of total DPG was recovered in the artificial sweat fraction. The mean amount recovered in artificial sweat was 811 μg/g for the polyisoprene gloves, and 1 μg/g for the nitrile gloves.

Discussion

Methodological considerations

Questionnaire studies in dermatology

Concern in formulating questions is necessary, especially in order to avoid ambiguous phrasing and double-barrelled questions. For study II questions on hand eczema, wet work exposures and history of atopic dermatitis was pivotal. For these issues we used questions that had been previously tried and where attempts at assessing of the validity of question had been made. The question on hand eczema within the past 12 months has been shown to underestimate the true prevalence (237,238). It has been shown that there is a risk to overestimate time exposed to wet work including use of gloves, and to underestimate frequency of exposures to hand washing with soap and use of alcoholic disinfectant (239-242). In a recent Danish study that compared observed and self-reported data, a multivariate analysis was made to examine impact of gender, age and prevalence of wet work (242). Workers older than 27.5 years underestimated duration of wet work compared with the younger workers. Females overestimated the frequency of hand washing and hand disinfection compared with males. In professions with a high prevalence of wet work exposure the duration was overestimated while the frequency of hand washes was underestimated. Hand disinfection was least overestimated compared with professions with a lower prevalence of wet work exposure. With regard to a history of atopic dermatitis the question "Have you had childhood eczema" was used. A validation study showed that this question may overestimate the prevalence of childhood atopic dermatitis. and may overestimate atopic dermatitis as a risk factor hand eczema. However, when applied on the assessment of 1-year prevalence of hand eczema, this question did not seem to overestimate atopic dermatitis as a risk factor (243).

The distribution method of the questionnaire can influence the results. Electronically distributed questionnaires save time and costs compared with paper questionnaires and can therefore be applied on large study groups. It eliminates manual data entry, which is time-consuming and carries the risk of incorrect entry of data. A disadvantage however, is that a lower response rate has been noticed in online compared with paper surveys (244). Likewise, there is balance between

mandatory questions to diminish missing answers and the risk of increasing drop-out rates associated with forced response in e-based surveys (245, 246).

In study II, the questionnaire was distributed in 4 administrative regions, 1 large, Regions Skåne, with approximately 20000 hospital employees, and 3 smaller regions with less than 3000 each. The response rate was higher in the smaller regions, about 50%, while 40% responded in Region Skåne. Within Region Skåne, the hospital with most employees had the lowest response rate (37%). This can be pure coincidence, or one could speculate if organisation structure might influence response rates. Furthermore, timing of distribution might influence the question on hand eczema. We studied the 1-year prevalence of hand eczema, and if eczema was not present at the time of the study, the respondent had to recall if she/he had had hand eczema within the past 12 months. Irritant dermatitis, the most frequent type of occupational hand eczema in healthcare workers, is more common in winter (114, 247, 248). The questionnaire was distributed in late spring and early autumn., which might increase the risk of recall bias.

The response rate carries a risk of skewed selection of respondents with regard to the prevalence of hand eczema. However, with regard to wet work exposures, it is not obvious that among the respondents without hand eczema only those with a low amount of wet work should chose to participate, or vice versa. Thus, it is less likely that a low response rate should lead to a bias of the associations between hand eczema and wet work exposures.

The robustness of patch test data.

Patch testing is the well-established way to diagnose contact allergy of delayed type. As mentioned earlier, much efforts have been made to standardise the patch test procedure concerning the optimal vehicle, dose of the test substance, and reading of the patch test. There are also test chamber systems with different designs available. Differences include materials (aluminium or plastic), volume, shape (round or rectangular). In some filter papers are only used for liquid haptens, but in some the filter papers is fixed with an adhesive and thus all haptens are applied on the filter paper. How these factors can influence the delivery of the hapten to the skin, as well as the reading and interpretation of the test reaction is not fully known.

Still even with standardised methods of testing, repeated testing shows that there is a variability of the test results. Possible factors that has been discussed with regard to this includes time of the year, concomitant disease, and hormonal influences in women (249-251).

In conclusion, both when interpreting and discussing questionnaire results as well as the occurrence of contact allergies one has to bear in mind the pitfalls and the limitations of the methods

Hand eczema prevalence

Study II. In the study 21% of healthcare workers reported hand eczema at some time within the past 12 months. This is consistent with other data of self-reported 1-year hand eczema in hospital personnel (161,162), and higher than the proportion of 11–12% reported in females in previous Swedish studies in the general adult population. (60, 61). This indicates that healthcare work entails an increased risk for hand eczema.

Exposures in healthcare workers

Wet work exposures

Study II. Comparison with older reports is hampered by different methods and study population selections. However, our figures on daily hand washing with soap at work, alcoholic hand disinfectant use and time with gloves are higher than reported in a previous Danish questionnaire study, which was also based on self-reported exposure data from hospital personnel (104). In that study 46–48% used alcoholic hand disinfectants > 20 times daily, and 30% used gloves occlusive gloves >2 hours daily compared with 85% and 54%, respectively, among our respondents This possibly indicates increased use of alcoholic hand disinfectants and disposable gloves during the last decade and hopefully reflects an increased implementation of the hygiene procedures.

Allergen exposures

Study III. As expected, the most apparent allergen exposure was related to additives in rubber gloves. The study confirms previous reports that thiurams are rarely encountered in medical gloves (202, 203). It is noticeable that benzisothiazolinone, which has previously been reported in vinyl gloves (220), was present in 2 of the non-sterile nitrile examination gloves. In contrast, according to European regulations, benzisothiazolinone is not allowed in cosmetic products, not even in rinse off products, owing to the risk of sensitisation (252). One could perhaps expect hospitals to be free of fragranced products, but according to labelling fragrance was present in 3 hygiene/hand care products supplied by the hospitals. Furthermore, during the investigation, we were often informed on the use of soaps and hand creams not supplied by the hospital administration. According to labelling some of these products contained fragrances. Given the high frequency of contact allergy to fragrances only fragrance-free products should be supplied at the workplace.

Wet work exposures and hand eczema

Use of occlusive gloves

Study II. Although use of disposable gloves has been associated with hand eczema in clinical investigations (104, 161, 253) and glove use > 2 hours daily is included in the definition of wet work in the German regulation, experimental data on the effect of glove occlusion has been conflicting (180). There are 2 observational studies where prolonged work with gloves did not alter barrier function (111, 112). However, in these studies glove use was not associated with frequent hand washing with soap. In our study, a dose-dependent association between hand eczema and time with glove was found, but not between hand eczema and daily number of gloves. This discrepancy as well as the dose dependent pattern of association indicate that occlusion by gloves could add to the risk for hand eczema in work that also includes soap exposure. The proposed time limit of 2 hours to define wet work seems reasonable as > 2 hours daily glove exposure was associated with increased odds for hand eczema.

Use of alcoholic hand disinfectant

Study II. Albeit a high exposure to alcoholic hand disinfectant, no association between the use of alcoholic hand disinfectant and hand eczema could be demonstrated. This supports experimental studies that indicates that alcoholic hand disinfectants are considerably less irritating than soap and water (254-257).

Hand washing with soap and water

Study II. The dose dependent association between occupational hand washing with soap and water is consistent with previous reports (104, 161). Therefore, it is of special concern both that hand washing > 20 times daily at work was reported by almost one third of the respondents (compared with 12–19% in the Danish study (104), and that there was a correlation between alcoholic hand disinfectant use and hand washing with soap. Already hand washing 11–20 times daily at work was associated with an increased odds ratio for hand eczema compared to hand washing <10 times daily at work (Table 4). This might be a reason to consider if an occupational hand washing frequency > 10 times daily is indicative of wet work.

Atopy and hand eczema

Study II. As expected, we found an association between hand eczema and a history of atopic dermatitis (87). There is 1 report that found that atopic dermatitis was only a risk factor at ages below 30 years, while in the age group 30–65 years no

association between atopic dermatitis and hand eczema was found (63). However, in study II, adjustment for age (or other risk factors) did not alter the association found between hand eczema and atopic dermatitis. According to the literature the increased risk for hand eczema is in part explained by the altered barrier function in atopic dermatitis and an increased susceptibility to irritant dermatitis (86, 258-261). Experimental studies often, but not always support this view (84, 141, 262-267). However, interaction analysis failed to demonstrate any increased effect of wet work exposures on the odds ratio for hand eczema in the atopic dermatitis group. This is in line with an older study that found that the relative increase of odds ratio for hand eczema was the same both in workers performing wet work and in workers performing dry work (85).

Study III. No association was found between atopic dermatitis and the presence of a contact allergy. Equally, no association was found between atopic dermatitis and glove-related allergy. Data on the risk for contact allergy in atopic dermatitis are conflicting. Some, but not all, studies have found an increased risk for contact allergy in individuals with atopic dermatitis (268). An impaired barrier could possibly facilitate allergen penetration into the skin, but there are also studies that indicates a reduced risk of contact sensitisation compared with healthy controls (269).

Importance of hand eczema in healthcare workers

Study II, Study III. Hand eczema impairs the work capacity, and it is of concern that it can cause non-compliance to hygiene procedures, especially the use of alcoholic hand disinfectants. Although alcoholic hand disinfectants have a low potential to cause irritant dermatitis, they sting, and stinging was more commonly reported among healthcare workers with hand eczema compared with those without hand eczema. Furthermore, the use of soap and water appears to be better tolerated with regard to stinging. Unrecognised or/and untreated hand eczema could lead to an increased use of soap instead of alcoholic hand disinfectants, and a subsequently aggravated eczema.

A history of sick leave owing to hand eczema was associated with allergic contact dermatitis, but no association was found with irritant or endogenous dermatitis. This is consistent with previous reports that found more time off work in allergic contact dermatitis compared with irritant contact dermatitis or atopic hand eczema (62, 270, 271), although there is 1 study on occupational hand eczema where presence of atopic dermatitis was associated with prolonged sick leave due to hand eczema (272). In the present study, contact allergy to rubber allergens, but not fragrances, was associated with sick leave. This highlights that glove-related contact allergy

could cause severe hand eczema that greatly impairs the working capacity of the diseased.

Allergic contact dermatitis in healthcare workers

Glove-related allergies

Study III. Rubber additive contact allergies were the most frequent occupational allergies detected, which shows that contact allergy to substances in gloves remains an important issue in healthcare work (165, 166, 205, 273-276). In 14 of the 17 participants with glove-related contact allergy, the allergic contact dermatitis was related to surgical gloves. In comparison, hospital purchasing data shows that the number of examination gloves procured is almost 20 times higher than the number of surgical gloves (personal communication).

Study I and III. The studies show that DPG is a relevant contact allergen in medical gloves and that contact allergy to DPG has become more frequent. There has been a concern of irritant reactions when patch testing DPG at 1.0% (198, 210), and it has been proposed to test with only 0.3%. We have patch tested DPG 1.0% and 2.0% with a defined amount of the test preparations. We did find doubtful reactions, but no test reactions to DPG fulfilled the ICDRG criteria for irritant reactions. We do not refute that a doubtful patch test reaction could be the result of either a very weak irritant effect or a very weak contact allergy, but in our experience irritant reactions when testing with 1.0% in petrolatum is not a great problem. We do not recommend patch testing with lower concentrations as this might reduce the detection of contact allergies. However, we did not find any advantage of patch testing DPG 2.0% over testing with 1.0%.

We found a thiuram contact allergy in 2% of all healthcare workers patch tested, all in the group of healthcare workers with hand eczema (Study III). This is higher than the prevalence of 0.2% reported in the general population from our region of Sweden (277), but lower than the 5%-12% reported in retrospective studies on healthcare workers investigated for eczema (165, 169, 205, 209, 278). The retrospective design can contribute to the higher frequencies found in these studies. A recent Danish report based on cross-sectional inclusion of participants found thiuram contact allergy in 5% (206). Previous reports have indicated a decrease in thiuram contact allergy among patch tested dermatitis patients (166, 208, 209, 279, 280). However, data from our department's patch test database did not indicate any decrease in thiuram allergy. Of note is that in study III, one third of the contact allergy to thiurams were not detected by thiuram-mix, only by patch testing with individual thiurams. One reason for this can be the higher test concentration used

for the separately tested thiurams, 1.0%, compared with the test concentration of 0.25% for each of the 4 thiurams in the mix. A negative thiuram mix patch test does not rule out thiuram contact allergy, and if there is a strong suspicion of glove-related hand eczema it is advisable to test with the individual thiurams (1.0%). The importance of identifying contact allergy to medical gloves must be stressed, as there is a good chance for hand eczema resolution if gloves without the offending additive can be provided (179). It must be stressed that in study I, while most of the healthcare workers had been working in operating theatres for many years, 11 of the 12 healthcare workers with DPG contact allergy presented with hand eczema of recent onset. Furthermore, 4 of those with recent onset of hand eczema had concomitant thiuram contact allergy. One can speculate if the development of a thiuram contact allergy was a secondary event to the hand eczema caused by the DPG contact allergy. As dithiocarbamates is common in surgical gloves, it is very likely that these workers had previously been exposed to dithiocarbamates without getting sensitised. Thus, contact allergy to more than 1 type of accelerator occurs, and preferably accelerator-free gloves should be supplied to healthcare workers with allergic contact dermatitis caused by rubber accelerators (179).

Rubber allergy of unknown significance

Contact allergy to cyclohexylthiopthalimide was found in 3 (1%) of the healthcare workers with hand eczema, and in 1 (1%) of the healthcare workers without hand eczema. Cyclohexylthiopthalimide was not identified in any of the gloves, and the relevance of these contact allergies could not be established. Medical glove-related contact allergy to cyclohexylthiopthalimide has been described (216, 281, 282), although information obtained from manufacturers indicates that it is not used in the production of gloves (283). It has been suggested that observed patch test reactions might be irritant and not allergic (282). In the European Chemicals Agency Registration dossier cyclohexylthiopthalimide is classified as skin sensitiser, and slightly skin irritating. Based on experimental data in rats on primary irritation it was categorized as "slightly irritating" (284). The source of cyclohexylthiopthalimide exposure is often unknow and remains to be clarified.

Other allergens

Disinfectants

Study III. There have been earlier occasional reports on isopropyl alcohol contact allergies, mainly when used in disinfectant swabs (285-288), but a more recent report has indicated that it might more common than previously thought (171), although this has been questioned (289). In the present study population, with a high

use of alcoholic hand disinfectants, no positive test reactions to any monoalcohols were found, indicating that sensitisation is uncommon. Chlorohexidine is mostly used for patient skin disinfection, but occurs in some hand skin disinfectants. In a recent Australian report 3% of 840 healthcare workers investigated for dermatitis had positive patch test to chlorhexidine that in the majority (2% of the tested) was found relevant to their dermatitis (170). However, we found no cases in the present study, which is consistent with a Danish study that found contact allergy to chlorhexidine to be rare (< 1%) (206). It is possible that this reflects different exposure patterns in different countries. Occupational contact allergy to didecyldimethylammonium chloride caused by exposure to surface disinfectants has been reported (290-292). In the present study 1 of the alcoholic hand disinfectant used at operating theatres contained didecyldimethylammonium chloride, but no contact allergy was detected.

Fragrances

Study III. Fragrance allergies were more common among healthcare workers with hand eczema than without, although no occupational contact allergy to fragrances could be ascertained. However, assessment of allergen exposure in fragrance allergy is difficult, and in the setting of the study aimed testing with individual fragrance substances was not feasible. The finding supports previous reports that hand eczema is associated with fragrance allergy (293-295). Of interest is the finding that contact allergy to fragrances were more common among those with contact allergy to glove-related rubber additives. Associations between fragrance contact allergy and allergy to epoxy, (296, 297), as well as allergy to preservatives (298) have been shown previously. It is not obvious that the simultaneous allergy to fragrances and rubber additives could be explained by similarities in chemical structures or by simultaneous exposure. The finding opens the question if previous allergy to fragrances can increase the risk of acquiring contact allergy to rubber additives or vice versa. This emphasizes that fragranced products should be avoided in hand hygiene and hand care products, especially in products for occupational use.

Immediate allergy

Study III. We found a low prevalence of specific IgE antibodies to latex and chlorhexidine in healthcare workers, and no cases of occupational allergy could be ascertained. The prevalence of specific IgE antibodies to latex was not higher than found in a previous study of blood donors in Sweden and Norway (299). This supports that the preventive measures for IgE-mediated latex allergy has largely been effective. It is well known that a clinical history is essential in establishing immediate hypersensitivity to latex and test results should not be used in isolation

for the diagnosis of latex allergy (300). The prevalence of clinical sensitisation may be over-estimated if only laboratory parameters are used (301).

Skin exposure from DPG in medical gloves

Studies I and IV. Alcoholic hand disinfectant prior to glove donning doubled the amount of DPG recovered on hands after working with isoprene gloves for 1 hour. Although there was an obvious variation between the individuals of the amount of DPG recovered from the hands, more DPG was consistently recovered from the hand exposed to alcoholic hand disinfectant than from the unexposed hand. The mechanism for this effect is unclear. DPG is easily dissolved in monoalcohols, and in study I we confirmed that ethanol is an effective extraction medium for DPG (302). Still, an extracting effect of the disinfectant monoalcohols is not obvious. At least in theory, the amount of monoalcohols left on the hand should be very low, as the disinfectant were rubbed on the hands till dry before donning. We noticed visually that the hand exposed to the alcoholic hand disinfectant appeared more humid under the glove, than the unexposed hand. Still, an increase in DPG recovered on hands was also noted in the comparisons made with the humectant-free alcoholic hand disinfectants. Thus, presence of humectant appears not to be needed for this effect, although an additional effect of the humectants cannot be ruled out, as indicated by our data.

We also studied a commonly used nitrile glove with a relatively low DPG-content compared to the polyisoprene glove, and no or very small amounts of DPG could be detected on the hands after using gloves for 60 minutes. Furthermore. in vitro extraction studies with artificial sweat from the inside of the gloves showed a striking difference between the polyisoprene and the nitrile gloves. While from the polyisoprene gloves approximately 70% of the DPG could be extracted with artificial sweat only 0.3% could be extracted from the nitrile gloves. Thus, for the skin exposure, not only the total content of DPG is of importance, but also factors related to the design of the gloves. We found that amount of DPG released from the inside of a similar polyisoprene glove was up to 10 times the amount released from the outside (study I). As DPG is added at the vulcanization process one would expect it to be rather evenly distributed in the glove material and not concentrated at the inside of the glove. It is likely that the higher amounts of DPG on the inside of the gloves are caused by an extraction effect of the cetylpyridinium chloride containing lubricant.

Long-time occlusion with gloves can increase the risk for irritant dermatitis (180), as well as glove-related allergen exposure. However, with the polyisoprene gloves

we studied, even short time use of gloves could lead to substantial allergen exposure — after only 10 minutes more than 80% of DPG was released into artificial sweat.

The variation between the participants of DPG recovered from the hands makes it likely that the exposure to DPG could be influenced by factors inherent to the subject using the glove. Potential factors contributing to this difference could be different constitutional humidity of the skin, skin temperature or pH. Although the solubility of DPG increases with pH in the range 4 to 6, the release of DPG from the gloves into artificial sweat did not differ between artificial sweat buffered at pH 4, 5 or 6. Furthermore, individual differences in absorption of DPG to the skin and in possible skin metabolism of DPG might contribute. In rats the rate of absorption of DPG is relatively slow and DPG seems to be rather stable on and in the skin (303). To our knowledge this has not been studied in humans, but if the animal data applies to humans, the possible impact of skin absorption and metabolism should be small when assessing the amount of DPG left on the skin after 60 minutes of glove exposure.

Summary and conclusions

The self-reported 1-year prevalence of hand eczema in healthcare workers was 21%, which is higher than the 1-year prevalence for hand eczema in the general Swedish population reported in previous studies. Healthcare workers reported high use of non-sterile examination gloves, and high frequencies of hand washing with soap, and alcoholic hand disinfectant use. We found a dose-dependent association between hand eczema and time with non-sterile examination gloves, and with number of hand washing with soap, but no association between use of alcoholic hand disinfectant and hand eczema was found. In healthcare workers with occupational hand eczema, 11% had an occupational allergic contact dermatitis, the majority owing to contact allergy to additives in their surgical gloves. The most frequent rubber allergies found were DPG and thiuram allergy. Both contact allergy to glove-related allergens and fragrance allergens were more common in healthcare workers with hand eczema than in healthcare workers without hand eczema. Although irritant contact dermatitis was the most common cause of hand eczema, it was not associated with sick leave. In contrast allergic contact dermatitis, and contact allergy to rubber gloves, were both associated with sick leave. This indicates that on group level occupational allergic contact dermatitis has comparably more impact on the work ability than irritant dermatitis in healthcare workers.

The observed increase of contact allergy to surgical gloves can most probably be related to the introduction of surgical gloves with a high content of DPG. Furthermore, the design of the gloves with an inside coating of cetylpyridinium

chloride is likely to have enhanced the skin exposure of DPG from the gloves. It is also possible that the rubber material itself can be of importance, as the proportion of DPG extracted into artificial sweat from a polyisoprene glove is considerably higher compared with a DPG-containing nitrile glove.

At the time of the investigation, the DPG-containing polyisoprene gloves constituted about 60% of the number of surgical gloves procured at hospitals in Region Skåne (personal communication). DPG-containing gloves are still on the market, and remains a current cause of occupational allergic contact dermatitis in healthcare workers (304), but as a consequence of our project, Region Skåne no longer procures gloves with DPG.

A change of work routines and introduction of new products can lead to considerable consequences for occupational health. The epidemic of latex allergy was related to the increased use of powdered latex gloves. On a smaller scale, in the present case, the introduction of a new brand of surgical gloves led to an epidemic of occupational hand eczema caused by rubber glove allergy in healthcare workers without previous hand eczema. With regard to contact allergy, nitrile examination glove does not seem to cause any large problem currently, although this was a hypothesis at the beginning of this project. However, it appears that the high exposure to examination gloves contributes to the risk for occupational irritant contact dermatitis. Longitudinal Swedish data on hand eczema occurrence in healthcare workers are not available. Data from the UK indicate an increase of occupational irritant contact dermatitis in healthcare workers (but not among workers in other occupations) parallel to the successive introduction of national level interventions to improve hygiene (305). Given the large number of individuals affected by these kinds of modification of work routines, a modest or even a small risk for occupational disease leads to consequences for many workers and workplaces. An analysis of possible occupational risk is warranted before the implementation of new routines. With regard to medical gloves better information on additives are needed. When assessing the safety of medical gloves, it would be preferable if this is not only based on the presence or the total content of added and remaining accelerators in the gloves, but also on knowledge of the potential skin exposure.

Hand eczema in healthcare workers implies a hygiene risk. The high level of soap exposure is a question of concern. Attempts to modify the behaviour and encourage skin protection by primary prevention campaigns have often resulted in rather modest and temporary effects (306-313). The effect of educational programs for secondary prevention is varying (314-319). Hand eczema is a treatable disease but treatment must be based on knowledge of the cause(s) of hand eczema on an individual basis. Long-standing eczema and delay in treatment initiation carries the risk of worse prognosis (271, 320, 321). As irritant and allergic contact dermatitis

can be indistinguishable clinically, proper examination including qualified investigations for contact allergy and treatment must be instituted promptly.

Sammanfattning på svenska

Handeksem är en hudsjukdom som tydligt påverkar livskvaliteten och många gånger är ett arbetshinder. I den vuxna befolkningen förekommer handeksem hos ca 10%. Utländska studier talar för att handeksem är ännu vanligare hos sjukvårdspersonal. Vad gäller sjukvårdspersonal har det saknats aktuella svenska data om hur vanligt handeksem är och vilka orsakerna till handeksem är. Förutom personligt lidande medför handeksem även kostnader för samhället p.g.a. behandling och sjukfrånvaro. Dessutom innebär handeksem hos sjukvårdspersonal en ökad risk för smittspridning inom sjukvården. På eksemsjuk hud bär man mer bakterier än på frisk hud. Handeksem försvårar också god handhygien, vilket är ett måste i sjukvårdsarbetet. Det finns flera möjliga orsaker till handeksem. Kontakt med kemiska ämnen som är nötande och irriterande för huden, t ex tvål och vatten, kan orsaka ett irritativt kontakteksem (icke-allergiskt kontakteksem). Vid ett allergiskt kontakteksem däremot, behöver inte det kemiska ämnet i sig vara irriterande, utan avgörande är att individen har utvecklat en överkänslighet (kontaktallergi) mot ämnet i fråga. Vid ny hudkontakt med ämnet gör kontaktallergin att det uppstår ett eksem. Handeksem kan också orsakas av att man har en medfödd benägenhet för eksemsjukdom. I det enskilda fallet är det ofta av en kombination av flera faktorer som leder till eksem.

Den yrkesmässiga exponeringen för kemikalier i sjukvården har på senare år förändrats, dels genom en ökad användning av engångshandskar och handdesinfektionsmedel (handsprit), dels genom förändringar av material i sjukvårdens handskar. Vid tillverkning av gummihandskar tillsätts olika kemikalier, bl.a. vulkaniseringsämnen, för att handsken skall få de egenskaper man eftersträvar. Kontaktallergi mot vulkaniseringsämnen av thiuramtyp har varit mycket vanligt vid allergiskt kontakteksem orsakat av medicinska gummihandskar, medan kontaktallergi mot difenylguanidin (DPG) har ansetts sällsynt.

Under senare år har vi på Yrkes- och miljödermatologiska avdelningen i Malmö och på andra sjukhus i Skåne sett en tydlig ökning av handeksem orsakade av engångshandskar som används vid sjukvårdsarbete. Denna ökning är utgångspunkten för det aktuella projektet där vi har undersökt hur vanligt handeksem är bland sjukvårdspersonal och vilka ämnen som orsakar handeksem. Ett speciellt fokus har varit kemiska ämnen i handskar.

I delarbete I. beskrivs 16 sjukvårdsanställda på olika sjukhus i Region Skåne med handeksem orsakat av kontaktallergi mot ämnen i deras operationshandskar. De flesta hade arbetat med operationshandskar i 10–30 år utan att få handeksem, och hade först senaste månaderna–året fått ett handeksem. Alla genomgick en yrkesdermatologisk utredning med test för kontaktallergi. Testningen omfattade även de aktuella operationshandskarna och en speciell serie med gummitillsattser. Handskarna analyserades kemiskt och en metod för kemisk analys av DPG i handskar togs fram. Kontaktallergi för thiuramer sågs hos 8 av 16 patienter, medan 12 av16 var allergiska för DPG. Samtliga med kontaktallergi mot DPG hade använt operationshandskar som innehöll DPG. Vid kemisk analys av dessa handskar fann man att mängden DPG var högre på handskarnas insida än på handskarnas utsida.

I nästa steg gjordes en undersökning av handeksemförekomst och orsaker till handeksem bland sjukhusanställda i Södra sjukvårdsregionen (Skåne, södra Halland, Kronoberg och Blekinge). En enkätundersökning (delarbete II) skickades ut till mer än 28 000 anställda på sjukhusen i Södra sjukvårdsregionen. Enkäten besvarade av drygt 12 000 (43%). I gruppen sjuksköterskor-undersköterskor-läkare (drygt 9 000) hade var 5:e haft handeksem senaste året. I samma grupp tvättade 30% händerna med tvål och vatten mer än 20 gånger per dag på arbetet, 45% använde handsprit mer än 50 gånger per dag och 54% använde täta handskar mer än 2 timmar per dag. Ju oftare man tvättade händerna med tvål och vatten, desto vanligare var det att man hade handeksem. Ju fler timmar per dag man använde handskar i arbete, desto vanligare var handeksem. Däremot sågs inget samband mellan hur ofta man använde handdesinfektionsmedel och handeksem.

I delarbete III redovisas resultaten av en yrkesdermatologisk utredning av ca 500 sjukhusanställda i Södra Sverige. Alla allergitestades med en speciell testserie med allergiframkallande ämnen som fanns i de handskar, desinfektionsmedel, tvålar och handkrämer som var upphandlade i Södra sjukvårdsregionen. Bland de med patientnära arbete var irritativt kontakteksem den vanligaste orsaken till handeksem. Hos hälften var orsaken en kombination av irritativt kontakteksem, anlagsberoende handeksem och/eller allergiskt kontakteksem. Arbetsorsakade handeksem sågs hos 62%. Av de med arbetsorsakade handeksem hade 11% ett allergiskt kontakteksem. Den vanligaste orsaken till allergiskt kontakteksem var kontaktallergi mot gummitillsatser i operationshandskar. Kontaktallergi mot DPG var lika vanligt som kontaktallergi mot thiuramer. Kontaktallergi mot ämnen i tvålar och handdesinfektionsmedel var ovanligt. Sjukskrivning p.g.a. handeksem var vanligare hos dem med kontaktallergi mot handskar.

Delarbete IV var en experimentell undersökning av faktorer som kan påverka hur mycket DPG som frisätts från en operationshandske som innehåller DPG. Mängden DPG som kunde uppmätas på handen efter 60 minuters handskanvändning var högre om man hade använt handdesinfektionsmedel innan man tog på handsken, jämfört

med om man inte hade använt handdesinfektionsmedel. Undersökning av tidsförloppet för frisättning av DPG från operationshandsken till konstgjort svett visade att inom 10 minuter hade 80% av tillgängligt DPG frisatts. Vi jämförde också frisättning av DPG från operationshandsken som var tillverkad i isoprengummi, med frisättningen av DPG från en undersökningshandske i nitrilgummi. Resultaten talar för att en större andel av handskens DPG frisätts från polyisoprenhandsken jämfört med från nitrilhandsken. Det kan bero på skillnader i vilka övriga kemikalier som tillsätts vid tillverkningen av respektive handske, men man det kan också vara så att själva typen av gummi (nitril eller polyisopren) i sig har betydelse.

Det aktuella projektet visar att introduktion av nya arbetsrutiner liksom val av upphandlade produkter såsom handskar, kan medföra ogynnsamma förändringar av arbetsmiljön. När en möjlig arbetsrelaterad sjukdom uppstår, såsom handeksem, måste en adekvat utredning av orsakerna hos den enskilde medarbetaren genomföras. Det behövs kunskap om orsaken till handeksem, dels för rätt behandling av handeksem hos den drabbade, dels för att möjliggöra korrekta förebyggande åtgärder i sjukvårdsorganisationen. Ett exempel på det sistnämnda är att de medicinska engångshandskar som nu upphandlas i Region Skåne inte får innehålla DPG.

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