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PhD thesis

Exposure assessment in occupational contact dermatitis

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NATIONAL ALLERGY RESEARCH CENTRE

Exposure assessment in occupational contact dermatitis

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Preface

This thesis is based on scientific work carried out from May 2011 to May 2014 at the National Allergy Research Centre, Copenhagen University Hospital Gentofte, Denmark and the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Denmark. The study was funded by the Danish Working Environment Research Fund.

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Abbreviations

ACD – Allergic Contact Dermatitis
ACU – Allergic Contact Urticaria
DB – Danish industrial classification
DISCO – Danish International Standard Classification of Occupations
DCOIT – Dichloroisothiazolinone
GPMT – Guinea Pig Maximization Test
HRIPT – Human Repeated Insult Patch Test
ICD – Irritant Contact Dermatitis
IgE – Immunoglobulin E
INCI-name – International Nomenclature of Cosmetic Ingredients-name
KC – Keratinocytes
LLNA – Local Lymph Node Assay
LC – Langerhans Cells
MC – Mast Cells
MCI – Methylchloroisothiazolinone
MCI/MI – Methylchloroisothiazolinone / Methylishothiazolinone
MI – Methylisothiazolinone
MSDS – Material Safety Data Sheets
NACE – Nomenclature générale des Activités économiques dans les Communautés Européennes
OCD – Occupational Contact Dermatitis
OIT – Octylisothiazolinone
OICD – Occupational Irritant Contact Dermatitis
OACD – Occupational Allergic Contact Dermatitis
OSD – Occupational Skin Disease
PR no – Product Register number
SCL - Specific Concentration Limits
Th – T-Helper cell
WEA – The Danish Working Environment Authority

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Abstract

Background Approximately 2,600 new cases of occupational skin diseases are reported annually to the National Board of Industrial Injuries in Denmark. Hand dermatitis is the most frequently reported skin disease. Those affected are often young persons under the age of 35 years, with women being affected twice as often as men. To classify whether the dermatitis is work related, an exposure assessment is necessary. An exposure assessment is facilitated by material safety data sheets (MSDS) and ingredients labelling, but these can be difficult to understand, incorrect, have missing information, and be insufficient.

Objectives To evaluate whether a systematic stepwise exposure assessment could aid in revealing patients with occupational allergy, to investigate whether MSDS contain information important for the diagnosis irritant contact dermatitis, to detect whether there are any specific shortcomings linked to the use of MSDS, and to map the product types containing the isothiazolinone preservatives with the aid of the Danish Product Register.

Methods We invited 316 patients with suspected occupational contact dermatitis seen at the Department of Dermato-allergology at Copenhagen University Hospital Gentofte, Denmark during January 2010–August 2011 to a clinical investigation. Of the 316 patients, 88 were excluded, leaving 228 in the study population. MSDS and ingredients labelling were reviewed for allergens and irritants, for constructing a tailored allergen test and for locating shortcomings in the MSDS. Information on products registered in the Danish Product Register (PROBAS) was obtained by using the chemical names and Chemical Abstracts Service (CAS) numbers for seven isothiazolinones.

Results We developed a systematic stepwise exposure assessment consisting of six steps. By using this tool, we found additional, relevant allergies in 36% of the patients. In total 132 different allergens were present in the work environment and relevant for the patients' dermatitis. Of these, 103 allergens were not included in the European baseline series.
No new irritants were found; however, we found that the patients diagnosed with occupational irritant contact dermatitis were in contact with the same allergens as were patients diagnosed with occupational allergic contact dermatitis.

Our medically oriented scrutiny of the MSDS revealed that 18.6% (137/738) contained errors or had missing information.
The seven known sensitizing isothiazolinones were found in many products registered for use in the work environment and could occur in high concentrations. Benzisothiazolinone was the most frequently used isothiazolinone: it was found in 985 products with a concentration range of 0.01ppm to 45%. The most frequent product type with one or more isothiazolinones was “paint and varnish”.

Conclusion A systematic exposure assessment has a significant, direct value for diagnosing occupational allergy and an indirect value for diagnosing irritant contact dermatitis by excluding allergy. MSDS rarely contain information relevant for the identification of irritants and are often insufficient in terms of medically relevant information regarding allergens. By using the Danish Product Register, we documented that exposure to isothiazolinones was widespread in many work-related products.
It is possible to improve the content and quality of the MSDS to make them effective tools in the diagnosis and prevention of occupational allergic and irritant contact dermatitis.

Introduction

The human body is a complex organism. The skin is part of the innate and adaptive immune system and provides first-line defence against dehydration, microbial and bacterial infections, and chemical and physical challenges (1;2). The skin is approximately 2 m^2. It consist of and an outer (epidermis) and an inner layer (dermis) (2). Everybody experiences daily skin contact with chemicals, both at home and at work. Some of these chemicals are skin irritants or skin sensitizers.

Hand dermatitis

Hand dermatitis is an inflammatory skin disease clinically characterized primary by erythema, infiltration, oedema and vesicles. The disease may change over time. Secondary characteristics are scaling, hyperkeratotic areas, fissures, erosions and bacterial infections (3). Clinically allergic contact dermatitis and irritant contact dermatitis may appear the same, making it difficult to distinguish one from the other (2).

If hand dermatitis persists for more than 3 months or if it returns twice or more within 12 months, it is characterized as chronic hand dermatitis (4). Chronic irritant contact dermatitis is mainly caused by contact with organic solvents, oil, detergents or water, for instance. The diagnosis is given if the dermatitis has persisted for longer than 6 weeks and if an allergy can be excluded, Figure 1 (5;6).

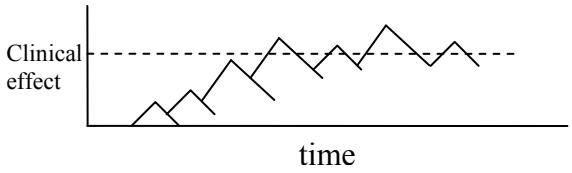


Figure 1. Shows consecutive, multiple contact to an irritant, developing into chronic irritant contact dermatitis. The figure is inspired by Malten K.E 1981 (6).

Hand dermatitis often becomes chronic and can lead to sick leave, change or loss of job or early retirement (7;8). Based on data from the year 2000 from Denmark, the annual direct cost of this disease is estimated at €133 million (9).

Skin allergy

In general, there are two phases in the development of contact allergy. The first phase is where the patient has skin contact with the allergen (also called a hapten when it is a low-molecular weight substance, which needs to bind to protein before becoming allergenic) for the first time: the sensitization phase. The second phase is where the patient has skin contact with the allergen for the second time and develops a flare up: the elicitation phase (2). There are four different types of immune defence response; in this thesis, only type I and type IV allergies are relevant. Type I allergy is immunoglobulin-E (Ig-E) mediated allergy, and type IV is cell-mediated immune response (2;10). Type I reactions are usually caused by proteins and induce the formation of IgE-antibodies by the plasma cells in response to the activation of the Th2 cells. The IgE antibody binds to mast cells and the next time the mast cell encounters the allergen, it releases histamine, which acts as the target tissue (10). The typical clinical skin reaction is contact urticaria. In type IV reactions the allergen penetrates the skin and is presented to the Langerhans cells (LC), which then migrate to the local lymph node where they present the allergen to the native Th1 cells. The new T_H-specified cells (memory- and effector cells) then migrate to the blood vessels. The next time the allergen penetrates the skin, the Th1-cells are triggered by the LC bound allergen; this activates the keratinocytes (KC), producing an inflammatory reaction (2). The typical clinical reaction is acute dermatitis. The typical substances causing type IV allergy are low-molecular weight chemicals. The potency of the individual allergen can be defined by clinical observations and experimentally by the Local Lymph Node Assay (LLNA) (11;12), and/or experimental induction studies in humans, Human Repeat Insult Patch Test (HRIPT) (13) and/or on other animal assays such as the Guinea Pig Maximization Test (GPMT) (14).

In 2006 the prevalence of contact allergy in adults in Denmark was 10.0% (15). There are various inherent reasons why some persons might become allergic more easily than others, for example, atopic dermatitis and/or mutation in the filaggrin gene (*FLG*) (16). These inherent causes are not discussed in this thesis.

Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) is an allergic inflammatory reaction of the skin. The clinical description of the disease can be seen in the section “Hand dermatitis”. Exposure to allergens can occur at home and/or at work. Exposure to allergens in the work environment can be during a manufacturing or work process (e.g. contact with raw materials in high concentrations), when

cleaning (e.g. contact with the detergents, concentrate or work solutions), through personal hygiene (e.g. contact with preservatives in liquid soaps, work solutions) or through allergens in personal protection equipment (e.g. accelerators in rubber gloves, work solutions). Allergic contact urticaria (ACU) may clinically be seen as immediate skin reactions or as dermatitis (protein contact dermatitis) and in this thesis is described under ACD.
Studies exist concerning exposures in persons in specific occupations, for example, hairdressers (17), metalworker apprentices (18), painters (19); and to different allergens, for example, foodstuff (20), linalool (21), epoxy resin (22;23), natural rubber latex (24).

Patch testing

Type IV contact allergy is diagnosed by the in vivo test named patch testing. A small amount of the suspected chemical, typically diluted in petrolatum, is applied to the upper back and occluded for 2 days. Reading is done on Day 2 (D2), D3/D4, and D7, according to the recommendations of the International Contact Dermatitis Research Group (ICDRG) (25). The reactions +1, +2 or +3 are interpreted as positive (+3 is the strongest reaction); +? is a doubtful reaction; IR an irritant reaction; and no reaction means the test is negative. Patients attending our department are routinely patch tested with the European Baseline Series, which at the time of this study contained 28 allergens, additional baseline series containing various preservatives and fragrances mandatory to declare on cosmetics.

Prick testing

Type I skin allergy is diagnosed by the in vivo test named prick test. This test is performed with standard allergen extracts of inhalation allergens, latex protein, chlorhexidine, persulfates and/or food proteins, for example, oat flour, wheat, chicken, eggs, raw cow's milk, rye flour. The test is done by applying a drop of allergen extract to the skin of the volar side of the lower arm and pricking using a lancet. Saline water is used as a negative control and histamine as a positive control. The test reaction is read after 15 minutes and is interpreted as positive if the diameter of the skin papule is larger than 3mm.

Irritant Contact Dermatitis

Irritant contact dermatitis can be defined as "a non-allergic inflammatory reaction of the skin to an external agent" (5). Irritant dermatitis is mainly caused by toxic chemicals but thermal, mechanical

or climatic effects can contribute to the reaction (5). Clinical irritant reactions may result from chemicals and can be divided into the following 11 groups: i) chemical burns, ii) irritant reactions, iii) chronic irritant contact dermatitis, iv) acute irritant contact dermatitis, v) contact urticaria, vi) acneiform eruptions, vii) miliaria, viii) alopecia, ix) pigmentary alterations, x) folliculitis and xi) granulomatous (5).

Some of the mentioned reactions are briefly described in the following. Chemical burns can be caused by acid or highly alkaline substances even through brief skin contact (Figure 2A). Irritant reactions are mainly caused by "mild irritants" after a longer skin contact (<1hour) or when there is a consecutive contact with the irritant, preventing the skin from fully healing (Figure 2B) (5;6).

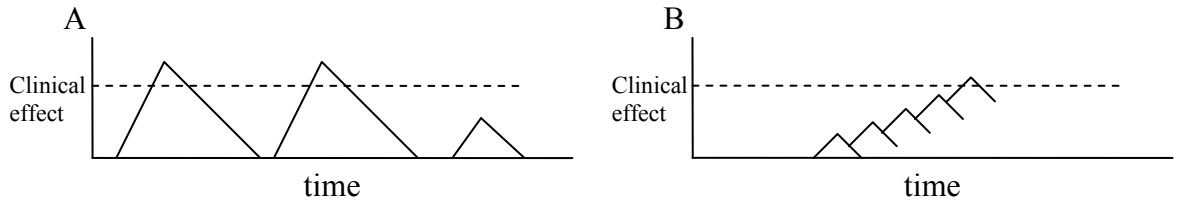


Figure 2. Fig A shows that a single contact with the irritant can give an irritant reaction e.g. contact with an acid and Fig B shows that consecutive contact with irritants can give an irritant reaction when the skin is not fully healed e.g. contact with oil products 5 times a day. The figures are inspired by Malten K.E 1981 (6).

There is no diagnostic test similar to the patch test to test for an irritant; accordingly, the diagnosis irritant contact dermatitis is based on the medical history, the morphology and on the exposure to allergens and irritants in the work environment.

Occupational Contact Dermatitis

Occupational contact dermatitis (OCD) is dermatitis caused or worsened by exposure in the workplace (26).

The National Board of Industrial Injuries receives annually approximately 2,600 new reports of occupational skin diseases (27;28). Occupational hand dermatitis frequently affects young people under the age 35 years, and twice as many women as men are affected(29).

Diagnosis

A correct diagnosis is crucial to the patient. The diagnosis affects treatment and prognosis (30-33). If there is a delay in diagnosing the patient's skin disease, it can lead to a worse short-term prognosis (34).

When a positive patch test reaction has been read, it is important to evaluate the clinical relevance (3). If a patient is allergic to 3 or more unrelated allergens, the individual is classified as having multiple contact allergies (35).

The diagnosis of occupational allergic contact dermatitis (OACD) is given when there is a positive patch test to an allergen found in one or more products/exposures in the workplace. In some cases the allergen is found in products used both at home and in the workplace.

The diagnosis of occupational irritant contact dermatitis (OICD) is given if an allergy can be excluded by a patch test and if the patient is exposed to a specific chemical with irritant properties or physical factors, such as cold, which match the criteria for irritant exposure (3).

The German guidelines for wet work are generally used by clinicians (36). The criteria for wet work are listed in Table 1. Wet work is defined as having hands in a wet environment for more than 2 hours during a working day, frequent hand washing or use of protective gloves for more than 2 hours during a working day (36) or change of gloves 20 times or more during a working day (3).

Table 1. Criteria for different types of irritant exposure leading to increased risk of contact dermatitis

Irritant	Criteria
Wet hands	2 hours during a working day (3;36;37)
Frequent hand washing	20 times or more during a working day (3;36)
Use of hand disinfectant	20 times or more during a working day*
Use of protective gloves	2 hours or more during a working day (36) (or) change of gloves 20 times or more during a working day* (3)

* The frequent use of hand disinfectants and change of rubber gloves 20 times during a working day comes from the frequent hand washing of 20 times during a working day set by the German guidelines from the TRGS 401 (36) and the Danish guidelines (3).

Exposure assessment

An exposure assessment is based on the medical history and knowledge of chemicals and allergens in the workplace, chemical analysis of products, spot tests (nickel (38) and cobalt(39)), air measurements (e.g. latex (40)), analysis of skin (e.g. nickel (41)) and/or visiting the work environment. It is pivotal that the physician has knowledge about exposures and chemicals so

he/she can ask the patient for detailed information about the work task. Such details can provide the missing link in locating the allergen, and even drawings can be helpful (42). The usual steps in an exposure assessment are shown in Table 2.

Table 2. Steps used in an exposure assessment

Step	Execution of step
1	Review of medical history
2	Review of products for allergens and irritants from home and workplace
3	Patch testing with individual allergen test
4	Chemical analysis of products
5	Diagnosis

In Step 1 the patient's medical history is reviewed, for example, when and where the dermatitis developed. The products and product labelling from the home and workplace together with the material safety data sheets are reviewed in Step 2. From the information gathered in Step 1 and 2, the individual allergy test is setup in Step 3 and the patient is tested. If a positive reaction is seen, for example, to nickel, cobalt or formaldehyde, a chemical analysis can be made in Step 4, for example, a nickel spot test (38) or a sweat test on the product (43), or if there is a positive reaction to a specific allergen, a chemical analysis can be done, for example, diethyl thiourea (44). In Step 5 the diagnosis is given.

Ingredients labelling

It is required by law in Europe that all ingredients used in cosmetic products be listed on the product, either on the packaging or on the product itself. The ingredients must be labelled with their International Nomenclature of Cosmetic Ingredients-name (INCI-name). If an INCI name has not been given to the substance, the manufacturer must apply for one, until then, another name must be used, for example, the chemical name. Mandatory labelling applies to only 26 of the more than 2000 known fragrance substances. If other fragrance substances are used, they are labelled as parfum or aroma (45). However, if the product is for industrial use, it is not necessary to put the ingredients list on the packaging, providing it is listed on material safety data sheets (MSDS).

Material Safety Data Sheets (MSDS)

According to the legislation, all chemicals and products marketed in the EU shall be classified according to the CLP before they can be launched on the marked (46). Unlike cosmetic products,

there is no legislation on full ingredients labelling on industrial products. Nonetheless, according to the legislation on classification, labelling and packaging of substances and mixtures (CLP) (46), a manufacturer of a product must develop MSDS for the specific product. According to the legislation of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (47), the MSDS must contain 16 sections about the composition, the physical- and chemical properties, and there are formal requirements to these sections. If a product contains one or more substances classified as allergenic in category 1 or 1B and the substance(s) is present in concentrations ≥1% by weight, the product shall be classified as allergenic and shall be labelled according to the regulations (47). The risk wording for an allergenic product is H317: "May cause an allergic skin reaction" and in the former classification system it was R43: "May cause sensitisation by skin contact" (47). If an allergen in Category 1 or 1B is present in a mixture in concentrations ≥0.1%, the product label and the MSDS must be labelled with the wording "Contains (name of sensitising substance). May produce an allergic reaction" (48). For substances classified as allergenic in Category 1A, the limit for classification and labelling of a mixture is 0.1% and the limit for the specific labelling wording is 0.01% (48). Some allergenic substances have a specific concentration limit (SCL) indicating the concentration above which a mixture shall be classified. For example, this applies to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), which has a specific concentration limit of 15 ppm. This means that chemical products containing MCI/MI in concentrations ≥15 ppm shall be classified and labelled as allergenic according to CLP (46). For these chemicals, there is a "self-classification" and it is the importer's and manufacturer's duty to classify these chemicals correctly (49). In the risk assessment of products it is often stated that products intended for human skin may contain extremely potent contact allergens, providing the exposure concentration are below a certain level (50). For some substances and products there is restriction on the use of these allergens. These restrictions are listed in REACH annex XVIII (47).

Shortcomings in the use of MSDS

Different shortcomings can arise in a stepwise exposure assessment and some of these are linked to the MSDS. The MSDS may be insufficient, incomplete and can be difficult to understand (51-53). As already mentioned, the MSDS does not provide information on all ingredients, only on those meeting certain criteria. When performing an exposure assessment, one of the major shortcomings is that not all known allergens are listed as hazardous or dangerous and not all have an individual concentration limit. Accordingly, not all allergens appear in the MSDS even if the allergen is used

in concentrations above the general limits or is used as a raw material, for example, formaldehyde (54). As exposures to allergens even at low concentrations can elicit an allergic reaction (55;56), detecting the culprit allergen is problematic when it is not listed in the MSDS. Consequently, allergens can be overlooked (52;57), affecting the outcome of the allergy test and, ultimately, workers' compensation.

The Danish Product Register – PROBAS

PROBAS is a database at the Danish Product Register where the composition of chemical products and substances for occupational use is registered, but only if they contain hazardous substances. The products are registered if (a) the product/substance annually is manufactured or imported for occupational use in quantities above 100kg, (b) the product contains at least one substance registered as harmful/dangerous according to the Danish Ministry of the Environment and the Danish Working Environment Authority (WEA), (c) the product contains ≥1% of the substance (for preservatives it is 0.1%), (d) an occupational exposure limit in the WEA list of limit values for substances and materials is assigned and/or (e) an occupational exposure limit in the WEA list of limit values for substances and materials is assigned and the material contains ≥1% of that substance (58). When a substance or product is registered in the database, it is given a product registration number (PR no).

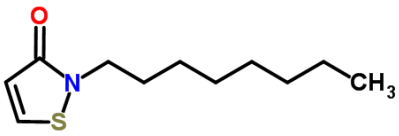
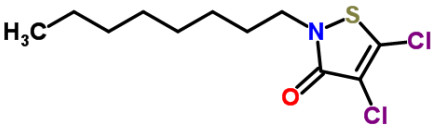
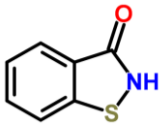
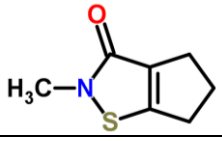
At the end of every odd-numbered year, the database is updated with data collected from the manufacturers in even-numbered years. If a specific product type contains products from fewer than three manufactures, the information on these products is classified as confidential.

All chemicals and products registered in PROBAS are categorised according to the Use Categories Nordic (UCN) code system (59). This system is used in the Scandinavian countries (Sweden, Norway and Denmark). The system consists of a main group with 3 characters; the subgroup has 6 characters: the first 3 characters are identical to those of the main group and the last 3 characters specify the subgroup. One substance can be given more than one UCN code.

Isothiazolinones

Isothiazolinones are biocides used in a wide variety of occupational and consumer products for more than 30 years (60). The six known sensitizing isothiazolinones are listed in Table 3 (61).

Table 3. The six known sensitizing isothiazolinones (61)

Substance	CAS no:	Structure
Methylisothiazolinone (MI)	2682-20-4	
Methylchloroisothiazolinone (MCI)	26172-55-4	
Octylisothiazolinone (OIT)	26530-20-1	
Dichlorooctylisothiazolinone (DCOIT)	64359-81-5	
Benzisothiazolinone (BIT)	2634-33-5	
2-methyl-4,5-trimethylene-isothiazolin-3-one (MTMIT)	82633-79-2	

There is a seventh isothiazolinone, which is a combination of methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) (CAS: 55965-84-9) and is used in a ratio of 3:1, with the commercial name Kathon CG. The isothiazolinones were recognized early as allergens with strong or extreme potency (62).

MI was introduced as a stand-alone preservative in the year 2000 and has largely replaced the use of MCI/MI. Isothiazolinones have been reported to cause allergy in painters (19;63-65), paint-production workers (66-68), and those in the paper and textile industry (69-72).

Benzisothiazolinone (BIT) and octylisothiazolinone (OIT) have been reported to cause contact allergy in metal workers (73). These 2 allergens have also been found in cooling agents (74). In a new study, 19 different water-based paints from the Danish retail market were analysed, all 19 paints contained MI, 16 contained BIT and 4 contained MCI (75).

Wearing protective gloves is a form of protection, but a recent study by Espasandin-Arias, M. and Goossens, A. from 2014 showed that MI can penetrate natural rubber gloves (76).
Chemical burns followed by sensitization can be the result of a single exposure to high concentrations of the isothiazolinones (77-82). Several accidental exposures to high concentrations might lead to generalised dermatitis together with systemic contact dermatitis and subjective symptoms (83). Both MI and BIT have been found to cause airborne contact dermatitis (63;83). It has been demonstrated that BIT, MCI and MI can evaporate from a painted surface (75).

The new epidemic – Methylisothiazolinone

In the last couple of years there has been an increase in cases of contact allergy caused by MI and MCI (69;83-87), and there is a current epidemic of contact allergy caused by MI (60;88-94). The most frequent source is cosmetics (92;93). MI is not listed as a dangerous or hazardous substance and has a "self-classification" with a concentration limit above or equal to 0.1% in industrial products (46). As mentioned earlier, MCI and MI can evaporate and cause airborne allergic contact dermatitis; this has been increasingly seen in paints preserved with MI (63-65;95).

Objectives

This thesis is based on descriptive clinical studies and one register study. The overall objective was to develop and evaluate a stepwise exposure assessment based on consecutive patients seen at the department of Dermato-allergology, Copenhagen University Hospital Gentofte, Denmark.
The aims were:

- To evaluate whether a stepwise exposure assessment could aid in revealing patients with occupational allergic contact dermatitis (Manuscript I)

- To identify the allergens causing occupational allergy (Manuscript I)

- To investigate whether MSDS contain information important for the diagnosis of irritant contact dermatitis (Manuscript II)

- To identify the irritants causing occupational irritant dermatitis (Manuscript II)

- To detect whether there are any specific shortcomings linked to the use of MSDS (Manuscript III)

- To map, by using the Danish Product Register, in which product types the potent allergens, the isothiazolinones, are used (Manuscript IV)

Manuscript I

Friis UF, Menné T, Flyvholm MA, Bonde JP, Johansen JD. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. Contact Dermatitis. 2013 Sep;69(3):153-63

Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment

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Summary

Background. Information on the presence of contact allergens and irritants is crucial for the diagnosis of occupational contact dermatitis. Ingredient lists and Material Safety DataSheets (MSDSs) may be incomplete.

Objectives. To evaluate the workability of a systematic exposure assessment in consecutive patients with suspected occupational contact dermatitis, and to study how it could potentially aid correct diagnostic classification.

Methods. A tool for systematic stepwise assessment of exposures in the work environment was developed, consisting of six steps spanning medical history and workplace visits. The programme included 228 consecutive patients diagnosed with occupational contact dermatitis; all patients underwent a clinical examination, the stepwise exposure assessment, and extensive patch and prick testing.

Results. Of the participants, 48.2% were classified as having occupational allergic contact dermatitis. The diagnosis was made at the stepwise exposure assessment for 50.0% of patients at Step 1 (medical history) and for 34.5% at Step 2 (ingredient labelling/MSDS). We found 132 different occupational allergens of relevance to the patients' eczema, of these, 78.0% were allergens not included in the European baseline series.

Conclusions. Systematic stepwise exposure assessment provides information that results in the identification of occupational allergies caused by allergens not included in the European baseline series in a substantial number of patients.

Key words: allergens; exposure analysis; occupational; occupational allergic contact dermatitis; occupational contact allergy; systematic exposure assessment; systematic stepwise exposure assessment.

Approximately 2000 new cases of occupational skin disease are reported annually to the National Board of Industrial Injuries in Denmark. The number of cases reported has increased since 2008, and reached 2660 in 2011 (1). Occupational hand eczema often affects young people under the age of 35 years, and women are affected twice as often as men (2). Hand eczema is often chronic, and can lead to job changes, job loss, or early retirement (3, 4). The cost of occupational eczema in Denmark is estimated to be approximately €133 million (~1 billion DKK) annually, on the basis of data from the year 2000 (5).

Comprehensive exposure assessment combined with patch testing is essential to establish the diagnosis of

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occupational allergic and irritant contact dermatitis. The correct diagnosis of patients is a fundamental requirement for clearing of the disease (6–8). Delayed diagnosis and treatment may lead to a worse short-term prognosis (9).

Exposure assessment is primarily based on the medical history and expert knowledge of the work environment. Tools that can be used in an exposure assessment are textbooks and reference books, product/ingredient labelling, databases (10), screening of the material safety datasheets (MSDSs), inspection of the workplace, chemical analysis, and measurements of airborne allergens. In some cases, skin exposure can be measured, and for some allergens a spot test can be performed.

Few studies have evaluated the performance of systematic exposure assessment in diagnosing occupational contact dermatitis, and they primarily addressed exposures in workers in specific professions, such as hairdressing apprentices (11) and metalwork trainees (12), or exposures to specific allergens, for example natural rubber latex (13), linalool (14), and epoxy resin (15, 16).

In this article, we present the results of a systematic stepwise exposure assessment in consecutive patients with suspected occupational contact dermatitis, using a set of predefined available tools.

Patients and Methods

Study population

The study included 316 patients with suspected occupational contact dermatitis seen in the Department of Dermato-Allergology at Copenhagen University Hospital Gentofte, Denmark, during January 2010 to August 2011, who were invited to the clinical investigation described below.

Of the 316 cases, 57 were of non-occupational origin and a further 31 were not patch or prick tested or did not show up for a complete examination, leaving 228 in the study population. The 31 cases did not differ significantly from the 228 with regard to sex and age. The Danish version of the International Standard Classification of Occupations codes (ISCO88) was used for classification of the occupation.

Exposure assessment

The systematic exposure assessment was organized in six steps (Fig. 1), and the results were structured in a standard form.

All patients were seen in the clinic by a dermatologist, and a thorough medical history was taken, including exposures at the workplace and at home (Step 1). The primary investigator (U.F.F.), who has a degree in chemistry, was either present at the consultation or contacted the patient afterwards for more detailed information.

Information was received from the patients about products used at home and at work, together with their lists of ingredients, use of protective equipment, and MSDSs. This information was analysed (Step 2).

If the contents of the MSDSs did not add up to 100% and if preservatives were not specified, or in the case of other incomplete information, the manufacture, supplier, salesperson workplace or the Danish Product Register Database was contacted to gather more information (Step 3). The Danish Product Register is a database where the full ingredient lists for products for professional use are registered if they contain one or more chemicals registered as harmful according to the Danish Ministry of the Environment. The manufacturer of the products supplies the Products Register with this information, so, in principle, the same information can be obtained from the manufacturer. The Product Register is described in more detail in Flyvholm et al. (17).

After patch/prick testing, exposures were again reviewed to determine whether an allergen or irritant had been overlooked, and, in the case of an unexpected positive result, to determine the relevance. If a positive patch test reaction to nickel (18), cobalt (19) or formaldehyde (20) was found, a spot test was performed (Step 4). If patients reacted to their own material (patch test or use test), it was sent for chemical analysis at the Danish Technological Institute or the Technical University of Denmark (Step 5). As Step 6, the workplace could be visited. The steps could be ordered differently if necessary.

Patch testing

All patients were tested with the European baseline series supplemented with allergens identified in the stepwise exposure assessment. The patch tests (Finn Chambers®, and TROLAB® or Chemotechique® patch test allergens) were applied to the upper back, fixed with Scanpor® tape, and occluded for 2 days. Readings were made on D2, D3 or D4, and D7, according to the recommendations of the International Contact Dermatitis Research Group (21). Reactions of strength 1+, 2+ or 3+ were interpreted as positive reactions. Irritant responses, doubtful responses (?+) or negative readings were interpreted as negative. If the patient was in contact with a known allergen not available from the suppliers of patch test material, we contacted the manufacturer or supplier to obtain a sample.

Prick test

Prick testing was performed with standard allergen extracts from ALK-Abello® (Hørsholm, Denmark).

		Yes	Not relevant
Step 1:	Medical History		
	- Exposure assessment of irritants and allergens	☐	☐
	o Products from workplace	☐	☐
	o Products from home	☐	☐
	- Protective equipment (e.g. gloves)	☐	☐
	Interview of the patient by a chemist	☐	☐
Step 2:	Review of product ingredient lists	☐	☐
	Review of Material Safety Data Sheets	☐	☐
Step 3:	Contact with manufacturer	☐	☐
	Contact with workplace	☐	☐
	Contact with the Danish Product Register Database	☐	☐
	Patch testing		
Step 4:	Spot tests	☐	☐
	- Nickel test	☐	☐
	- Cobalt test	☐	☐
	- Formaldehyde test	☐	☐
Step 5:	Chemical analysis of material/product	☐	☐
Step 6:	Visiting the workplace	☐	☐
Results: Clinically relevant exposure identified		Yes ☐	No ☐
		If Yes, at which step:_____	

Fig. 1. The stepwise exposure assessment.

These were an inhalation panel and food proteins – oat flour, wheat flour, chicken eggs, raw cow's milk, rye flour, soybeans, pork, and cod. Additionally, all those who used rubber gloves and had hand eczema were prick tested with natural rubber latex extract (500 μg/ml). Hairdressers were prick tested with serial dilutions of ammonium and potassium persulfate (0.1–2% in water) prepared at our own laboratory. Prick tests with other chemicals, such as chlorhexidine gluconate 0.5% in water, were performed on suspicion, and test preparations were prepared at our own laboratory.

The prick test was performed with a drop of allergen extract applied to the skin on the volar aspect, and pricked with a lancet (EWO Pricklancett; AB Nordic Medifield Service, Täby, Sweden). Saline water was used as a negative control and histamine as a positive control. The test reaction was read after 15 min, and considered to be positive if the diameter of the skin papule was > 3 mm.

In the case of occupational exposure to foods, most patients were tested with allergen extracts and the Gentofte Hospital standard fresh food series 'Fresh fruit and vegetables' and 'Fresh meat and fish', as described elsewhere (22). The test was performed as a prick–prick test, and results were interpreted as described above. If other foods not covered by the test series were suspected of provoking the skin symptoms, those foods were provided by the patients and used for testing.

Diagnosis

On the basis of all the investigations, a final diagnosis was made by the treating dermatologist according to the clinical guidelines from the Danish Dermatological Society (23). The criteria for occupational allergic contact dermatitis were: (i) positive patch test reaction to a substance present at the workplace; (ii) skin contact

with the substance at the relevant skin area; and (iii) sufficient exposure intensity and duration to explain the dermatitis. If allergic contact dermatitis could be excluded and there was significant exposure to irritants, occupational irritant contact dermatitis was diagnosed. Protein contact dermatitis was diagnosed if the patient had eczema and relevant positive prick test reactions to proteins such as foods and latex (22).

In this study, patients were classified as having either allergic contact dermatitis or irritant contact dermatitis. Individuals with both diagnoses were classified as having allergic contact dermatitis only.

The step of the systematic exposure assessment at which the exposure relevant for the diagnosis was identified was recorded.

Statistics

The data were processed in the Statistical Products and Service Solutions package (SPSS™ Statistics, Inc., Chicago, IL, USA; IMB PASW statistics) for Windows™, edition 19.0.

Chi-square tests were used to analyse differences in proportion between groups, and *t*-tests were used when continuous variables, for example age, were compared.

Results

The total study population

Occupational contact dermatitis was diagnosed in 228 patients, of whom 63.6% (145/228) were women, with a mean age of 35.6 years, and 36.4% (83/228) were men, with a mean age of 41.0 years. The top five professional groups in the study population were hairdressers (n = 32), chefs (n = 23), nurses and nursing assistants (n = 16), cleaners (n = 15), and painters (n = 12).

Of the patients, 34.6% (79/228) provided MSDSs, ingredient lists, or other types of product information.

Allergens

Of the patients included, 48.2% (110/228) were diagnosed with occupational allergic contact dermatitis; 64.5% (71/110) were women, with a mean age of 37.4 years, and 35.5% (39/110) were men, with a mean age of 42.4 years.

In 36% (82/228) of patients, additional allergies were found through the extended testing based on the exposure assessment.

In total, 132 different occupational allergens of relevance to the patients' eczema were found. Of these, 103 (78.0%) were allergens not included in the European baseline series.

The main additional allergens were: methylisothiazolinone (9 patients), oxidized linalool (7 patients), oxidized limonene (5 patients), *Evernia furfuracea* (treemoss) (5 patients), benzisothiazolinone (4 patients), persulfates (3 patients), bisphenol F (3 patients), 7-ethyl bicyclooxazolidine (Bioban CS-1246) (2 patients), and isophorone diisocyanate (IPDI) (2 patients). The steps of identification of the different allergens are shown in Table 1 (the European baseline series) and Table 2 (allergens outside the European baseline series). The 132 allergens were identified at different steps; the lowest step that was necessary for identification of the allergen are shown in Fig. 2. In 34.5% (38/110) of the relevant reactions, the allergens were identified by systematic work-up of the MSDS.

Of the 110 patients with occupational allergic contact dermatitis, 10.9% (12/110) reacted positively to a prick test with food, 4.5% (5/110) reacted to latex, and 2.7% (3/110) reacted to persulfates (ammonium persulfate and potassium persulfate). Of the patients, 0.9% (1/110) reacted with contact urticaria to a hair dye product, and 3 patients reacted to different chemicals (dimethyl fumarate, chlorhexidine, and didecyl-dimethylammonium chloride). See the different allergens in Table 3.

The top five professional groups among those with allergic contact dermatitis are shown in Fig. 3. Irritant contact dermatitis was diagnosed in 51.8% (118/228); this will be reported in a separate paper.

Steps

The diagnosis of allergic contact dermatitis was based on Step 1 (medical history) of the systematic stepwise exposure assessment in 50.0% (55/110) of cases, and on Step 2 (ingredient labelling/MSDS) in 34.5% (38/110); for 15.5% (17/110), further steps (such as chemical analysis) had to be performed to reach a conclusion. Spot tests for nickel were performed in 7 cases, and a relevant occupational exposure was detected in 2.7% (3/110). Cobalt spot tests were performed in 3 cases, with 0 relevant exposures. The formaldehyde spot test was performed nine times; in 8 cases, an occupational exposure was detected, and in 1 case a non-occupational exposure was detected.

Four products were sent for analysis (Step 5): two for the presence of diethyl thiourea (24), one for the qualitative analysis of nickel (25), and one for the presence of dimethyl fumarate. In all four cases, the allergen was found in the product. For insignificantly more women (60.6%; 43/71) than men (38.5%; 15/39), a conclusion was made at Step 1.

Table 1. Positive patch test reactions to allergens from the European baseline series, and the step of the systematic exposure assessment at which the allergen was found

Main group	Number of patients who reacted to the main group	Allergen	CAS no.	Number of patients who reacted to the allergen	Step at which the allergen was identified	Number of patients at the different steps
Preservatives	25	Formaldehyde	50-00-00	12	1	3
					2	1
					4	8
		Methylchloroisothiazolinone/ methylisothiazolinone	55965-84-9	10	1	2
					2	8
		Methyldibromo glutaronitrile	35691-65-7	3	1	3
		Quaternium-15	4080-31-3/51229-78-8	1	2	1
		Clioquinol	130-26-7	1	2	1
Rubber chemicals	19	Thiuram mix	NA	17	1	17
		Tetraethylthiuram disulfide	97-77-8	8	1	8
		Tetramethylthiuram monosulfide	97-74-5	4	1	4
		Mercaptobenzothiazole	149-30-4	4	1	4
		Mercapto mix	NA	3	1	3
		Tetramethylthiuram disulfide (TMTD)	137-26-8	2	1	2
		Dipentamethylenethiuram disulfide (PTD)	94-37-1	2	1	2
Fragrance	10	Fragrance mix I	NA	5	1	3
					2	2
		Fragrance mix II	NA	3	1	1
					2	2
		Evernia prunastri (oakmoss)	90028-68-5	2	1	1
					2	1
		Hydroxyisohexyl 3-cyclohexene carboxaldehyde	31906-04-4/51414-25-6	2	1	1
					2	1
		Isoeugenol	97-54-1	2	1	1
					2	1
		Myroxylon pereirae (balsam of Peru)	8007-00-9	2	1	1
					2	1
Metals	10	Nickel	7786-81-4	7	1	4
					4	2
					5	1
		Cobalt	7646-79-9	3	1	2
					2	1
		Chromium	7778-50-9	2	1	2
Other chemicals	8	Colophonium	8052-47-9	6	1	4
					2	2
		Sesquiterpene lactone mix	NA	2	1	2
Hair dyes	6	*p*-Phenylenediamine	106-50-3	6	1	5
					2	1
Epoxy chemicals	4	Epoxy resin	26875-67-2	4	1	1
					2	3
		p-tert-Butylphenyl glycidyl ether	3101-60-8	2	1	1
					2	1
Steroids	1	Budesonide	51333-22-3	1	1	1
		Hydrocortisone	50-23-7	1	2	1

NA, not available.

Table 2. Positive patch test reactions to allergens not included in the European baseline series and the step of the systematic exposure assessment at which the allergen was found

Main group	Number of patients who reacted to main group	Allergen	CAS no.	Number of patients who reacted to the allergen	Step at which the allergen was identified	Number of patients at the different steps
Preservatives	19	Methylisothiazolinone	2682-20-4	9	1	3
					2	5
					3	1
		Benzisothiazolinone	2634-33-5	4	2	3
					3	1
		7-Ethyl bicyclooxalidine	7747-35-5	2	1	1
					2	1
		Benzyl hemiformal	14548-60-8	2	1	1
					2	1
		3,3-Methylenebis(5-methyloxazolidine)	66204-44-2	2	1	1
					2	1
		Dimethyl oxazolidine [Bioban CS-1135(F)]	51200-87-4	2	1	1
					2	1
		Chloroacetamide	79-07-2	1	1	1
		Chlorhexidine diacetate	56-95-1	1	2	1
		Iodopropynyl butylcarbamate	55406-53-6	1	2	1
		DMDM hydantoin	6440-58-0	1	2	1
		Butylated hydroxytoluene (BHT)	128-37-0	1	1	1
		Tris(*N*-hydroxyethyl) hexahydrotriazine (Grotan BK)	4719-04-4	1	2	1
		Chlorocresol	1321-10-4	1	2	1
		Chloroxylenol	88-04-0	1	2	1
Oxidized terpenoids	8	Linalool	78-70-6	7	1	2
					2	5
		D-Limonene	5989-27-5	5	1	1
					2	4
Other chemicals	8	Abietic acid	514-10-3	2	1	1
					2	1
		Chlorphenesin	104-29-0	1	3	1
		Sorbic acid	110-44-1	1	1	1
		Allyl isothiocyanate	57-06-7	1	1	1
		Ginseng extract	NA	1	1	1
		White tea water extract	NA	1	1	1
		Potassium sorbate	24634-61-5	1	1	1
		Pyridoxine	65-23-6/8059-24-3	1	1	1
		Lanolin	8006-54-0	1	2	1
		Abitol	1333-89-7	1	1	1
		Cyclohexanone resin	NA	1	1	1
		Tosylamide/formaldehyde resin	25035-71-6	1	2	1
		Propyl gallate	121-79-9	1	1	1
Hair dyes and bleaching chemicals	7	Ammonium persulfate	7727-54-0	3	1	2
					2	1
		Toluene-2,5-diamine	95-70-5	3	1	3
		m-Aminophenol	591-27-5	1	2	1
		Resorcinol	108-46-3	1	2	1
		Hydroquinone	123-31-9	1	2	1

Table 2. *Continued*

Main group	Number of patients who reacted to main group	Allergen	CAS no.	Number of patients who reacted to the allergen	Step at which the allergen was identified	Number of patients at the different steps
Rubber chemicals	5	*N*-cyclohexyl-2-benzothiazolesulfenamide	95-33-0	3	1	3
		2-(4-Morpholinylmercapto) benzothiazole	102-77-2	3	1	3
		2,2′-Dithiobis(benzothiazole)	120-78-5	2	1	2
		Diethyl thiourea	105-55-5	2	5	2
Fragrance	5	*Evernia furfuracea* extract (treemoss)	90028-67-4	5	1	3
					2	2
Epoxy chemicals	5	Bisphenol F	28064-14-4	3	2	3
		Bisphenol A glycidyl methacrylate	1565-94-2	1	2	1
		m-Xylylenediamine	1477-55-0	1	2	1
		Phenyl glycidyl ether	122-60-1	1	2	1
		4-tert-Butylcatechol	98-29-3	1	2	1
Textile dye	3	Textile mix[a]		2	1	2
		Disperse Orange 1	2581-69-3	1	1	1
		Disperse Red 17	3179-89-3	1	1	1
Metals	2	Palladium	7440-05-3	2	1	1
					2	1
Isocyanates	2	Isophorone diisocyanate (IPDI)	4098-71-9	2	2	2
		4,4′-Methylenedianiline	101-77-9	1	2	1
		4,4′-Diphenylmethane diisocyanate (MDI)	101-68-8	1	2	1
Acrylates	2	*N*,*N*-dimethylaminoethyl methacrylate	2867-47-2	1	1	1
		2-Hydroxyethyl methacrylate	868-77-9	1	2	1
		Triethylene glycol diacrylate	1680-21-3	1	2	1
		Diethylene glycol diacrylate	4074-88-8	1	2	1
Foods	1	Belgian endive (Witloof)	NA	1	2	1
		Laurus nobilis	NA	1	2	1
Flowers	1	*Alstromeria aurea*	NA	1	1	1
		Trachelium caeruleum	NA	1	1	1

NA, not available.
[a]Supplied by courtesy of Bruze M and Ryberg K, Malmö.

Discussion

In this study, we organized the systematic exposure assessment for occupational contact dermatitis in six steps. In 36% (82/228) of patients, additional allergens not included in the European baseline series were found through additional testing based on the systematic exposure assessment. These additional allergens accounted for the majority of the allergens found to be of relevance to the patients' occupational eczema (78.0%, 103/132).

A conclusion was made for 50.0% of patients at Step 1 (medical history); for 34.5%, a conclusion was made at Step 2 (ingredient labelling or MSDS); and for 15.5%, further steps (such as chemical analysis) had to be taken to reach a conclusion.

For Step 2, patients should be instructed to collect all of the MSDSs and product labels from the workplace and home, and give them to the physician. This requires the physician to have specialist knowledge of both the legislation and the many different allergens, in order to correctly identify relevant exposures. Although many studies concentrate on occupational contact dermatitis, only rarely is it reported how the diagnosis was made, and even more rarely are reports given on work-up of the MSDS (26, 27). If Step 2 is neglected, relevant allergens will be overlooked, and patients will not receive correct information; accordingly, interventions may be inadequate. Another challenge in the exposure assessment is an incomplete MSDS, which is a substantial drawback for the dermatologist. In 2007, Keegel et al. (26) found that three of 100 MSDSs contained allergens that were clinically relevant to the patients' eczema. In 34.5% (38/110) of the patients in our study, we found allergens of clinical relevance in the MSDSs or ingredients lists. However, in 28 cases (137 MSDSs), the MSDSs were

Table 3. Positive reactions to prick test allergens or to a 20-min open patch test of occupational relevance

Main group	Number of patients who reacted to main group	Subgroup	Number of patients who reacted to subgroup	Allergen	Number of patients who reacted to the allergen	Step at which the allergen was identified	Number of patients at the different steps
Protein contact allergy	16	Natural rubber latex	5	Latex	5	1	5
		Food	12	Cod	4	1	4
				Tomato	4	1	4
				Potato	4	1	4
				Kiwi fruit	3	1	3
				Halibut	3	1	3
				Flounder	3	1	3
				Herring	3	1	3
				Wheat flour	3	1	3
				Lemon peel	3	1	3
				Lettuce	3	1	3
				Cress	3	1	3
				Shallots	3	1	3
				Chives	3	1	3
				Shrimp	2	1	2
				Chicken	2	1	2
				Salmon	2	1	2
				Turkey	2	1	2
				Pork fat	2	1	2
				Rye flour	2	1	2
				Orange peel	2	1	2
				Apple	2	1	2
				Celery	2	1	2
				Parsley	2	1	2
				Oatmeal	2	1	2
				Carrot	2	1	2
				Dried plum	2	1	2
				Kiwi peel	1	1	1
				Hazelnut	1	1	1
				Cinnamon	1	1	1
				Garlic	1	1	1
				Yellow onions	1	1	1
				Pork	1	1	1
				Beef	1	1	1
				Short pastry	1	1	1
				Soybean	1	1	1
				Watercress	1	1	1
				Basic cold wheat flour	1	1	1
				Dust-free wheat	1	1	1
Contact urticaria	7	Hair products	4	Ammonium persulfate (CAS no. 7727-54-0)	3	1	3
				Potassium persulfate (CAS no. 7727-21-1)	3	1	3
				Hair dye	1	1	1
		Disinfectant/ fungicides	3	Chlorhexidine digluconate (CAS no. 18472-51-0)	1	1	1
				Didecyl dimethyl ammonium chloride (CAS no. 7173-51-5)	1	2	1
				Dimethyl fumarate (CAS no. 624-49-7)	1	5	1

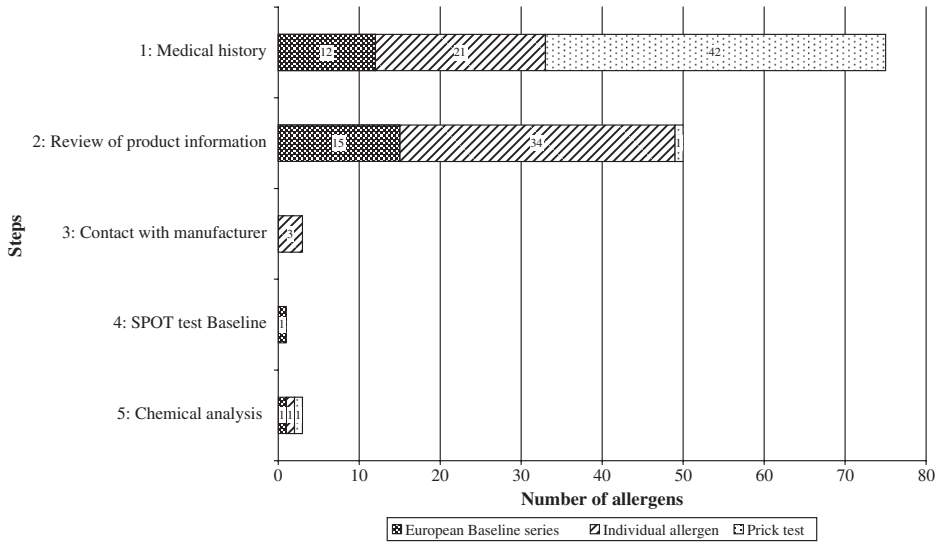

Fig. 2. Number of relevant allergens found at the different steps. In this graph, each allergen is presented only once. This means that if methylisothiazolinone was detected at Step 2 (ingredient labelling) in 1 patient and at Step 3 (contact with manufacturer) in another patient, it will appear only once on the graph, and at the highest step where it was detected. At Step 4 (spot tests), one allergen is registered, formaldehyde; nickel is registered only at Step 5 (chemical analysis), as in 1 case a chemical analysis was performed (guitar strings).

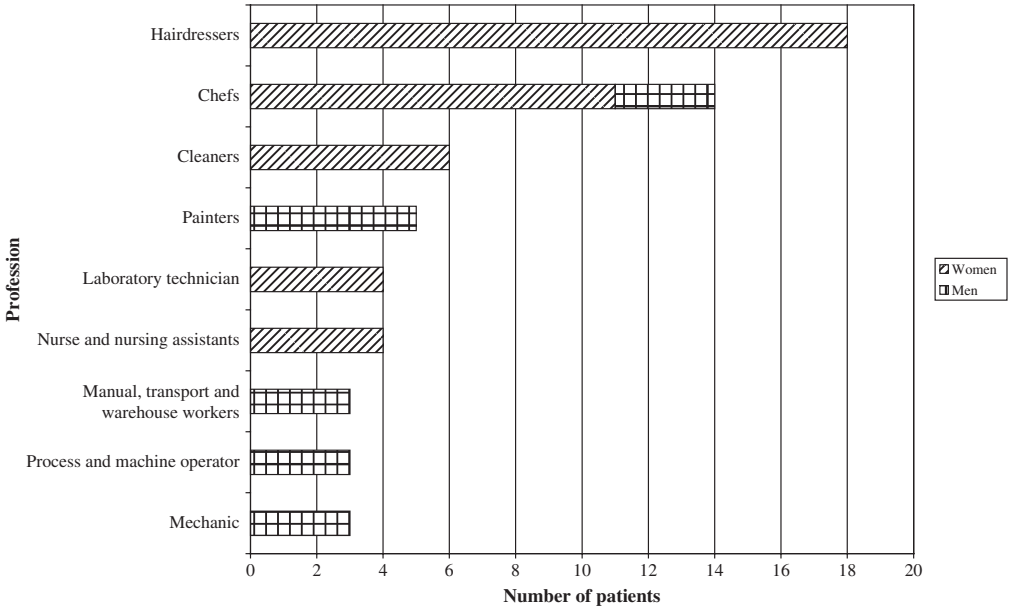

Fig. 3. The top five professions for a group of 110 patients with occupational allergic contact dermatitis.

thought to be incomplete, necessitating contact with the manufacturer to obtain the full composition – this was performed in Step 3. In 2.7% (3/110) of cases, a hidden allergen of relevance to the patient was identified through this procedure. Even if no relevant allergens are identified, this is an important step in excluding allergy. Steps 4 and 5 are chemical analyses, and, with the exception of nickel and cobalt spot tests, require specially trained laboratory staff. Formaldehyde analysis, in particular, may reveal hidden exposures, as most formaldehyde is added to products as releasers or exists as impurities (28, 29). In this study, the formaldehyde spot

test was performed nine times; in 8 patients, we found a relevant occupational exposure to formaldehyde, and in 1 we found a non-occupational exposure.

In our stepwise exposure assessment, Step 6 (visiting the workplace) was not performed in any of the cases included in our study, because the relevant patients were on sick leave, had taken early retirement, or had changed job. In such cases, it is important to gather as many details as possible about their workplace tasks with other methods such as drawings and photographs (30).

The systematic exposure assessment revealed additional allergens for 36% of the patients through testing with additional substances not included in the European baseline series. Furthermore, many more patients benefited from the overall exposure assessment, as we also identified the allergens from the European baseline series in products and/or materials from their workplace, and thereby established the occupational relevance.

These additional allergies concerned 103 different allergens. One of the main additional allergens was methylisothiazolinone (see Table 2), which is a preservative used in consumer and industrial products. It is a well-known contact allergen (31), and has also been known to cause airborne contact dermatitis (32). It can be problematic for patients who acquire allergy to methylisothiazolinone to avoid the allergen because exposure can come from products used both at home and at their workplace. In our study, the exposure to methylisothiazolinone came from paint (n = 5), products from hair salons (n = 3), and a detergent (n = 1), which is in agreement with the literature (31, 33).

Another additional allergen was benzisothiazolinone (Table 2), which is also a preservative and is usually used in paints, metalworking fluids, and rubber gloves (29, 34). According to the Scientific Committee on Consumer Safety, benzisothiazolinone cannot be approved for cosmetics, owing to its sensitization potential (35). In our study, the exposure to benzisothiazolinone came from paint (n = 2) and a detergent (n = 2), which is in agreement with the literature (29, 34).

Isophorone diisocyanate (IPDI) (Table 2), an additional allergen, is an aliphatic isocyanate and is commonly used in varnishes, coatings, and paints (36). In 1979, Lachapelle et al. found that IPDI and isophorone diamine cross-react (37). Exposure to isocyanates is mainly occupational. To avoid skin exposure, protective gloves and protective clothing should be worn when people are working with IPDI (38). In our study, the exposure to IPDI came from primers (n = 2).

The last main additional allergen was bisphenol F (Table 2), which is used in the manufacture of epoxy resins. Epoxy resins are used in a wide range of products, such as adhesives, paints, insulating materials for electric components, and wind turbine rotor blades (39, 40). Epoxy resin systems are among the most frequent causes of occupational allergic contact dermatitis (41). Epoxy resins can act as contact allergens and as airborne allergens (42). In our study, the exposure to bisphenol F came from an epoxy resin (n = 4), which is in agreement with the literature (40).

The weakness of this study is that it is an open study with consecutive patients and no controls. Moreover, the patients included in the study were those seen at a university hospital in the capital region; however, some were included who had been referred from other regions.

The study shows the benefits of systematic exposure assessment in patients with complex disease.

In conclusion, systematic exposure assessment provides information that leads to the identification of occupational allergies caused by allergens not included in the European baseline series in a substantial number of patients.

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References

1 Arbejdsskadestyrelsen. *Arbejdsskadestatistik 2011. The National Board of Industrial Injuries in Denmark*, 2012.
2 Skoet R, Olsen J, Mathiesen B, Iversen L, Johansen J D, Agner T. A survey of occupational hand eczema in Denmark. *Contact Dermatitis* 2004: **51**: 159–166.
3 Cvetkovski R S, Rothman K J, Olsen J, Mathiesen B, Iversen L, Johansen J D, Agner T. Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. *Br J Dermatol* 2005: **152**: 93–98.
4 Meding B, Wrangsjö K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol* 2005: **152**: 975–980.
5 Sundhedsstyrelsen. *Forebyggelse af Kontakteksemer*. Report No. 2: udgave 1 oplag, Copenhagen, Denmark, Danish Health and Medicines Authority, 2001.
6 Flyvholm M-A, Menné T. Allergic contact dermatitis from formaldehyde. A case study focussing on sources of formaldehyde exposure. *Contact Dermatitis* 1992: **27**: 27–36.
7 Holness D L, Nethercott J R. Is a worker's understanding of their diagnosis an important determinant of outcome in

occupational contact dermatitis? *Contact Dermatitis* 1991: **25**: 296–301.
8 Kalimo K, Lammintausta K, Jalava J, Niskanen T. Is it possible to improve the prognosis in nickel contact dermatitis? *Contact Dermatitis* 1997: **37**: 121–124.
9 Hald M, Agner T, Blands J, Johansen J D. Delay in medical attention to hand eczema: a follow-up study. *Br J Dermatol* 2009: **161**: 1294–1300.
10 Johansen J D, Frosch P J, Lepoittevin J-P. *Contact Dermatitis Textbook*, 5th edition: Berlin Heidelberg, Springer-Verlag, 2011.
11 Bregnhoj A, Søsted H, Menné T, Johansen J D. Exposures and reactions to allergens among hairdressing apprentices and matched controls. *Contact Dermatitis* 2011: **64**: 85–89.
12 Berndt U, Hinnen U, Iliev D, Elsner P. Hand eczema in metalworker trainees – an analysis of risk factors. *Contact Dermatitis* 2000: **43**: 327–332.
13 Amarasekera M, Rathnamalala N, Samaraweera S, Jinadasa M. Prevalence of latex allergy among healthcare workers. *Int J Occup Med Environ Health* 2010: **23**: 391–396.
14 Christensson J B, Matura M, Gruvberger B, Bruze M, Karlberg A T. Linalool – a significant contact sensitizer after air exposure. *Contact Dermatitis* 2010: **62**: 32–41.
15 Chu C Y, Pontén A, Sun C C, Jee S H. Concomitant contact allergy to the resins, reactive diluents and hardener of a bisphenol A/F-based epoxy resin in subway construction workers. *Contact Dermatitis* 2006: **54**: 131–139.
16 Bangsgaard N, Thyssen J P, Menné T et al. Contact allergy to epoxy resin: risk occupations and consequences. *Contact Dermatitis* 2012: **67**: 73–77.
17 Flyvholm M-A, Andersen P, Beck I D, Brandorff N P. PROBAS: the Danish product register data base – a national register of chemical substances and products. *J Hazard Mater* 1992: **30**: 59–69.
18 Thyssen J P, Skare L, Lundgren L, Menné T, Johansen J D, Maibach H I, Liden C. Sensitivity and specificity of the nickel spot (dimethylglyoxime) test. *Contact Dermatitis* 2010: **62**: 279–288.
19 Thyssen J P, Menné T, Johansen J D, Lidén C, Julander A, Moller P, Jellesen M S. A spot test for detection of cobalt release – early experience and findings. *Contact Dermatitis* 2010: **63**: 63–69.
20 Flyvholm M A, Tiedemann E, Menné T. Comparison of 2 tests for clinical assessment of formaldehyde exposure. *Contact Dermatitis* 1996: **34**: 35–38.
21 Wilkinson D S, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970: **50**: 287–292.
22 Vester L, Thyssen J P, Menné T, Johansen J D. Occupational food-related hand dermatoses seen over a 10-year period. *Contact Dermatitis* 2012: **66**: 264–270.
23 Menné T, Johansen J D, Sommerlund M, Veien N K. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema 1. *Contact Dermatitis* 2011: **65**: 3–12.
24 Friis U F, Menné T, Jellesen M S, Moller P, Verdingovas V, Jensen T R, Thyssen J P, Johansen J D. Allergic nickel dermatitis caused by playing the guitar: case report and assessment of nickel release from guitar strings. *Contact Dermatitis* 2012: **67**: 101–103.
25 Friis U F, Johansen J D, Krongaard T, Menné T. Quantitative assessment of diethylthiourea exposure in two cases of occupational allergic contact dermatitis. *Contact Dermatitis* 2011: **64**: 116–118.
26 Keegel T, Saunders H, La Montagne A D, Nixon R. Are material safety data sheets (MSDS) useful in the diagnosis and management of occupational contact dermatitis? *Contact Dermatitis* 2007: **57**: 331–336.
27 Kanerva L, Henriks-Eckerman M L, Jolanki R, Estlander T. Plastics/acrylics: material safety data sheets need to be improved. *Clin Dermatol* 1997: **15**: 533–546.
28 Lundov M D, Moesby L, Zachariae C, Johansen J D. Contamination versus preservation of cosmetics: a review on legislation, usage, infections, and contact allergy. *Contact Dermatitis* 2009: **60**: 70–78.
29 Flyvholm M-A. Preservatives in registered chemical products. *Contact Dermatitis* 2005: **53**: 27–32.
30 Friis U F, Menné T, Thyssen J P, Johansen J D. A patient's drawing helped the physician to make the correct diagnosis: occupational contact allergy to isothiazolinone. *Contact Dermatitis* 2012: **67**: 174–176.
31 Thyssen J P, Sederberg-Olsen N, Thomsen J F, Menné T. Contact dermatitis from methylisothiazolinone in a paint factory. *Contact Dermatitis* 2006: **54**: 322–324.
32 Lundov M D, Mosbech H, Thyssen J P, Menné T, Zachariae C. Two cases of airborne allergic contact dermatitis caused by methylisothiazolinone in paint. *Contact Dermatitis* 2011: **65**: 176–179.
33 Flyvholm M-A. Contact allergens in registered chemical products. *Contact Dermatitis* 1991: **25**: 49–56.
34 Aalto-Korte K, Ackermann L, Henriks-Eckerman M L, Valimaa J, Reinikka-Railo H, Leppanen E, Jolanki R. 1,2-Benzisothiazolin-3-one in disposable polyvinyl chloride gloves for medical use. *Contact Dermatitis* 2007: **57**: 365–370.
35 Scientific Committee on Consumer Safety. *Opinion on Benzisothiazolinone*: European Commission Health & Consumers, Brussel, Scientific Committee on Consumer Safety, 2012.
36 Aalto-Korte K, Suuronen K, Kuuliala O, Henriks-Eckerman M L, Jolanki R. Occupational contact allergy to monomeric isocyanates. *Contact Dermatitis* 2012: **67**: 78–88.
37 Lachapelle J M, Lachapelle-Ketelaer M J. Cross-sensitivity between isophorone diamine (IPD) and isophorone diisocyanate (IPDI). *Contact Dermatitis* 1979: **5**: 55.
38 Kelterer D, Bauer A, Elsner P. Spill-induced sensitization to isophoronediamine. *Contact Dermatitis* 2000: **43**: 110.
39 Ponten A, Carstensen O, Rasmussen K, Gruvberger B, Isaksson M, Bruze M. Epoxy-based production of wind turbine rotor blades: occupational dermatoses. *Contact Dermatitis* 2004: **50**: 329–338.
40 O'Boyle N M, Delaine T, Luthman K, Natsch A, Karlberg A T. Analogues of the epoxy resin monomer diglycidyl ether of bisphenol f: effects on contact allergenic potency and cytotoxicity. *Chem Res Toxicol* 2012: **25**: 2469–2478.
41 Dickel H, Kuss O, Schmidt A, Diepgen T L. Occupational relevance of positive standard patch-test results in employed persons with an initial report of an occupational skin disease. *Int Arch Occup Environ Health* 2002: **75**: 423–434.
42 Lodi A, Mancini L L, Pozzi M, Chiarelli G, Crosti C. Occupational airborne allergic contact dermatitis in parquet layers. *Contact Dermatitis* 1993: **29**: 281–282.

Manuscript II

Friis UF, Menné T, Schwensen JF, Flyvholm M-A, Bonde J.P.E., Johansen JD; Occupational irritant contact dermatitis diagnosed by analysis of contact irritant and allergens in the work environment; Contact Dermatitis 2014. (Submitted)

Title: Occupational irritant contact dermatitis diagnosed by analysis of contact irritants and allergens in the work environment

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Background. Irritant contact dermatitis is a common diagnosis in patients with occupational contact dermatitis. Studies are lacking on the usefulness of material safety data sheets (MSDS) in making the diagnosis irritant contact dermatitis.

Objective. To characterize irritant exposures leading to the diagnosis of occupational irritant contact dermatitis and to evaluate the occurrence of concomitant exposures to contact allergens.

Methods. We included 316 patients with suspected occupational hand eczema, referred to the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Denmark during January 2010–August 2011, in a programme consisting of a clinical examination, exposure assessment and extensive patch/prick testing.

Results. Occupational contact dermatitis was diagnosed in 228 patients. Of these, 118 patients were diagnosis with occupational irritant contact dermatitis. The main irritant exposures identified were wet work (n= 64), gloves (n=45), mechanical traumas (n= 19) and oils (n=15). Exposure to specific irritant chemicals was found in 9 patients and was identified by MSDS/ingredients labelling in 8 of these patients.
Review of MSDS and ingredients labelling showed that 41 patients were exposed to 41 moderate to potent contact allergens and 18 patients were exposed to 25 weak workplace contact allergens.

Conclusion. In the present study, the systematic exposure assessment did not reveal any new irritants. MSDS have a limited role in investigating irritant contact dermatitis.

Occupational irritant contact dermatitis (OICD) is diagnosed as dermatosis (typically hand dermatitis) initiated and maintained by a temporal, specific chemical or physical exposure (see Table 1) (1). Contact allergy needs to be excluded by exposure analysis and patch testing with a standard series and specific job-related allergens (2). We have previously developed a paradigm for a systematic search for irritants and contact allergens in the work environment (2). Among 228 patients with occupational contact dermatitis, 110 (48.2 %) were diagnosed with allergic contact dermatitis (ACD) and 118 (51.8 %) with irritant contact dermatitis (ICD) (2).

The aim of the present study was to characterize exposures leading to the diagnosis of OICD and to evaluate occurrence of concomitant exposure to contact allergens.

Materials and Methods

A total of 316 consecutive patients, mainly from the capital region, referred because of suspected occupational contact dermatitis to the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte by a physician or dermatologist were invited to a clinical investigation during January 2010–August 2011 and 228 were diagnosed with occupational contact dermatitis.

The patients were patch tested with the European baseline series supplemented with a specific job-related series and individual contact allergens. The patch tests (Finn Chambers®, and TROLAB® or Chemotechique® patch test allergens) were applied to the upper back, fixed with Scanpor® tape, and occluded for 2 days. Readings were made on D2, D3 or D4, and D7, according to the recommendations of the International Contact Dermatitis Research Group (3). Reactions of 1+, 2+ or 3+ were interpreted as positive reactions. Irritant responses, doubtful responses (?+) or negative readings were interpreted as negative.

Prick test material was from ALK-abello® (Hørsholm, Denmark). For occupational exposure to food items, most patients were tested with allergen extracts and the Gentofte Hospital standard fresh food series 'Fresh Fruit and Vegetables' and 'Fresh Meat and Fish' (2;4). The department provided the food. The test was performed using the prick to prick method. The test reaction was read after 15 min and considered positive if the diameter of the skin papule was >3 mm. If other foods not covered by the test series were suspected of provoking the skin symptoms, the foods were provided by the patients and used for testing.

Based on all the investigations, a final diagnosis was made by the treating dermatologist according to the clinical guideline by the Danish Dermatological Society (1). The criteria for occupational allergic contact dermatitis (OACD) were: (i) positive patch testing to a substance present in the workplace (ii) skin contact with the substance on the relevant anatomical area, and (iii) sufficient exposure intensity and duration to explain the dermatitis.

The diagnosis of ICD was assigned when ACD could be excluded by negative patch test results and a significant exposure to irritants was established. The criteria for wet work—using protective gloves, frequent hand washing and using hand disinfectants—can be seen in Table 1.

Protein contact dermatitis was diagnosed if the patient had dermatitis and a relevant positive prick test to proteins, such as foods and latex (4).

In this study, we classified patients either as having ACD or ICD. Individuals with both diagnoses were classified as having ACD. We did not take into account the effects of individual factors such

as atopic dermatitis and genetic factors. The methods and the cohort are described in detail in an earlier publication (2).

Statistics

The data were processed in the Statistical Products and Service Solutions package (SPSS statistics, Inc., Chicago, IL, USA; IMB PASW statics) for Windows, edition 19.0. The non-parametric Mann-Whitney U-test was used to examine the age distribution in men and women.

Results

The study population comprised 118 patients (74 women and 44 men) diagnosed with occupational irritant contact dermatitis. Median age for women was 30.0 years (mean = 33.8) and median age for men was 42.0 years (mean = 39.7) (*p*-0.027).

The most frequent occupations for both sexes with ICD are given in Figure 1. Jobs among women, ranked in order of frequency, were hairdresser, healthcare assistant, cook and cleaner; among men, the jobs were mechanic, cook and painter.

Exposure to irritants

The main causative exposures identified were wet work (n= 64), glove use (n=45), mechanical traumas (n= 19) and oils (n=15). In 8 of 9 patients, exposure to specific chemical irritants was identified in the MSDS/ingredients lists. See Table 2.

Exposure to contact allergens

Exposure to clinically relevant contact allergens and the number of patients exposed are listed in Table 3 and Table 4. Based on MSDS, ingredients labelling and information provided by manufactures, 41 patients were exposed to a total of 41 moderate to potent contact allergens, and 18 patients were exposed to 25 weak contact allergens. In 15 of the 118 patients, exposure to preservatives/antioxidants was found through the exposure assessment of workplace products. The exposures were to 14 different preservatives, of which 9 are not represent in the European baseline series.

In 10 patients, exposures to fragrance allergens and/or terpenes were identified. Metal exposure, to four different metals (copper, chrome, vanadium and nickel) was seen in 7 patients. In 8 patients, exposure to acrylates was seen. Exposure to isocyanates was seen in 4 patients, and exposure to epoxy chemicals was seen in 2 patients.

For hairdressers and cooks, no detailed exposure recording was done; exposures in the two professions were covered by testing with a supplementary series such as the hairdresser series and a prick test with fresh food.

Discussion

The classification of ICD and ACD depends upon defined, easily recognisable clinical signs with a temporal relation to the start and maintenance of the clinical disease, patch testing and exposure assessment (1).

For ACD, systematic studies of quantitative exposure assessment supported by experimental studies in already sensitised individuals support the relevance of occupational exposure to contact allergens from common exposures such as paints and cutting oils (5-8). Experimental studies have shown that repeated exposures, even in the concentration range of ppm, can elicit an allergic response in patients with a positive patch test to the chemical in question.

Quantification of the relevance of exposure to irritants is less studied (9). One of the main obstacles in this research is that no simple test similar to the patch test is available. Therefore, the diagnosis of ICD is based only on the clinical picture, temporal relationship and exposure assessment and the absence of a positive patch test to contact sensitizing chemicals in the work environment.

In a historical perspective, ICD has always been diagnosed by exclusion, with the diagnosis being applied only to contact dermatitis with considerable duration and when meticulous patch testing reveals no contact allergy explaining the disease (10). The available quantitative exposure data relevant for the diagnosis of ICD are listed in Table 1, with wet work and wet/dry cycles prominent in the diagnostic criteria.

The criteria for wet work are weakly defined and are primarily based on the legal classification set by the occupational dermatology in Germany (11). As no international definition of wet work exists, it is likely that the German classification is often used in occupational dermatology and by clinicians. Although these quantitative exposure data are currently the best available instruments for the diagnosis of ICD, they have inherent weaknesses.

According to the criteria, wet work is partly defined by hands regularly being in a wet environment for more than 2 hours per day, frequent hand washing (11) or using protective gloves for more than 2 hours a day (1). It has previously been shown that unprotected wet work for more than 2 hours a day is a risk factor for hairdressing apprentices (12). The criteria are primarily based on such epidemiological data, with experimental studies on water and skin barrier also contributing, for example, in 1996 Ramsing et al found that long-term use of occlusive gloves (6 h/d for 14 days) had a negative effect on the skin barrier (13) but in 2009 Wetzky et al could not demonstrate the same

negative effect (4 h/d for 7 days) (14), warranting more studies on the effect of occlusion of rubber gloves.

It is a fundamental problem that the ICD diagnostic criteria are based on known risk factors for the disease instead of a valid test. If used unwisely when diagnosing ICD, these risk factors, for example, wet work and wet/dry cycles, will probably overestimate the group of ICD. This overestimation is exemplified by the newly obtained knowledge of irritants and wet work in occupational settings, with up to 40% of all occupations being in excessive contact with irritants. Accordingly, persons in these occupations will most likely fulfil the criteria for ICD and wet work if they develop dermatitis (15). The unsuitability of diagnosing combined allergic and ICD is illustrated when patients diagnosed with ACD work in an environment where the wet work criteria are met (16). Exposure to both allergens and irritants can occur in the work environment, and although the combined diagnosis may be applicable, it should be used critically to avoid misclassification.

Research has tended to focus more on ACD than on ICD. Nevertheless, individual quality of skin barrier may influence the irritant response because predictive factors, such as former atopic dermatitis and the filaggrin gene mutation, favour the development of ICD (15;17-19).

The lack of understanding of the ICD diagnosis is reflected by the lack of a test for an irritant skin response and the inherent weaknesses in the diagnostic criteria. Based on the criteria listed and the exposure assessment, we diagnosed 118 patients with occupational ICD, who could be divided into 12 main groups (Table 2). Persons in occupations with exposure to wet work and fresh food were often diagnosed with OICD (Figure 1).

The information from MSDS covers only qualitative information, making them of limited use in the exposure analysis for OICD diagnosis. The diagnosis still depends on general factors, such as those listed in Table 1. In a recent study, we found that 18.6% of the MSDS had one or more shortcomings, seen from a medical viewpoint (20).

Notwithstanding this observation, MSDS have a central role in identifying exposure to contact allergens and the planning and execution of patch testing with the relevant allergens. It is interesting that the group classified with OICD has exposure to contact allergens similar to those classified as OACD (2).

The diagnosis of ICD cannot be made without excluding a type I allergy to food and latex in the relevant trades (4), neither should it be disregarded that chemicals, such as quaternary ammonium

compounds, frequently used in the biotechnology companies when a high degree of sterility is needed, may cause type I allergy (2;21). An ICD classification is not possible without addressing these points.

In our study of 228 consecutive patients with occupational contact dermatitis, the frequency of OACD and OICD were equally common. The study was undertaken in a university department where there is a systematic stepwise exposure programme. Our findings are in contrast to most other studies, where ICD is the dominating diagnosis (7;22-24). The discrepancy may be explained by two main elements: 1) our patient material could have been selected with a bias towards severe cases, where earlier undetected contact allergy is suspected 2) without a systematic exposure analysis, ICD may easily be over diagnosed. If only the baseline patch test series is done, important contact allergens will be missed, for example, rubber chemicals and preservatives, and the same applies for type I allergens, for example, testing for food allergens.

The diagnosis of OACD is based on systematic work searching for both type I and type IV allergens, involving extensive allergy testing in which the MSDS have a central role. OICD requires the same meticulous search for exposure to contact allergens, even if typical ICD is initially suspected.

In conclusion, the systematic exposure assessment in this study did not reveal any new irritants and MSDS had a limited role. The level of documentation differs greatly for assigning the diagnosis ACD and ICD. Care should be taken to exclude relevant allergies before making the diagnosis of ICD. Further improvement is needed in the classification of the combined diagnosis. Accordingly, the combined diagnosis of allergic and irritant contact dermatitis should be assigned only when specific information exists qualifying the role of irritant exposure in the disease. The diagnosis should not be based merely on knowledge of general risk factors.

Reference List

(1) Menne T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis 2011: 65(1):3-12.

(2) Friis U.F, Menne T., Flyvholm M-A., Bonde J.P., Johansen JD. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. Contact Dermatitis 2013: 69(3):153-63.

(3) Wilkinson DS, Fregert S, Magnusson B, Bandmann HJ, Calnan CD, Cronin E, Hjorth N, Maibach HJ, Malalten KE, Meneghini CL, Pirila V. Terminology of contact dermatitis. Acta Derm Venereol 1970: 50(4):287-92.

(4) Vester L, Thyssen JP, Menne T, Johansen JD. Occupational food-related hand dermatoses seen over a 10-year period. Contact Dermatitis 2012: 66(5):264-70.

(5) Thyssen JP, Gimenez-Arnau E, Lepoittevin JP, Menne T, Boman A, Schnuch A. The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals. Part II. Contact Dermatitis 2012: 66 Suppl 1:25-52.

(6) Thyssen JP, Gimenez-Arnau E, Lepoittevin JP, Menne T, Boman A, Schnuch A. The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals. Part III. Contact Dermatitis 2012: 66 Suppl 1:53-70.

(7) Fischer LA, Voelund A, Andersen KE, Menne T, Johansen JD. The dose-response relationship between the patch test and ROAT and the potential use for regulatory purposes. Contact Dermatitis 2009: 61(4):201-8.

(8) Johansen J.D., Frosch PJ, Menne T. Allergic Contact Dermatitis in Humans - Experimental and Quantitative Aspects. Contact Dermatitis. 4th edition ed. Berlin Heidelberg: Springer-Verlag: 2006. p. 189-98.

(9) Keegel T, Saunders H, LaMontagne AD, Nixon R. Are material safety data sheets (MSDS) useful in the diagnosis and management of occupational contact dermatitis? Contact Dermatitis 2007: 57(5):331-6.

(10) Frosch PJ, John S-M. Clinical Aspects of Irritant Contact Dermatitis. In: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. Contact Dermatitis Textbook. 5th edition ed. Berlin Heidelberg: Springer-Verlag: 2011. p. 305-45.

(11) Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). Risks resulting from skin contact - identification, assessment, measures - TRGS 401. 2008. Available at: http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/TRGS-401.pdf?__blob=publicationFile&v=6 (last accessed 5-4-0014)

(12) Uter W, Pfahlberg A, Gefeller O, Schwanitz HJ. Hand dermatitis in a prospectively-followed cohort of hairdressing apprentices: final results of the POSH study. Prevention of occupational skin disease in hairdressers. Contact Dermatitis 1999: 41(5):280-6.

(13) Ramsing DW, Agner T. Effect of glove occlusion on human skin (II). Long-term experimental exposure. Contact Dermatitis 1996: 34(4):258-62.

(14) Wetzky U, Bock M, Wulfhorst B, John SM. Short- and long-term effects of single and repetitive glove occlusion on the epidermal barrier. Arch Dermatol Res 2009: 301(8):595-602.

(15) Bandier J, Ross-Hansen K, Carlsen BC, Menne T, Linneberg A, Stender S, Szecsi PB, Meldgaard M, Thyssen JP, Johansen JD. Carriers of filaggrin gene (FLG) mutations avoid professional exposure to irritants in adulthood. Contact Dermatitis 2013:

(16) Schwensen J.F., Menne T, Johansen J.D. The combined diagnosis of allergic and irritant contact dermatitis in a retrospective cohort of one thousands consecutive patients with occupational contact dermatitis (Submitted). Contact Dermatitis 2014:

(17) Molin S, Vollmer S, Weiss EH, Ruzicka T, Prinz JC. Filaggrin mutations may confer susceptibility to chronic hand eczema characterized by combined allergic and irritant contact dermatitis. Br J Dermatol 2009: 161(4):801-7.

(18) Carson CG, Rasmussen MA, Thyssen JP, Menne T, Bisgaard H. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. PLoS One 2012: 7(11):e48678.

(19) Thyssen JP, Carlsen BC, Menne T, Linneberg A, Nielsen NH, Meldgaard M, Szecsi PB, Stender S, Johansen JD. Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: results from a general population study. Br J Dermatol 2010: 163(1):115-20.

(20) Friis U.F., Menne T, Flyvholm M-A, Bonde J.P., Johansen J.D. Challenges in using MSDS for analysis of occupational exposures to contact allergens (submitted). Contact Dermatitis 2014:

(21) Ruiz OA, Fischer FU, Duus JJ. Occupational contact urticaria caused by didecyl dimethyl ammonium chloride. Contact Dermatitis 2011: 64(5):297-8.

(22) Skoet R., Olsen J., Mathiesen B., Iversen L., Johansen J.D., Agner T. A survey of occupational hand eczema in Denmark. Contact Dermatitis 2004: 51(4):159-66.

(23) Cvetkovski RS, Rothman KJ, Olsen J, Mathiesen B, Iversen L, Johansen JD, Agner T. Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. Br J Dermatol 2005: 152(1):93-8.

(24) Caroe TK, Ebbehoj N, Agner T. A survey of exposures related to recognized occupational contact dermatitis in Denmark in 2010. Contact Dermatitis 2014: 70(1):56-62.

(25) Rustemeyer T, Elsner P, John S-M, Maibach H. Wet Work and Occlusion. Kanerva's Occupational Dermatology. 2nd ed. Berlin Heidelberg: Springer Verlag: 2012. p. 839-46.

Figure 1. The top 5 professions of women and men among the 118 patients with occupational irritant contact dermatitis.

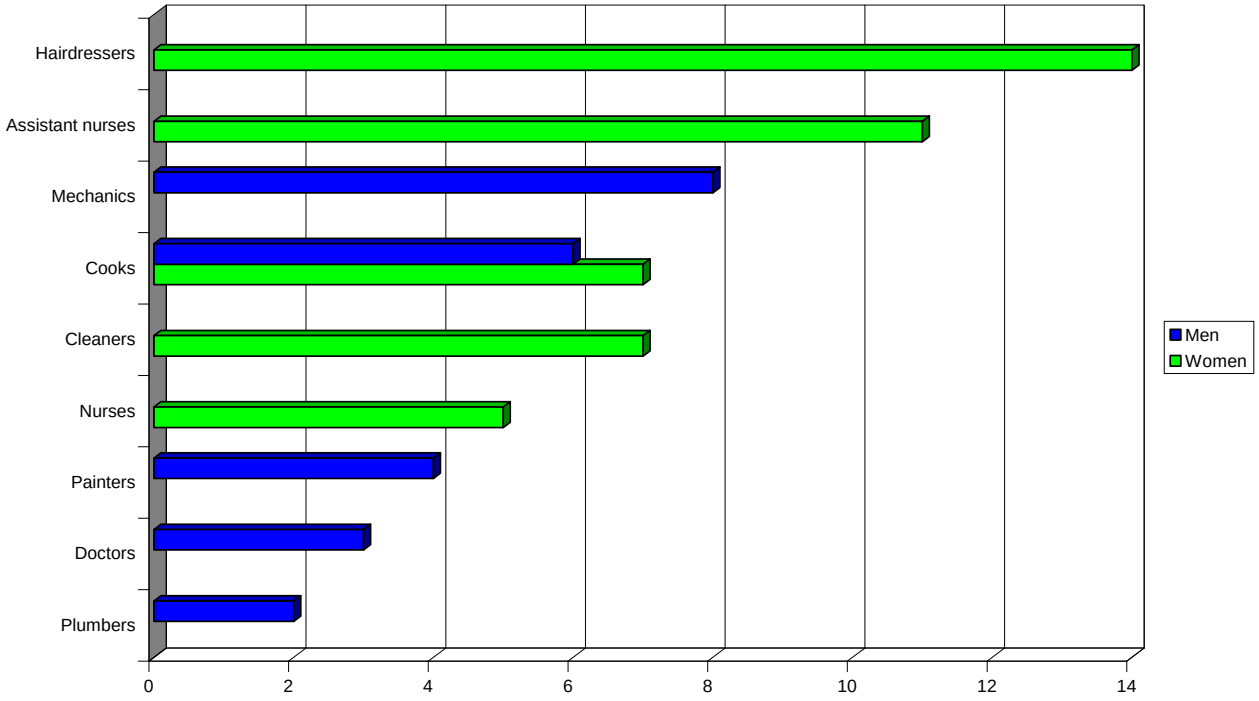

Table 1 . Criteria for different types of irritant exposure leading to increased risk of contact dermatitis

Irritant	Criteria
Wet hands	2h/day (1;11;25)
Frequent hand washing	20 times/day or more (1;11)
Use of hand disinfection	20 times in a working day*
Occlusion from rubber gloves	2 hours in a working day (11) (or) change of gloves 20 times in a working day* (1)

* The frequent use of hand disinfectants and change of rubber gloves 20 times a working day is a direct derivation of the frequent hand washing of 20 times in a working day set by the German guidelines from the TRGS 401 (11) and the Danish guidelines (1).

Table 2 Exposure to contact irritants in patients classified with occupational irritant contact dermatitis. N=118. Patients can appear in more than one subgroup.

Main Group	Number of patients in the main group	Subgroup	Number of patients in the subgroup
Wet work	64	Wet work	57
		Frequent hand washing	30
		Hand disinfection	9
Occlusion from rubber gloves	45	Occlusion from rubber gloves	45
Mechanical traumas	19	Working clothes	9
		Friction	6
		Working gloves	2
		Fiberglass	2
		Foam from headset	1
Oil products	15	Oils	15
Substances/Products	9	Chemicals	9
Food	9	Food	9
Detergents	9	Cleaning agents	9
Miscellaneous	3	Miscellaneous	3
Organic solvents	3	Solvents	3
Acids	3	Low pH	2
		Chemical burns (fruit colours)	1
Environment	3	Warm air	2
		Dry air	2
Paint	1	Paint	1

Table 3. Exposure to moderate to potent contact allergens in patients classified with occupational irritant contact dermatitis. All patch tests were negative. N=118. Patients can appear in more than one subgroup.

Main group	Allergen	CAS-no.	Number of exposed patients
Acrylates	Bisphenol A Glycidyl Methacrylate	1565-94-2	1
	Butyl acrylate	141-32-2	1
	Ethyl-cyanoacrylate	7085-85-0	2
	2-Hydroxyethyl methacrylate	868-77-9	1
	Methyl methacrylate	80-62-6	4
Additives and chemicals in food	Foods series	NA*	10
Epoxy chemicals	Bisphenol A	80-05-7	1
	Epoxy resin	26875-67-2	1
Fragrance	Alpha-hexylcinnamaldehyde	101-86-0	1
	Benzyl alcohol	100-51-6	1
	Benzylsalicylate	118-58-1	3
	Citral	5392-40-5	1
	Citronellol	106-22-9	1
	Unspecified perfume	NA*	5
Metal components	Copper	**NA***	4
	Chrome	7778-50-9	1
	Nickel	7786-81-4	1
	Vanadium(III)chloride	7718-98-1	1
Isocyanates	4,4'-Diphenylmethane diisocyanate (MDI)	**101-68-8**	4
	1,6-hexamethyldiisocyanate	822-06-0	1
	Isophorone diisocyanate	4098-71-9	2
	Phenylisocyanate	103-71-9	1
	Toluene-2,4-diisocyanate	584-84-9	1
Preservatives	Benzalkonium chloride	8001-54-5; 63449-41-2	1
	Benzisothiazolinone	2634-33-5	4
	2-Bromo-2-nitro-1,3-propanediol	52-51-7	2
	BHT (Butylated hydroxytoluene)	128-37-0	4
	Dimethyl oxazolidine (Bioban CS-1135(F))	51200-87-4	2
	Formaldehyde	50-00-00	2
	Glutaraldehyde	111-30-8	1
	Iodopropynyl butylcarbamate	55406-53-6	4
	Methyldibromoglutaronitrile	35691-65-7	2
	Methylisothiazolinone	2682-20-4	2
	MI/MCI	55965-84-9	4
	Paraben mix	99-76-3, 120-47-8, 94-13-3, 94-26-8	2
	Phenoxy ethanol	122-99-6	2
	Sodium hydroxymethylglycinate	70161-44-3	1
Terpenes	D-Limonene	5989-27-5	6
	Linalool	78-70-6	4
Rubber chemicals	2,5-Dimercapto-1,3,4-Thiadiazole	1072-71-5	1
	Zinc dimethyldithiocarbamate	137-30-4	1

*NA=not available.

Table 4. Exposure to weak contact allergens in patients classified with occupational irritant contact dermatitis. All patch tests were negative. N=118. Patients can appear in more than one subgroup.

Main group	Allergen	CAS-no.	Number of exposed patients
Other chemicals	Ammonium chloride	12125-02-9	1
	Amphotericin	12633-72-6	1
	Benzoic acid	65-85-0	1
	Benzoyl peroxide	94-36-0	1
	Cetylstearyl alkohol	67762-27-0	1
	Cocamide DEA	68603-42-9	**1**
	Cocamide MEA	68140-00-1	2
	Cocoamidopropyl betaine	61789-40-0	2
	Di-2-ethylhexyl phthalate	275818-89-8; 40120-69-2; 50885-87-5; 607374-50-5; 8033-53-2; 117-81-7	1
	Di-N-butyl phthalate	84-74-2	1
	DMSO	67-68-5	1
	EDTA	60-00-4	2
	Ferrous oxide	1345-25-1	1
	Hydroquinone	123-31-9	3
	N,N-dimethyl-p-toluidine	99-97-8	1
	Oxybenzone	131-57-7	1
	Phthalic anhydride	85-44-9	1
	Propylene glycol	123120-98-9	4
	Sodium hypochlorite	7681-52-9	1
	Sodium omadine	3811-73-2	1
	Tin oxide	69279-06-7	1
	Titanium dioxide	13463-67-7; 1317-80-2; 1317-70-0	2
	Tobramycin	32986-56-4	2
	Tricresyl phosphate	1330-78-5	1
	Zinc oxide	1314-13-2	1

Manuscript III

Friis UF, Menné T, Flyvholm MA, Bonde JP, Johansen JD. Difficulties in using MSDS to analyse occupational exposures to contact allergens. Contact Dermatitis. 2014 (Submitted)

Title: Difficulties in using MSDS to analyse occupational exposures to contact allergens

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Background: Information on the occurrence of contact allergens and irritants is crucial for the diagnosis of occupational contact dermatitis. Material Safety Data Sheets (MSDS) are important sources of information concerning exposures in the workplace.

Objective: From a medical viewpoint, to evaluate the information available from MSDS, and to ascertain whether MSDS are easy to obtain, whether they serve their purpose and whether they provide sufficient information regarding product allergens to enable correct diagnosis.

Methods: MSDS and ingredients labelling were collected from consecutive patients and reviewed. If it was suspected that the MSDS were incorrect, the manufacturer, supplier, salesperson or the workplace were contacted to gather more information.

Results: 25.0% (79/316) of patients provided material for the exposure assessment. One or more shortcomings were found in 18.6% (137/738) of the MSDS. The most frequent shortcoming was "Missing R43/H317 while known contact allergen was present", which was observed in 63.1% (84/137); "Names of preservatives were not included in section 3 of the MSDS despite preservatives being present" was observed in 48.9% (67/137); and "No mention of allergy in sections 2, 3, 11,15 or 16 in the MSDS despite the content of allergens", which was observed in 20.4% (28/137). The extra information retrieved led to additional testing of 21 patients.

Conclusion: Stepwise systematic exposure assessment is time consuming. The main shortcomings are errors and omissions in the MSDS. Improved independent quality assurance of MSDS is warranted as well as improved regulations to allow full ingredient labelling.

An exhaustive analysis of exposures to allergens and irritants in the work environment is the prerequisite for making a correct diagnosis of allergic and/or irritant contact dermatitis and for effective treatment and prevention of disease.

All chemical products marketed in the EU shall be classified and labelled according to the regulation on classification, labelling and packaging of substances and mixtures (the CLP Regulation) (1). In addition to the on-pack labelling, manufacturers of substances and mixtures for professional use shall also provide Material Safety Data Sheets (MSDS). MSDS consists of 16 sections and the content of each section is specified by the REACH Regulation (2). Substances classified as hazardous shall be reported in section 3 of the MSDS (1).

Substances with a harmonised EU classification are listed in Annex VI of the CLP regulation. These classifications are legally binding. All other substances need to be self-classified by the supplier of the substance. Substances with a harmonised classification covering certain hazard classes only (e.g. cancer and sensitisation) also need to be self-classified in other hazard classes not covered by the harmonised classification. Annex VI of the CLP regulation contains more than 12,000 substances and substance groups (3). This means that the vast majority of the 117,371 substances notified to the EU (the Classification and Labelling Inventory) are self-classified substances (4). These data increase over time. If a chemical product contains one or more substances classified as skin sensitizing in Category 1 or 1B and the substance(s) is present in concentrations equal to or above 1% by weight, the product shall be classified as skin sensitizing and shall be labelled as such. The risk wording for a skin sensitizer according to CLP is H317: “May cause an allergic skin reaction”. (The labelling wording used under the former classification system was R43: “May cause sensitisation by skin contact”) (2). Moreover, if a skin sensitizer in Category 1 or 1B is present in a mixture in concentrations equal to or above 0.1%, the product label (and the MSDS) must be labelled with the words “Contains (name of sensitising substance). May produce an allergic reaction”. For substances classified as skin sensitizers in Category 1A, the limit for classification and labelling of a mixture is 0.1% and the limit for the specific labelling wording is 0.01% (5). Some sensitising substances have a specific concentration limit indicating the concentration above which a mixture shall be classified. For example, this applies to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), which has a specific concentration

limit of 15 ppm. This means that chemical products containing MCI/MI in concentrations equal to or above 15 ppm shall to be classified and labelled as skin sensitising according to CLP (1).

Ingredients lists and MSDS can be incorrect or incomplete and difficult to understand (6;7). As already mentioned, industrial products must be labelled as sensitising only if a contact allergen is present in more than 1 weight %, and its chemical name must appear if it is present in amounts above or equivalent to 0.1% or in amounts above its individual concentration limit (1;6;8;9). Exposure to a low concentration of allergen can lead to allergic eczema (10;11). This means that exposures to allergens can easily be overlooked (8;12).

We have previously published the benefits of using a stepwise exposure analysis in detecting relevant exposures in the workplace (13). MSDS are central in assessing workplace exposures. Here, we present a study of the process of obtaining information through MSDSto give the correct diagnosis. Further we want to pinpoint potential shortcomings and the need for improvements.

Patients and methods

During January 2010–August 2011, 316 consecutive patients with suspected occupational contact dermatitis were seen in the Department of Dermato-allergology at Copenhagen University Hospital Gentofte, Denmark.

The patients underwent a standard examination and investigation including a stepwise exposure analysis of allergens in the work environment. The cohort and the results have been described in detail (13).

Briefly, all patients were seen in the clinic by a dermatologist and a thorough medical history was taken including exposures in the workplace and at home (Step 1). The primary investigator (UFF), who has a degree in chemistry, was either present at the consultation or contacted the patient later for more detailed information.

Information was collected from the patients about products used at home and at work together with the ingredients list and information about use of protective equipment; material safety data sheets (MSDS) were also collected. This information was subsequently analysed (Step 2).

If the MSDS were incomplete and/or if the contents did not sum up to 100%, if preservatives were not specified or in case of other incomplete information, the manufacture, supplier, salesperson or the workplace was contacted to obtain more information (Step 3). In the event of a positive patch test for nickel, cobalt or formaldehyde, a spot tests was performed (Step 4) and in cases where only a positive reaction to a product was seen, chemical analysis could follow (Step 5). A visit to the workplace could be made at Step 6. The steps could be organised in a different order.

This paper concerns the potential difficulties in obtaining correct and complete information from the MSDS i.e. the shortcomings experienced at Steps 2 and 3.

As mentioned earlier, the MSDS consist of 16 sections (2); the sections that had our focus can be seen in Table 1. These different sections contained information regarding allergens. The missing/incorrect/incomplete information identified was grouped as shown in Table 2

- if the MSDS had information regarding an allergen in section 3 but it was not listed as R43/H317, it was listed as “Missing R43/H317 while known contact allergen was present”.
- If an allergen in section 3 was listed with an incorrect chemical name, it was listed as “Incorrect chemical name”,
- If the MSDS was illegible, it was listed as “Illegible MSDS”,
- If the MSDS was labelled R43/H317 even though the allergen was not listed, it was listed as “Missing name of chemical and CAS-no but labelled R43/H317”,

- If an allergen was labelled in section 3 but no information was listed in section 11, it was listed as "Allergen listed as R43/H317 but nothing mentioned about allergy in section 11",
- If the product contained additives but no chemical name was listed, it was listed as "product contains additives but no chemical names given",
- If the MSDS stated that the product contained azo-colours but did not mention which chemical names, it was listed as "Azo-textile colour but nothing about which colour is used",
- If nothing was mentioned in sections 2, 3, 11, 15 or 16 even though an allergen was used, it was listed as "Nothing about allergy in sections 2, 3, 11, 15 or 16 in the MSDS despite the content of allergens" and
- If nothing about a preservative was mentioned even though a preservative was present, it was listed as "Names of preservatives not included in section 3 despite containing preservatives".

Results

Of the patients, 20.9% (66/316) provided a total of 738 material safety data sheets (MSDS) for one or more products they had been in contact with at their workplace. The average number of MSDS per patient was 11 (range 1–106). From a medical viewpoint, 42.4% (28/66) of the patients' datasheets had shortcomings; 18.6% (137/738) of the MSDS contained errors or had missing information.

The most frequent shortcoming was that known allergens were not identified by R43/H317 in the MSDS because the product contained less than 1% of the allergen, see Table 3; this was observed in 61.3% (84/137) of MSDS. Another frequent problem observed in 48.9% (67/137) of the MSDS was that preservatives used in water-based products were not mentioned by name, even though the information 'contains preservatives' was given. This was followed by the shortcoming that no information was given in the MSDS despite the contents having one or more allergens, which was observed in 20.4% (28/137). Table 2 shows an overview of the shortcomings and Table 3 lists the allergens where important information was omitted. To obtain the information missing from the MSDS, contact had to be taken to the manufacturer, supplier or salesperson. For example, we requested information about which preservatives were used in a water-based paint along with information on the other ingredients used in the product in cases where perhaps only 2% of the total content was given in the MSDS. We also requested additional information if the MSDS mentioned the use of additives but without specification. In some instances the manufacturer wanted data breaching the anonymity of the patient under investigation in exchange for delivering the information we requested. In one case we retrieved an illegible MSDS, but the company's e-mail address was legible, which enabled us to contact the company and ask for details about the manufacturer of the product. Our request was denied on the grounds of confidentiality. Confidentiality also played a role in another case where the manufacturer would not provide a list of ingredients used in the company's product. In another instance the patient had provided a product, but we were unable to find any product information on the product (e.g. product code or serial number); consequently, we were unable to find the matching MSDS; all the products in the series had the same name but had different ingredients. In 10 cases the manufacturer would not provide the information we needed on the grounds of confidentiality. The extra information retrieved led to additional testing of 21 patients. The average time used in the stepwise systematic exposure

assessment was 2 hours per patient. The five most frequent shortcomings we found are shown in Figure 1.

Discussion

In this study the MSDS were collected from 66 patients and were reviewed for chemicals well-known as allergens. In our study 18.6% (137/738) of the MSDS had one or more deficiencies. The three most frequent shortcomings were "Missing R43/H317 while known contact allergen was present" in 61.3% (84/137) of the MSDS; "Names of preservatives not included in section 3 despite containing preservatives" in 48.9% (67/137) of the MSDS; and "Nothing about allergy in sections 2, 3, 11, 15 or 16 in the MSDS despite the content of allergens" in 20.4% (28/137) of the MSDS. The reason for these shortcomings could be that even though the "self-classification" is met, known allergens are not labelled in the MSDS because of the 1% concentration limit and 0.1% for labelling limit. Another reason could be that very few allergens are on the official REACH list as sensitizers, which is a legally binding classification. In all other cases, manufacturers are obliged to consider whether an ingredient meets the criteria necessitating classification as an allergen. The evaluation of substances according to the criteria requires toxicological insight, which may not always be present to a sufficient extent in small enterprises. As we did not ask the manufacturers about the concentrations, it could be that the MSDS fulfilled the legislation but were insufficient from a medical point of view. In 2001 Frazier et al found that 26.7% of the MSDS examined did not contain the word "asthma" or allergic or sensitizing respiratory reactions even though the products contained the allergen toluene-2,4-diisocyanate (14). In 2002 Bernstein reported that if the MSDS did not sum up to 100%, the physician should be alert because manufacturers might have omitted material that they deemed not to be hazardous (15).

The two concentration limits (1% and 0.1%) tend to be insufficient to protect against sensitization and will not protect the sensitized individual (10;11). In 1997 Kanerva et al. found that one product, a UV lacquer, contained 46% of undeclared tripropylene glycol diacrylate (CAS: 42978-66-5) (16). In a review from 2000, Basketter et al. (17) found that 61% (17/28) of analysed acrylic products contained undeclared (meth)acrylates. In 2010 Welsh et al found that by analysing the chemical contents of three different products and comparing the data with the MSDS, respectively, all three MSDS contained substances not listed according to legislation (18).

Occupational skin disease is frequent and leads to major expense for society (19). It is not reasonable to restrict information that would allow workers to properly protect themselves. Under Danish law it is the Danish Working Environment Authority that supervises and advises the manufacturer, importer etc. in complying with the legislation for MSDS given in REACH (20). In 2007 Keegel et al found that only 58% of the provided MSDS met the criteria for listing of

hazardous substances according to Australian legislation (8). In our study, although we did not ask for concentrations, some manufacturers gave us the information about the concentration of substances. In those cases there was compliance with the law.

Because of the insufficient MSDS, we had to contact the manufacturers to obtain information concerning the products' contents. In 10 cases the manufacturer refused to give us this information on the grounds of confidentiality, even though our requests often concerned the preservatives in a product. It is difficult to understand why a preservative, for example in paint or cutting oil, needs to be kept confidential, especially if the information is for medical purposes.
Manufacturers should be legally obliged to provide the information needed for medical investigation of workers suspected to have an adverse reaction to their products.
Based on the extra information we obtained from the manufacturer, 31.8% (21/66) of the patients were patch tested with additional allergens. Such additional testing is time consuming for the patient. If all the ingredients were labelled or if all known allergens were labelled, the time used for the exposure assessment could be reduced and the patient would need only one patch test. This would reduce costs for both the patient and society. Based on the knowledge of use of chemicals and of chemical exposure combined with the contact allergic potential of the chemicals and the clinical diseases related to the exposures, we recommend addressing the following main points: chemicals should be listed down to their analytical limit, revision should be done concerning the allowed concentration of certain allergens in some product types, obligatory labelling of all preservatives independent of their concentration in the product and inclusion in section 3 of the MSDS, quality assurance and independent review of the MSDS by authorities (see the pinpoints in more detail in Table 4). It is disturbing that it is so difficult to obtain information concerning allergens in products intended for the workplace. Accordingly, it is likely that many doctors and patients abandon their attempts at the expense of the worker's health. In 2010, by reviewing articles published from 1997 to 2007, Nicol et al found that there is a significant problem with the accuracy and completeness of MSDS (7). Our results add to these findings. From a medical and societal viewpoint this missing information is a major drawback and makes the investigation of the patient time consuming, expensive and most likely insufficient.

Seen from a medical viewpoint, we conclude that the insufficiencies in the MSDS are probably accounted for by the "self-classification", that not all known allergens need to be labelled

R43/H317, and that the labelling concentration is too high in relation to the level of elicitation. These insufficiencies mean that the information the patients give the dermatologist is often incomplete or inaccurate, necessitating further efforts to obtain the relevant details, making a complete stepwise systematic exposure assessment extremely time consuming.

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Reference List

(1) ECHA. Regulation on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. the European Parliament and the Council of the European Union;2010 Oct 29. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF (last accessed 2-1-2014)

(2) The European Parliament and the Council of the European Union. REGULATION (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. 2006 Dec 18. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:136:0003:0280:en:PDF (last accessed 3-6-2014)

(3) ECHA. Registered substances under REACH. 17-4-2014. Available at: http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances. (Last accessed 3-6-2014).

(4) ECHA. C&L Inventory database. 8-5-2014. Available at: http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database. (Last accessed 3-6-2014).

(5) The Commission of the European Communities. Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures. 2011 Mar 10.

(6) Noiesen E., Munk M.D., Larsen K., Johansen J.D., Agner T. Difficulties in avoiding exposure to allergens in cosmetics. Contact Dermatitis 2007: 57(2):105-9.

(7) Nicol AM, Hurrell AC, Wahyuni D, McDowall W, Chu W. Accuracy, comprehensibility, and use of material safety data sheets: a review. Am J Ind Med 2008: 51(11):861-76.

(8) Keegel T, Saunders H, LaMontagne AD, Nixon R. Are material safety data sheets (MSDS) useful in the diagnosis and management of occupational contact dermatitis? Contact Dermatitis 2007: 57(5):331-6.

(9) Nicol AM, Hurrell AC, Wahyuni D, McDowall W, Chu W. Accuracy, comprehensibility, and use of material safety data sheets: a review. Am J Ind Med 2008: 51(11):861-76.

(10) Fischer LA, Voelund A, Andersen KE, Menne T, Johansen JD. The dose-response relationship between the patch test and ROAT and the potential use for regulatory purposes. Contact Dermatitis 2009: 61(4):201-8.

(11) Friedmann PS. The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. Br J Dermatol 2007: 157(6):1093-102.

(12) Nixon RL. Material safety data sheets and allergic contact dermatitis: a misleading case. Australas J Dermatol 1997: 38(3):165.

(13) Friis U.F, Menne T., Flyvholm M-A., Bonde J.P., Johansen JD. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. Contact Dermatitis 2013: 69(3):153-63.

(14) Frazier LM, Beasley BW, Sharma GK, Mohyuddin AA. Health information in material safety data sheets for a chemical which causes asthma. J Gen Intern Med 2001: 16(2):89-93.

(15) Bernstein JA. Material safety data sheets: are they reliable in identifying human hazards? J Allergy Clin Immunol 2002: 110(1):35-8.

(16) Kanerva L, Henriks-Eckerman ML, Jolanki R, Estlander T. Plastics/acrylics: material safety data sheets need to be improved. Clin Dermatol 1997: 15(4):533-46.

(17) Basketter D.A., Kanerva L. Identification and Assessment in Relation to the Material Safety Data Sheets. In: Kanerva L, Elsner P, Wahlberg J, Maibach HI, editors. Handbook of Occupational Dermatology.Berlin Heidelberg: Springer Verlag: 2000. p. 395-401.

(18) Welsh MS, Lamesse M, Karpinski E. The verification of hazardous ingredients disclosures in selected material safety data sheets. Appl Occup Environ Hyg 2000: 15(5):409-20.

(19) Diepgen TL, Scheidt R, Weisshaar E, John SM, Hieke K. Cost of illness from occupational hand eczema in Germany. Contact Dermatitis 2013: 69(2):99-106.

(20) The Ministry of Employment. The Working Environment Act (Arbejdsmiljøloven). 7-9-2010. (Last accessed 2-4-2014).

Table 1. The sections of MSDS in focus (2).

Section	Heading
2	Hazards identification
3	Composition of/information on ingredients
9	Physical and chemical properties
11	Toxicological information
15	Regulatory information
16	Other information

Table 2 Shortcomings found in MSDS. One MSDS can have more than one shortcoming. Observed in 28/66 patients. MSDS: N = 137.

Shortcomings observed	Sum of MSDS (%)
Missing R43/H317 while known contact allergen was present	84 (61.3)
Names of preservatives not included in section 3 despite containing preservatives	67 (48.9)
Nothing about allergy in sections 2, 3, 11,15 or 16 in the MSDS despite the content of allergens	28 (20.4)
Allergen listed as R43/H317 but nothing mentioned about allergy in section 11	15 (10.9)
Product contains additives but no chemical names given	6 (4.4)
Azo-textile colour but nothing about which colour is used	3 (2.2)
Incorrect chemical name	2 (1.5)
Missing name of chemical and CAS-no but labelled R43/H317	1 (0.7)
Illegible MSDS	1 (0.7)

Table 3. Allergens observed in MSDS where information was insufficient from a medical viewpoint. N = 137 MSDS.

Name	CAS no	Concentration given in the MSDS [%]	Concentration given by manufacturer	Specific Concentration Limit (SCL) [%]	Not listed in MSDS with R43/H317
Benzisothiazolinone (BIT)	2634-33-5	0.01-0.04	0.00182-0.0727	0.05	x
Methylchloroisothiazolinone/ Methylisothiazolinone (MCI/MI)	55965-84-9	0.0015	0.00008-0.00142	0.0015	x
Iodopropynylbenzylcarbamate (IPBC)	55406-53-6	0.5-1	NG	NL	x
Linalool	78-70-6	<1	NCM	NL	x
Limonene	138-86-3, 5989-27-5	20-50	30-35	No SCL	x
Bronopol	52-51-7	0.016-0.03	0.016-0.08	NL ,NC	x
ethyl-2-cyanoacrylate	7085-85-0	60-100	NG	NL, NC	x
Formaldehyde…%	50-00-0	NG	NG	0.2	x
Glutarladehyde	111-30-8	NG	NG	0.5	x
Methyl methacrylate	80-62-6	NG	NG	No SCL	x
Fatty acids, C6-19-branched, cobalt(2+) salts	68409-81-4	NG	NCM	NL	x
Reaction product: bisphenol-A(epichlorhydrin); epoxy resin (number average molecyle weight more than 700)	25068-38-6	75-100	NCM	No SCL	
Benzyl alcohol	100-51-6	25-50	NCM	NL	x
Methylisothiazolinone	2682-20-4	0.01	0.00005-0.0269	No SCL	x
Triethylenetetraamine	112-24-3	5-10	NCM	No SCL	
4,4-methylen-bis-cyclohexanamin	1761-71-3	25-50	NCM	NL	x
DMDM hydantoin	6440-58-0	NG	NG	NL	x
Dichlorooctylisothiazolinone (DCOIT)	64359-81-5	NG	NG	NL	x
Perfume	NA	NG	NCM	-	x
m-xylylentriamin	1477-55-0	15-35	NCM	NL	
Diethylentriamin	111-40-0	10-25	NCM	No SCL	
Triethanolamine	102-71-6	5-15, 10-30	10-30	NL	x
Dibutyltindilaurant	77-58-7	0.1-1	NCM	NL	x
Cocamide MEA	68140-00-1	10-20	NCM	NL	x
Methylparaben	96-76-3	NG	NCM	NL	x
Ceteareth-25	68439-49-6	NG	NCM	NL	x
Cetearyl alcohol	67762-27-0	5-10	NCM	NL	x
Polyurethane dimethacrylate	NA	10-20	NCM	-	x

Bisphenol-A polyethylenglycidyl ether dimethacrylate	41637-38-1	3-8, 45-55	NCM	NL	x
Methacrylates	NA	25-50	NCM	-	x
Bisphenol-A-Diglycidylether dimethacrylate	1565-94-2	2-6	NCM	NL	x
Urea hydrogen peroxide	124-43-6	2.5-10	NCM	NL	x
Diurethane dimethacrylate	41137-60-4	3-8	NCM	NL	x
7-ethylbicyclooxazolidine	7747-35-5	NG	NCM	NL	x
Orangeterpen	8028-48-6	25-35	NCM	NL	x
Additives	NA	NG	NCM	-	x
Lanoline derivates	NA	10	10	-	x
Cobalt carboxylate	NA	NG	NG	-	x
Azo-color	51868-46-3	10-15	NCM	NL	x
Methacrylate copolymer	NA	1-4.9	NCM	-	x
Poly alkyl methacrylate	NA	NG	NCM	-	x
Cocamide DEA	61721-31-9, 68603-42-9	5-10	NCM	NL	x
Butylated hydroxytoluene (BHT)	128-37-0	NG	NCM	NL	x
Substituted thiadiazole	91648-65-6	0.1-0.5	NCM	NL	
Lanolin	8006-54-0	1-5	NCM	NL	x
Citronellol	106-22-9	<1	NCM	NL	x
Hydroxycitronella	107-55-6	<1	NCM	NL	x
propylene glycol	57-55-6	<1	NCM	NL	x
Sodium benzoate	532-32-1	<1, 15-30	NCM	NL	x
Malic acid	617-48-1	<1	NCM	NL	x
Olus oil	68956-68-3	1-5	NCM	NL	x
Hexyl cinnamal	101-86-0	<1	NCM	NL	x
Phenol formaldehyde resin	9003-35-4	2.5-10	NCM	NL	x
Butyl acrylate	141-32-2	NG	NG	No SCL	x
Ethyl acrylate	140-88-5	NG	NG	No SCL	x
Octylisothiazolinone	26530-20-1	NG	NG	0.05	x
polysorbate 60	9005-67-8	1-5	NCM	NL	x

"NA" – Not available
"NL" – Not listed in Annex VI in CLP
"NG" – Concentration not given by the manufacturer or in the MSDS
"NC" – Not classified as allergenic R43/H317
"NCM" – No contact made to the manufacturer
"No SCL" – No Specific Concentration Limit.

Table 4. Our findings show the following points need to be addressed.

Problem	Solution
Concentration	- A low concentration of an allergen can elicit an allergic response. Legislation regarding chemicals not reportable in the MSDS should be changed to require chemicals down to analytical limit to be listed. -The use concentrations in different exposure scenarios need to be revised.
MSDS	- All types of preservative independent of concentration should be labelled on the product and included in the MSDS section 3. - There should be no grounds for misinterpretation of the information obtained from the MSDS
Control	- Periodic reviewing of the MSDS by competent authorities

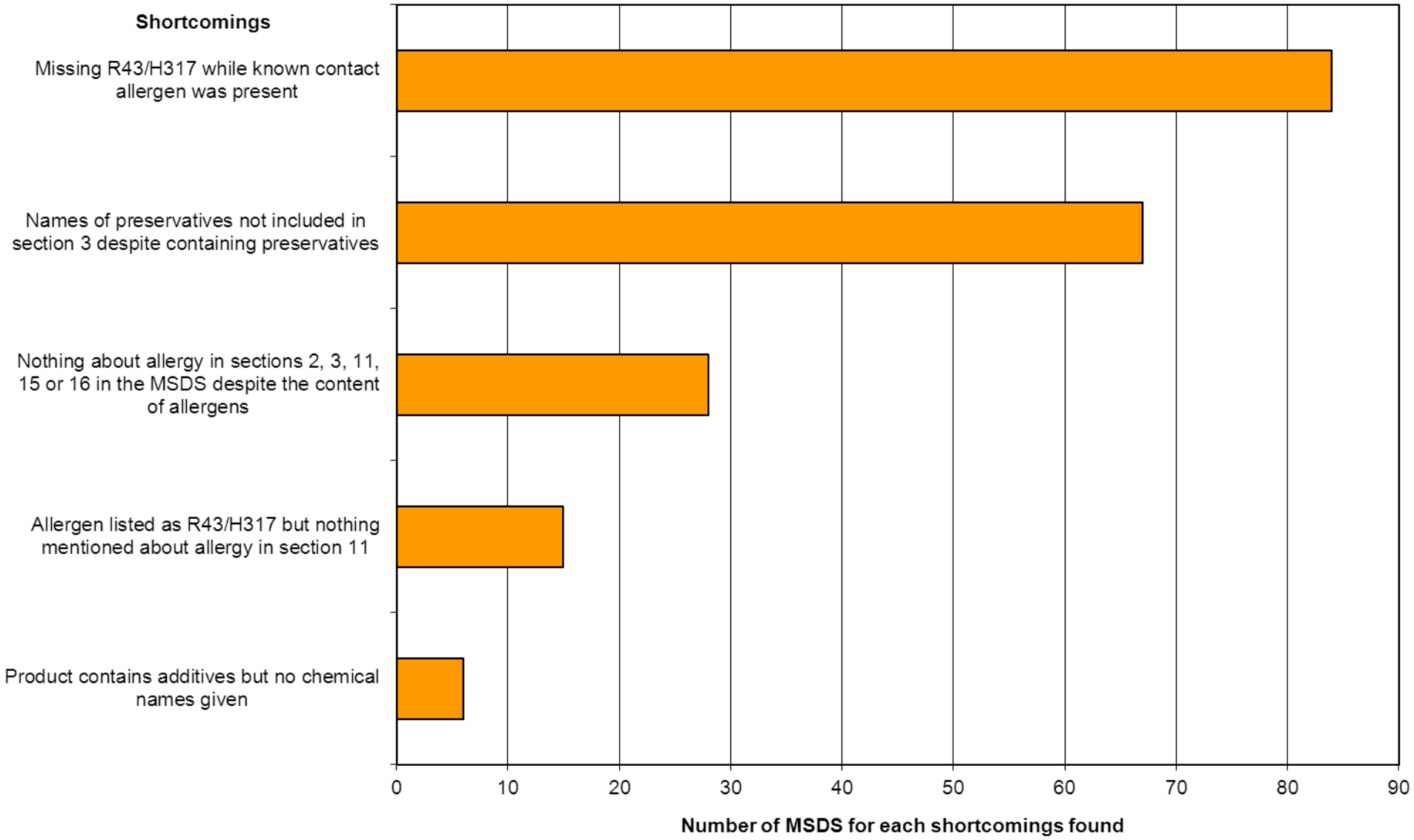

Figure 1. Top 6 most frequent shortcomings observed. One MSDS can have more than one shortcoming. N=137.

Manuscript IV

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Isothiazolinones in commercial products at Danish workplaces

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Summary

Background. In recent years, a steep increase in the frequency of occupational contact allergy to isothiazolinones has been reported from several European countries.
Objective. To examine the extent and occurrence of isothiazolinones in different types of product at Danish workplaces.
Methods. Seven different isothiazolinones were identified in the *Dictionary of Contact Allergens: Chemical Structures, Sources, and References* from *Kanerva's Occupational Dermatitis*. By use of the chemical names and Chemical Abstracts Service numbers for these chemicals, information on products registered in the Danish Product Register Database (PROBAS) was obtained.
Results. All seven isothiazolinones were registered in PROBAS. The top three isothiazolinones registered were: benzisothiazolinone (BIT), registered in 985 products, methylisothiazolinone (MI), registered in 884 products, and methylchloroisothiazolinone (MCI)/MI, registered in 611 products. The concentration ranges were 0.01 ppm to 45% for BIT, 0.01 ppm to 10% for MI, and 0.01 ppm to 14.1% for MCI/MI. The most common product type was 'paint and varnish'; five of the seven isothiazolinones were registered in this type of product.
Conclusion. Isothiazolinones are present in multiple products registered for use at workplaces, and may occur in high concentrations.

Key words: 2-methyl-4,5-trimethylene-4-isothiazolin-3-one; allergic contact dermatitis; benzisothiazolinone; dichlorooctylisothiazolinone; isothiazolinones; methylchloroisothiazolinone; methylisothiazolinone; octylisothiazolinone.

Knowledge regarding the individual and general exposures to hazardous chemicals in our environment is pivotal for understanding the individual and general disease risk related to these chemicals. Such information is also essential for the planning of preventive initiatives. Information on the production and use of the chemicals may be retrieved from national and international statistical offices, databases, and manufacturers; this data collection is difficult and time-consuming. The Scandinavian countries have developed registers that contain information on the contents of hazardous chemicals in products registered for occupational use in the respective countries.

The isothiazolinones are preservatives (Table 1) that have been in use for > 30 years in products for both

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occupational and consumer use (1). This group of chemicals was soon recognized as containing strong or extremely potent allergens (2). Nevertheless, these chemicals were permitted (Table 1), and registered in different product categories (3). The general argument made in risk assessment has been that even extremely potent contact allergens can be used safely in products if the exposure concentration is sufficiently low (4). The risk assessment methods rest primarily on animal assays such as the guinea-pig maximization test (GPMT) (5) or the local lymph node assay (LLNA) (6, 7), and/or experimental induction studies in humans (human repeated insult patch test) (8). However, these methods have either failed or been incorrectly interpreted with regard to fulfilling the expectations of safety in terms of the risks of sensitization (1, 6, 7, 9, 10). The consequences have been serious, and have given rise to numerous occupational cases of severe allergic contact dermatitis (11–17) and an epidemic of contact allergy resulting from the use of cosmetic products caused by methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI) (1, 18–21).

In view of the above, we provide an overview of the occurrence of isothiazolinones in registered chemical products, and discuss the clinical and general health implications.

Methods

Identification of allergens

We selected the isothiazolinones listed in the *Dictionary of Contact Allergens: Chemical Structures, Sources, and References* from *Kanerva's Occupational Dermatitis* (33).

In the examination of product types registered with content of the isothiazolinones, the chemical names and the Chemical Abstract Service (CAS) numbers for these isothiazolinones were searched for in the Danish Product Register Database (PROBAS) (September 2012).

The Danish Product Register Database

PROBAS is a database in which the composition of, primarily, hazardous chemical products for occupational use is registered. Products are registered: (i) if the product/substance is manufactured or imported for occupational use in a quantity of > 100 kg annually; (ii) if the product contains at least one chemical that is registered as harmful according to the Danish Ministry of the Environment and the Danish Working Environment Authority (WEA); (iii) if the product contains $\geq 1\%$ of the substance (for preservatives, the limit is 0.1%); (iv) if the product/substance is assigned an occupational exposure limit in the WEA list of limit values for substances and materials; and/or (v) if materials contain $\geq 1\%$ of a substance that has been assigned an occupational exposure limit in the WEA list of limit values for substances and materials (34). When a product is registered in PROBAS, we assume that it is used in the Danish work environment.

PROBAS is updated at the end of every odd year with data collected from the manufacturers in even years. In cases where there were fewer than three manufacturers, the specific product types were classified as confidential.

In PROBAS, the chemicals are categorized according to the Use Categories Nordic (UCN) code system (35). The system is the same in Norway, Sweden, and Denmark. The system consists of main groups and subgroups. The code for the main group consists of three characters, and the code for the subgroup consists of the main group plus three digits. One chemical can have more than one UCN code. According to the principal manufacturer of MCI/MI, MCI is not sold as an independent substance, so, even though it is listed on its own in PROBAS, it is likely to be used together with MI.

All confidential information was omitted from the dataset. No main groups were deleted, but subgroups that had a ratio of $< 2\%$ between the main group and the subgroup were deleted by the authors to maintain a more relevant overview.

Results

The isothiazolinones included in this study are shown in Table 1. All seven isothiazolinones were registered in PROBAS. The results of the search in the database for different types of registered product are shown in Tables 2 and 3. The concentrations listed in the two tables are in the same format as used in PROBAS. It is not possible to compare the different product types, because some of them are raw materials and others are products for the downstream user.

Benzisothiazolinone (BIT) (CAS no. 2634-33-5)

BIT was registered in 985 different products registered in PROBAS, and was the isothiazolinone most often found in products registered in PROBAS. The top three product types containing BIT were paints and varnishes (544), cleaning/washing agents (108), and polishing agents (65). BIT was registered in concentrations from 0.01 ppm to 45%.

Table 1. Marketed isothaizolinones and their regulation

Isothiazolinones	CAS numbers	Regulations			
		Cosmetics	REACH	CLP	BPR
Benzisothiazolinone (INCI) (1,2-benzisothiazolin-3-one)	2634-33-5	Not allowed (22, 23)	Intended but not registered (24)	Harmonized classification: R43/H317 with specific concentration limit: 0.05% (25)	Review programme: PT 2, 6, 9, 11, 12, and 13 (26) Non-included: PT 7, 10, and 22 (27)
4,5-Dichloro-2-n-octyl-4-isothiazolin-3-one	64359-81-5	Not allowed (23)	Intended but not registered (24)	Not classified	Approved: PT 8 Review programme: PT 7, 9, 10 11, and 21 (26) Non-included: PT 6, and 12 (27)
2-Methyl-4,5-trimethylene-4-isothiazolin-3-one	82633-79-2	Not allowed (23)	–	Harmonized classification: R43/H317 (25)	Not allowed
Methylchloroisothiazolinone (INCI) (5-chloro-2-methyl-4-isothiazolin-3-one)	26172-55-4	Not allowed (23)	Preregistered for 2010, but not registered (28)	Not classified	Not allowed
Methylchloroisothiazolinone (INCI) (5-chloro-2-methyl-4-isothiazolin-3-one) and methylisothiazolinone (INCI) (2-methyl-4-isothiazolin-3-one)	55965-84-9 and 96118-96-6	Allowed at 15 ppm (3:1) (29, 23)	Preregistered for 2010, but not registered	Harmonized classification: R43/H317 with specific concentration limit: 15 ppm (25) RoI France, concerning environmental classification: by end of 2014 (30)	First product: Review programme: PT 2, 4, 6, 11, 12, and 13 (26) Non-included: PT 3, 7, 9, and 10 (27) Second product: not allowed
Methylisothiazolinone (INCI) (2-methyl-4-isothiazolin-3-one)	2682-20-4	Allowed at 100 ppm (23, 31)	Preregistered for 2010, but not registered (28)	Harmonized classification: R43/H317 with non-specific concentration limit Inventory (self-classification): R43/H317 with specific concentration limit: 0.1%* Slovenia by end of 2013 (32)**	Review programme: PT 2, 6, 11, 12, and 13 (26) Non-included: PT 4, 7, 9, 10, and 22 (27)
Octylisothiazolinone (INCI) (2-n-octyl-4-isothiazolin-3-one)	26530-20-1	Not allowed (23)	Preregistered for 2010, but not registered (28)	Harmonized classification: R43/H317 with specific concentration limit: 0.05% (25)	Review programme: PT 6, 7, 9, 10, 11, and 13 (26) Non-included: PT 4, 8, and 12 (27)

BPR, biocidal products regulation; CLP, the regulation on classification, labelling and packaging of substances and mixtures; INCI, International Nomenclature of Cosmetic Ingredients; PT, product type; REACH, Registration, Evaluation, Authorization and Restriction of Chemical substances; RoI, registry of intention – 'warning' of future proposal.

*According to CLP there is non-specific concentration limit for MI but according to the inventory there is a ''self-classification'' with a specific concentration limit on 0.1%. This concentration is not validated or authorized but is used by some manufactures because of the allergenic potency of MI. For those manufacturer this concentration will be effective from 1st of June 2015.

**The European Commission requested Slovenia to classify MI according to the Annex XV dossier in REACH. The deadline was December 2013.

Methylisothiazolinone (CAS no. 2682-20-4)

MI was the second most frequently registered isothiazolinone, with 884 different products registered in PROBAS. The top three product types containing MI were paints and varnishes (471), cleaning/washing agents (87), and polishing agents (60). MI was registered in concentrations from 0.01 ppm to 10%.

Table 2. The results from the Danish Product Register Database (PROBAS) for benzisothiazolinone, methylisothiazolinone, methylchloroisothiazolinone, and Methylchloroisothiazolinone/methylisothiazolinone

		Benzisothiazolinone; CAS no. 2634-33-5					Methylisothiazolinone; CAS no. 2682-20-4					Methylchloroisothiazolinone; CAS no. 26172-55-4					Methylchloroisothiazolinone/methylisothiazolinone; CAS no. 55965-84-9				
Main group	No. of products in group	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)
Absorbents and adsorbents	90	3	3.3	75	0.1	369	6	6.7	4	0.02	147	–	–	–	–	–	–	–	–	–	–
Air cleaners and anti-odour agents	45	–	–	–	–	–	6	6.7	4	0.02	147	–	–	–	–	–	–	–	–	–	–
Biocides	1174	26	2.2	0.04	45	5.5*	34	2.9	0.05	10	1.1*	25	2.1	0.11	17.2	0.9*	27	2.3	0.03	14.1	1.6*
Car care products	96	21	21.9	2.5	5.4	0.26*	18	18.8	2	0.008	33.5	–	–	–	–	–	–	–	–	–	–
Binding agents	366	20	5.5	0.6	0.1	201	21	5.7	0.4	0.138	182	5	1.4	0.9	0.01	21.4	19	5.2	4.71	0.01	23.3
Binding agents for paints, adhesives, etc.	184	15	4.1	0.6	0.1	254	14	3.8	8	0.138	282	–	–	–	–	–	10	2.7	11	0.01	24.2
Other binding agents	168	–	–	–	–	–	–	–	–	–	–	4	1.1	0.9	0.01	21.3	8	2.2	4.71	0.004	21.7
Softeners	59	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5	8.5	12	0.01	33.8
Other softeners	32	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	6.8	12	0.01	38.8
Colouring agents	324	25	7.7	12.5	1	486	36	11.1	0.25	0.05	56.4	22	6.8	0.75	0.01	38.8	7	2.2	1.4	0.015	29.2
Pigments for paints and printing inks	191	16	4.9	12.5	0.1	265	25	7.7	1.4	0.01	50.5	17	5.2	4.2	0.01	46.1	4	1.2	1.4	0.001	8.7
Other colouring agents	125	8	2.5	14.7	1	0.13*	10	3.1	0.25	0.05	83.2	–	–	–	–	–	–	–	–	–	–
Flooring materials	146	6	4.1	93.9	0.05	199	5	3.4	7.5	0.05	137	–	–	–	–	–	–	–	–	–	–
Impregnation/proofing	122	7	5.7	10.5	0.03	126	8	6.6	1.36	0.013	22.1	4	3.3	0.01	0.0037	10.0	–	–	–	–	–
Cosmetics	484	–	–	–	–	–	9	1.9	0.75	0.085	174	–	–	–	–	–	8	1.7	0.01	0.003	4.9
Construction materials	201	3	1.5	500	0.29	0.13*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Adhesives	752	28	3.7	0.23	0.10	173	17	2.3	0.5	0.023	47.6	6	0.8	0.96	0.003	7.6	24	3.2	0.09	0.05	30.9
Paint and varnish	3567	544	15.3	0.01	0.33	176	471	13.2	0.01	0.085	36.3	275	7.7	0.01	0.07	12.9	363	10.2	0.01	3.9	103
Paint: water-based, decorative/protection, industrial use	219	144	4.0	0.01	0.05	196	110	3.1	0.01	0.024	20.3	75	2.1	0.04	0.001	1.5	105	2.9	0.02	0.022	25.4
Paint and varnishes: additives	77	6	7.8	0.55	0.03	118	7	9.1	0.86	0.018	65.9	–	–	–	–	–	–	–	–	–	–
Metal surface treatment remedies	468	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	0.9	40	0.2	816
Solvents	797	–	–	–	–	–	4	0.5	1	0.1	251	4	0.5	3	0.1	254	–	–	–	–	–
Surface active agents	517	16	3.1	0.1	0.04	73.2	16	3.1	0.53	0.01	36.0	6	1.2	0.98	0.001	6.0	5	1.0	2.7	0.001	7.6

Table 2. Continued

Main group	No. of products in group	Benzisothiazolinone; CAS no. 2634-33-5					Methylisothiazolinone; CAS no. 2682-20-4					Methylchloroisothiazolinone; CAS no. 26172-55-4					Methylchloroisothiazolinone/ methylisothiazolinone; CAS no. 55965-84-9				
		No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)
Surface treatment for paper, cardboard, and other non-metals	106	3	2.8	0.15	0.02	56.4	4	3.8	1.35	0.012	47.8	3	2.8	3.6	0.01	37.3	8	7.5	2	0.023	31.3
Surface treatment for paper and cardboard	73	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	5.7	2	0.023	38.1
Polishing agents	350	65	18.6	0.66	0.04	76.9	60	17.1	0.25	0.024	31.3	20	5.7	0.15	0.9	433	32	9.1	0.08	1	345
Polishing agents for lacquers (car wax)	93	18	5.1	0.78	0.02	57.4	22	6.3	1.4	0.024	60.1	7	2.0	4.2	0.07	281	–	–	–	–	–
Wax and other polishing preparations for floors	81	27	7.7	0.66	0.02	51.3	24	6.9	0.25	0.009	9.41	10	2.9	0.39	0.001	5.4	18	5.1	0.08	0.048	41.8
Other polishing agents	71	9	2.6	35.4	0.04	194	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cleaning/washing agents	3560	108	3.0	0.06	0.17	83.4	87	2.4	0.02	0.19	55.8	34	1.0	0.03	0.6	156	50	1.4	0.04	0.9	363
Cracking indicators	56	2	3.6	0.75	0.0045	30.3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Rust inhibitors	421	11	2.6	0.7	0.06	90.7	12	2.9	0.01	0.06	48.8	3	0.7	0.04	0.001	3.4	–	–	–	–	–
Corrosion inhibitors	169	10	2.4	0.7	0.06	93.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Raw materials and intermediate products	572	–	–	–	–	–	3	0.7	75	0.01	91.7	–	–	–	–	–	–	–	–	–	–
Rinsing agents	95	11	11.6	160	0.1	263	3	3.2	1.8	0.0004	3.56	6	6.3	2.3	0.001	6.1	–	–	–	–	–
Rinsing agents (for dishwashing machines)	50	–	–	–	–	–	3	3.2	1.8	0.0004	3.56	3	3.2	5.3	0.001	9.9	–	–	–	–	–
Lubricants	1225	3	0.2	0.21	0.02	127	–	–	–	–	–	–	–	–	–	–	5	0.4	2.8	0.071	173
Toners	56	10	17.9	26.4	0.05	271	6	10.7	3.9	0.049	98.3	–	–	–	–	–	4	7.1	1.07	0.001	10.8
Printing inks	293	10	3.4	8	0.13	413	14	4.8	2.4	0.07	62.1	12	4.1	7.4	0.07	65.6	13	4.4	1	0.43	834
Filling agents	956	16	1.7	5.4	0.17	206	18	1.9	0.28	0.1	78.8	13	1.4	0.76	0.5	343	8	0.8	0.14	0.002	7.5
Viscosity changers	71	–	–	–	–	–	3	4.2	9.9	0.005	30.0	–	–	–	–	–	–	–	–	–	–
Total	**–**	**985**	**–**	**0.01**	**45**	**–**	**884**	**–**	**0.01**	**10**	**–**	**474**	**–**	**0.01**	**17.2**	**–**	**611**	**–**	**0.01**	**14.1**	**–**

*Percentages.

Table 3. The results from the Danish Product Register Database (PROBAS) for dichlorooctylisothiazolinone and octylisothiazolinone

		Name Dichlorooctylisothiazolinone; CAS no. 64359-81-5					Name Octylisothiazolinone; CAS no. 26530-20-1				
Main group	No. of products in group	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)	No. of products	% of main group	Concentration (minimum) (ppm)	Concentration (maximum) (%)	Mean (ppm)
Biocides	1174	12	1	0.11*	28.1	11.1*	16	1.4	7.1	16	1.7*
Binding agents	366	–	–	–	–	–	2	0.5	10	0.02	71.2
Cooling agents for metal processing	201	–	–	–	–	–	3	1.5	100	0.03	177
Adhesives	752	–	–	–	–	–	4	0.5	67.5	16.3	4.1*
Paint and varnish	3567	38	1.1	405	0.2	0.11*	60	1.7	0.02	0.1	177
Filling agents	956	5	0.5	94	0.1	368	5	0.5	25	0.5	0.13*
Total	**–**	**58**	**–**	**94**	**28.1**	**–**	**111**	**–**	**0.02**	**16.3**	**–**

*Percentages.

Methylchloroisothiazolinone/methylisothiazolinone (CAS no. 55965-84-9)

MCI/MI was the third most frequently registered isothiazolinone, with 611 different products registered in PROBAS. The top three product types containing MCI/MI were paints and varnishes (363), cleaning/washing agents (50), and polishing agents (32). MCI/MI was registered in concentrations from 0.01 ppm to 14%.

Methylchloroisothiazolinone (CAS no. 26172-55-4)

MCI was the fourth most frequently registered isothiazolinone, with 474 different products registered in PROBAS. The top three product types containing MCI were paints and varnishes (275), cleaning/washing agents (34), and biocides (25). MCI was registered in concentrations from 0.01 ppm to 17%.

Octylisothiazolinone (OIT) (CAS no. 26530-20-1)

OIT was the fifth most frequently registered isothiazolinone, with 111 different products registered in PROBAS. The top three product types containing OIT were paints and varnishes (60), biocides (16), and filling agents (5). OIT was registered in concentrations from 0.02 ppm to 16.3%.

Dichlorooctylisothiazolinone (DCOIT) (CAS no. 64359-81-5)

DCOIT was registered in 58 different products, which was the second lowest number among the isothiazolinones in this study. The top three product types containing DCOIT were paints and varnishes (38), biocides (12), and filling agents (5). DCOIT was registered in concentrations from 94 ppm to 28.1%.

2-Methyl-4,5-trimethylene-4-isothiazolin-3-one (MTMIT) (CAS no. 82633-79-2)

MTMIT was the only isothiazolinone for which all of the use categories (UCN codes) were confidential. The chemical was registered in seven products in concentrations from 47.6 to 150 ppm.

Discussion

The present study shows that thousands of products are registered in PROBAS as containing isothiazolinones.

BIT and MI were registered in 985 and 884 products, respectively; MCI/MI was registered in 611 products.

The most prominent product type containing these three isothiazolinones was paints and varnishes (with a total of 3567 products), in which BIT, MI and MCI/MI were the predominant isothiazolinones. This is in accordance with clinical experience (Table 4), where isothiazolinone allergies have been reported in painters (36–39) and paint production workers (12, 40, 41). It is also known that MCI/MI and MI may evaporate and cause airborne allergic contact dermatitis, a manifestation that has been increasingly seen with particular MI-preserved paints (36–38, 42). MI and BIT have been found to cause airborne contact dermatitis, respiratory symptoms, including acute asthma, and systemic allergic contact dermatitis (15, 36). The presence of MI in paints was further highlighted in a study in which, of 19 different water-based paints from the Danish retail marked, all contained MI, four contained MCI, and 16 contained BIT (43). The emission of BIT, MCI and MI from paint has also been shown (43).

Table 4. Clinical effects of cutaneous and airborne exposures to the isothiazolinone preservatives

Exposures	Concentrations	Clinical symptoms	Duration of eczema/ consequence	Reference
Cosmetic products	MCI/MI < 15 ppm MI < 100 ppm	Allergic contact dermatitis: face and hands	One event: 4–6 months Repeated events: chronic disease	(18–21)
Paint, glues, oils, etc.	MCI/MI < 14 ppm MI < 300 ppm BIT < 360 ppm (43)	Severe allergic contact dermatitis: face and hands Airborne dermatitis, respiratory symptoms	6–12 months Change or loss of job	(11–14, 36–38, 42, 44–46)
Biocides	MCI > 0.5% MI > 0.5% BIT > 0.5%	Chemical burns, generalized severe allergic contact dermatitis with subjective symptoms Systemic contact dermatitis, respiratory symptoms	Chronic disease, risk of disability	(11, 15, 45)
Airborne exposure	Probably < 60 mg/m^2 (43)	Primary sensitization may be possible Flare-ups of facial and systemic contact dermatitis	Acute and chronic disease	(15, 36–38, 42, 43, 47)

BIT, benzisothiazolinone; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

Preservative exposure from paints has changed since 2000, when MI was introduced as a stand-alone preservative and, to some extent, replaced MCI/MI. The reason may be that, whereas MCI/MI is on the list of dangerous substances, labelled R43/H317 (may cause sensitization), and has to be declared on the label if it is present in amounts > 15 ppm, no such requirements exist for MI (Table 1); instead, there is self-classification, with a specific concentration limit of 0.1% in industrial products (25). This may erroneously lead the manufacturers to assume that MI is unproblematic (29).

The products registered with the highest content of isothiazolinones were car care products, BIT being present in 21.9% of products, and MI in 18.8%; a similar pattern was seen for polishing agents for cars and floor products (Tables 2 and 3). We have not found any reports concerning contact allergy related to the use of such products.

Contact allergy to isothiazolinones in the paper and textile industry has also been reported (14, 17, 48, 49). In our study, BIT, MI and MCI/MI were registered in products for the surface treatment of paper, cardboard, and other non-metals, although not very frequently. In the paper industry, they may be present in the concentrated biocides that are used and added to the pulp. All of the isothiazolinones were registered as biocide products. This is a product group that may have multiple uses.

Contact allergy to BIT and OIT has been reported in metalworkers (50); these are also the two allergens found in cooling agents by chemical analysis in a Finnish study (51). In PROBAS, only OIT was registered in cooling agents for metal processing (Table 3). This emphasizes the importance of patch testing with these special isothiazolinones in metalworkers with occupational eczema.

Exposure to high concentrations of isothiazolinones (Table 4) can cause chemical burns followed by contact sensitization resulting from a single exposure (52–57). Further accidental exposure to such high concentrations may lead to generalized dermatitis accompanied by systemic contact dermatitis and subjective symptoms (15). Such cases may develop into chronic diseases.

A part of the problem is that much emphasis and reliance has been put on the results of animal assays, in particular the LLNA, to predict the sensitization potency of these substances. The reporting of these results is very brief in the scientific literature, as EC3 values only, not supported by data, and has also been shown to be misleading (9). This is in contrast to the amount of human data from the occupational setting and consumers, which, for a long period of time, have been ignored by industry and regulators.

In three product categories, namely paints and varnishes, biocides, and filling agents, all six isothiazolinones were registered, whereas, for all other product categories, some but not all isothiazolinones were used.

There are only few studies on cross-reactions between the different isothiazolinones. In 1992, Damstra et al. found, in an analysis of 556 patch tested patients, that 8 of 10 patients who reacted to BIT also reacted to MCI/MI, and 8 of 56 patients who reacted to MCI/MI also reacted to BIT (58). In a recent study, Mose et al. found that all patients with concomitant positive patch test reactions to OIT, BIT and MCI/MI were painters, which suggests concomitant sensitization rather than

cross-reactivity (16). Cross-reactivity can only be studied in animals or if the primary sensitizer in humans is known. In GPMTs, it was shown that cross-reactivity between MCI and MI exists, whereas no cross-reactivity could be shown between MCI, MI as primary sensitizer, and OIT, and probably BIT (59). In 2008, Isaksson et al. also showed, by testing workers accidentally sensitized to MCI, that cross-reactivity between MCI and MI is likely, depending on the degree of contact allergy (60), which is in accordance with clinical experience (61). This means that, in detecting cases of contact allergy to isothiazolinones, one cannot rely on testing only with MCI and MI in the baseline series.

It is very important for the physician and the clinical procedure that all information concerning the product be on the product label and/or in the Material Safety Data Sheet (MSDS) or other product datasheets, so that exposures to allergens can be identified, appropriate patch testing performed, and the correct diagnosis made. Otherwise, important allergens can be missed. The correct diagnosis is very important for patients with occupational allergic contact dermatitis, both for the medical prognosis and for the compensation, depending on national laws (62).

In conclusion, isothiazolinones are present in multiple products registered for use at the workplace, and may occur in high concentrations. BIT was the most frequent isothiazolinone, being registered in the most products (985), and the concentration range was 0.01 ppm to 45%.

Knowledge of the use and exposure to the isothiazolinone preservatives, together with the contact allergic potential and the clinical disease related to the exposure, leads to the following points to be addressed:

- The use concentrations in the different exposure scenarios need to be revised.
- All types of isothiazolinone, independently of concentration, should be labelled on the product and included in the MSDS.
- The use of concentrated solutions of isothiazolinones should only be permitted in closed systems, and the workers involved need proper education.
- Is the margin of safety for isothiazolinones so low that future use should be abolished?

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References

1 Thyssen J P, Johansen J D, Menné T. Contact allergy epidemics and their controls. *Contact Dermatitis* 2007: **56**: 185–195.
2 Basketter D A, Rodford R, Kimber I, Smith I, Wahlberg J E. Skin sensitization risk assessment: a comparative evaluation of 3 isothiazolinone biocides. *Contact Dermatitis* 1999: **40**: 150–154.
3 Flyvholm M-A. Preservatives in registered chemical products. *Contact Dermatitis* 2005: **53**: 27–32.
4 Loveless S E, Api A M, Crevel R W et al. Potency values from the local lymph node assay: application to classification, labelling and risk assessment. *Regul Toxicol Pharmacol* 2010: **56**: 54–66.
5 Magnusson B, Kligman A M. The identification of contact allergens by animal assay. The guinea pig maximization test. *J Invest Dermatol* 1969: **52**: 268–276.
6 Thyssen J P, Gimenez-Arnau E, Lepoittevin J P, Menné T, Boman A, Schnuch A. The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals. Part II. *Contact Dermatitis* 2012: **66**(Suppl. 1): 25–52.
7 Thyssen J P, Gimenez-Arnau E, Lepoittevin J P, Menné T, Boman A, Schnuch A. The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals. Part III. *Contact Dermatitis* 2012: **66**(Suppl. 1): 53–70.
8 Gerberick G F, Sikorski E E. In vitro and in vivo testing techniques for allergic contact dermatitis. *Am J Contact Dermat* 1998: **9**: 111–118.
9 Roberts D W. Methylisothiazolinone is categorised as a strong sensitiser in the Murine Local Lymph Node Assay. *Contact Dermatitis* 2013: **69**: 261–262.
10 Thyssen J P, Gimenez-Arnau E, Lepoittevin J P, Menné T, Boman A, Schnuch A. The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals. Part I. *Contact Dermatitis* 2012: **66**(Suppl. 1): 11–24.
11 Bregnbak D, Lundov M D, Zachariae C, Menné T, Johansen J D. Five cases of severe chronic dermatitis caused by isothiazolinones. *Contact Dermatitis* 2013: **69**: 57–59.
12 Mathias C G, Andersen K E, Hamann K. Allergic contact dermatitis from 2-n-octyl-4-isothiazolin-3-one, a paint mildewcide. *Contact Dermatitis* 1983: **9**: 507–509.
13 Alto-Korte K, Alanko K, Henriks-Eckerman M L, Kuuliala O, Jolanki R. Occupational allergic contact dermatitis from 2-N-octyl-4-isothiazolin-3-one. *Contact Dermatitis* 2007: **56**: 160–163.
14 Kawai K, Nakagawa M, Sasaki Y, Kawai K. Occupational contact dermatitis from Kathon 930. *Contact Dermatitis* 1993: **28**: 117–118.
15 Kaur-Knudsen D, Menné T, Christina C B. Systemic allergic dermatitis following

airborne exposure to 1,2-benzisothiazolin-3-one. *Contact Dermatitis* 2012: **67** 310–312.
16 Mose A P, Frost S, Ohlund U, Andersen K E. Allergic contact dermatitis from octylisothiazolinone. *Contact Dermatitis* 2013: **69**: 49–52.
17 Burden A D, O'Driscoll J B, Page F C, Beck M H. Contact hypersensitivity to a new isothiazolinone. *Contact Dermatitis* 1994: **30**: 179–180.
18 Lundov M D, Opstrup M S, Johansen J D. Methylisothiazolinone contact allergy – growing epidemic. *Contact Dermatitis* 2013: **69**: 271–275.
19 Lundov M D, Zachariae C, Menné T, Johansen J D. Airborne exposure to preservative methylisothiazolinone causes severe allergic reactions. *BMJ* 2012: **345**: e8221.
20 Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis* 2013: **69**: 231–238.
21 Uter W, Gefeller O, Geier J, Schnuch A. Methylchloroisothiazolinone/methylisothiazolinone contact sensitization: diverging trends in subgroups of IVDK patients in a period of 19 years. *Contact Dermatitis* 2012: **67**: 125–129.
22 Scientific Committee on Consumer Safety. *Opinion on Benzisothiazolinone*: European Commission Health & Consumers, June 26, 2012. Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_099.pdf (last accessed 2 January 2014).
23 The European Parliament and the Council of the European Union. Regulation (EC) No. 1223/2009 of the European Parliament and on the Council of 30 November 2009 on cosmetic products, 30 November 2009. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:EN:PDF (last accessed 2 January 2014).
24 ECHA. Intentions – Substances identified for 2013 registration, 27 May 2013. Available at: http://echa.europa.eu/documents/10162/13632/intentions_2013_en.pdf (last accessed 2 January 2014).
25 ECHA. Regulation on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No. 1907/2006, the European Parliament and the Council of the European Union, 29 October 2010. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF (last accessed 2 January 2014).
26 The Commission of the European Communities. Commission regulation – on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, 4 December 2007.
27 ECHA. Biocides: non-inclusion decisions, 8 December 2013. Available at: https://circabc.europa.eu/d/a/workspace/SpacesStore/491962c1-8f3e-4adb-9e0c-cf1a782895d9/Consolidated%20list%20of%20non-inclusion%20decisions.pdf (last accessed 2 January 2014).
28 ECHA. List of pre-registered substances, 8 December 2013. Available at: http://apps.echa.europa.eu/preregistered/attachments/prs_complete_20090327.csv (last accessed 2 January 2014).
29 Scientific Committee on Consumer Safety. Opinion on the mixture of 5-chloro-2-methylisothiazolin-3(2H)-one and 2-methylisothiazolin-3(2H)-one, Colipa no. P56. 8 December 2009. Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_009.pdf (last accessed 2 January 2014).
30 ECHA. Registry of current Harmonised Classification and Labelling intentions – Methylisothiazolinone: Methylchloroisothiazolinone (1:3), 9 March 2012. Available at: http://echa.europa.eu/registry-current-classification-and-labelling-intentions/-/substance/1301/search/+/del/20/col/NOTIFICATIONDATEROI_C/type/desc/pre/2/view (last accessed 2 January 2014).
31 The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers. 2004. Opinion on methylisothiazolinone, Colipa no. P94. 23 April 2004. Available at: http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out270_en.pdf (last accessed 2 January 2014).
32 ECHA. Registry of current Harmonised Classification and Labelling intentions – Methylisothiazolinone, 23 November 2013. Available at: http://echa.europa.eu/registry-current-classification-and-labelling-intentions/-/substance/2816/search/+/term (last accessed 2 January 2014).
33 Lepoittevin J-P, Le Coz C J. Dictionary of contact allergens: chemical structures, sources, and references. In: *Kanerva's Occupational Dermatology*, 2nd edition, Rustemeyer T, Elsner P, John S M, Maibach H (eds): Berlin, Heidelberg, Springer-Verlag, 2012: pp. 1737–1848.
34 Danish Working Environment Authority. Substances and materials that must be notified to the Product Registry, 0000. Available at: http://arbejdstilsynet.dk/en/engelsk/produktregistret/produkter-der-skal-anmeldes.aspx (last accessed 17 December 2013).
35 Substances in Products in the Nordic Countries. Substances in products in the Nordic Countries, Use Categories Nordic (UCN), 12 September 2007.
36 Lundov M D, Mosbech H, Thyssen J P, Menné T, Zachariae C. Two cases of airborne allergic contact dermatitis caused by methylisothiazolinone in paint. *Contact Dermatitis* 2011: **65**: 176–179.
37 Schubert H. Airborne contact dermatitis due to methylchloro- and methylisothiazolinone (MCI/MI). *Contact Dermatitis* 1997: **36**: 274.
38 Kaae J, Menné T, Thyssen J P. Presumed primary contact sensitization to methylisothiazolinone from paint: a chemical that became airborne. *Contact Dermatitis* 2012: **66**: 341–342.
39 Fischer T, Bohlin S, Edling C, Rystedt I, Wieslander G. Skin disease and contact sensitivity in house painters using water-based paints, glues and putties. *Contact Dermatitis* 1995: **32**: 39–45.
40 Gruvberger B, Bruze M, Almgren G. Occupational dermatoses in a plant producing binders for paints and glues. *Contact Dermatitis* 1998: **38**: 71–77.
41 Thyssen J P, Sederberg-Olsen N, Thomsen J F, Menné T. Contact dermatitis from methylisothiazolinone in a paint factory. *Contact Dermatitis* 2006: **54**: 322–324.
42 Lundov M D, Menné T. Airborne exposure to methylchloroisothiazolinone and methylisothiazolinone from a toilet cleaner. *Contact Dermatitis* 2013: **68**: 252–253.
43 Lundov M D, Kolarik B, Bossi R, Gunnarsen L, Johansen J. Emission of isothiazolinones from water-based paint, 2013 (in preparation).
44 Aalto-Korte K, Ackermann L, Henriks-Eckerman M L, Valimaa J, Reinikka-Railo H, Leppanen E, Jolanki R. 1,2-benzisothiazolin-3-one in disposable polyvinyl chloride gloves for medical use. *Contact Dermatitis* 2007: **57**: 365–370.
45 Friis U F, Menné T, Thyssen J P, Johansen J D. A patient's drawing helped the physician to make the correct diagnosis: occupational contact allergy to isothiazolinone. *Contact Dermatitis* 2012: **67**: 174–176.

46 Uter W, Uter M, Steen-Schuberth B, Schnuch A. Allergic contact dermatitis caused by methylisothiazolinone from a 'waist reduction belt'. *Contact Dermatitis* 2012: **66**: 347–348.
47 Aerts O, Cattaert N, Lambert J, Goossens A. Airborne and systemic dermatitis, mimicking atopic dermatitis, caused by methylisothiazolinone in a young child. *Contact Dermatitis* 2013: **68**: 250–251.
48 Podmore P. An epidemic of isothiazolinone sensitization in a flax spinning mill. *Contact Dermatitis* 1998: **38**: 165–166.
49 Estlander T, Jolanki R, Kanerva L. Occupational allergic contact dermatitis from 2,3-epoxypropyl trimethyl ammonium chloride (EPTMAC) and Kathon LX in a starch modification factory. *Contact Dermatitis* 1997: **36**: 191–194.
50 Geier J, Lessmann H, Dickel H et al. Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). *Contact Dermatitis* 2004: **51**: 118–130.
51 Henriks-Eckerman M L, Suuronen K, Jolanki R. Analysis of allergens in metalworking fluids 1. *Contact Dermatitis* 2008: **59**: 261–267.
52 Bayraktar A, Ozcan M. An unusual case: burn following an accidental exposure to methylchloroisothiazolinone/methylisothiazolinone. *J Burn Care Res* 2007: **28**: 195–197.
53 Monsalvez V, Fuertes L, Frutos J O, Vanaclocha F. Sensitization to methylchloroisothiazolinone–methyl isothiazolinone after a burn caused by massive accidental occupational exposure. *Actas Dermosifiliogr* 2011: **102**: 224–226.
54 Bruze M, Dahlquist I, Gruvberger B. Chemical burns and allergic contact dermatitis due to Kathon WT. *Am J Contact Dermatitis* 1990: **1**: 91–93.
55 O'Driscoll J B, Beck M H. Occupational allergic contact dermatitis from Kathon WT. *Contact Dermatitis* 1988: **19**: 63.
56 Kujala V, Niinimaki A. Occupational induction of hypersensitivity after an accidental exposure to chloromethylisothiazolinone and methylisothiazolinone (CMI/MI) in an industrial worker. *Occup Med (Lond)* 1999: **49**: 51–53.
57 Ng C K, Tay P. Two case reports of delayed skin burns from methylisothiazolines used in water treatment. *Singapore Med J* 1996: **37**: 577–578.
58 Damstra R J, van Vlotten W A, van Ginkel C J. Allergic contact dermatitis from the preservative 1,2-benzisothiazolin-3-one (1,2-BIT; Proxel): a case report, its prevalence in those occupationally at risk and in the general dermatological population, and its relationship to allergy to its analogue Kathon CG. *Contact Dermatitis* 1992: **27**: 105–109.
59 Bruze M, Fregert S, Gruvberger B, Persson K. Contact allergy to the active ingredients of Kathon CG in the guinea pig. *Acta Derm Venereol* 1987: **67**: 315–320.
60 Isaksson M, Bruze M, Gruvberger B. Cross-reactivity between methylchloroisothiazolinone/methylisothiazolinone, methylisothiazolinone, and other isothiazolinones in workers at a plant producing binders for paints and glues. *Contact Dermatitis* 2008: **58**: 60–62.
61 Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. *Br J Dermatol* 2011: **164**: 1316–1325.
62 Frosch P J, Aberer W, Agner T et al. International comparison of legal aspects of workers' compensation for occupational contact dermatitis. In: *Contact Dermatitis*, 5th edition: Berlin, Heidelberg, Springer-Verlag, 2010: pp. 1029–1051.

Comments and considerations on methodology and validity

In this section comments and considerations are included on the methodology and validity that are either not mentioned or described only briefly in the manuscripts.

Manuscripts I and II

The cohorts described in these two manuscripts are identical and information on exposures and products was provided by the patient and/or retrieved from the database "Allergen". There can be a selection bias in the cohort, which comprised consecutive patients seen at the Department of Dermato-allergology at Copenhagen University Hospital Gentofte, Denmark. This could have affected the results. Compared with patients seen in general or dermatological practice, the patients in our cohort had more severe dermatitis and may have had the disease for longer or have had more complex disease.

The database

In Manuscripts I and II some information concerning the included patients was retrieved from the clinical database of contact dermatitis patients in the Department of Dermato-allergology, Gentofte Hospital. This database contains information about the patients' age, sex, location of dermatitis, and positive reactions along with information from an exposure mapping of cosmetic products. The database also contains the "DISCO-code", the Danish version of the International Standard Classification of Occupations (ISCO). All information from the patient records was entered in the database by the same nurses who performed the patch test and the readings. In case of doubt, data can be checked in the original patient records.

Sometimes the patients' job titles do not fully represent how they were exposed, for example, one patient was a white-collar worker and worked in an office; however, he also had intermittent work as a mechanic in the same company.

From the Labour Market Supplementary Pension Scheme, it would have been possible to retrieve the exact job title for a given patient, a Danish version of the European industrial activity classification (Nomenclature générale des Activités économiques dans les Communautés Européennes – NACE) the so-called Dansk Branche code (DB). We looked for a connection between the DISCO and the DB code, but this could not be done because the DISCO code is an education classification code and the DB code is a classification of industrial activity. However, had

there been a connection, we still would not have known the exact exposures of a given patient in the workplace. This is the reason that exact exposure information was retried in each individual case.

Controls

In Manuscripts I and II it would have been ideal to compare the results found in the stepwise systematic exposure assessment with those from a control group. However, there is no skin clinic similar to the Department of Dermato-Allergology that could have functioned as a control. Further, it would not have been ethical to give one group of patients a systematic exposure assessment and not others. We tried unsuccessfully to match the study patients to a historical control group of patients registered in the clinical database. We tried to match 1 patient to 2 controls by age, sex and DISCO code but did not succeed as there were not enough controls. We then tried to change the age from ±2 years to ±5 years but it did not help, and it would not have made sense to compare the exposures between 2 persons with a ±10 years of age.

Neither would it have made sense to change the DISCO codes because then it could have resulted in matching a soldier with a painter or a painter with a baker.

The database was established in 2002 and in December 2013 it contained information on more than 67,000 patients. Despite the database contained more than 24,500 patients registered from department at Gentofte in April 2012, there were not enough to generate a matched control group (96).

Manuscript III

The data used in Manuscript III were the MSDS and ingredients labelling retrieved from patients in the cohort. When we contacted the manufacturers we did not ask for concentrations of the substances used in the products but only for the name of the chemicals. If we had asked all the manufacturers for a complete list of contents together with concentrations, we could have seen which and how many MSDS did and did not meet the legislation besides discovering which allergens were problematic from a medical viewpoint. It would also have given data about which allergens were frequently not listed in the MSDS.

Manuscript IV

In Manuscript IV we used information retrieved from the Danish Product Registers database PROBAS. Some of the information received was classified as confidential because fewer than 3 manufacturers made products in the specific group of product types. From a medicine viewpoint, access to this information could have been helpful in an exposure assessment. For example, all data received on 2-methyl-4,5-trimethylene-isothiazolin-3-one was confidential because only one or two manufacturers used this biocide in their products; it would have been valuable in the exposure assessment to have had this information on the product types where this allergen was used.

To facilitate clarity, we did not include all the data received from the Danish Product Register; instead, we included only main groups and product types with a cut-off above 2% of its main group remained. All other data were deleted.

As mentioned in Manuscript IV, the PROBAS database covers only products containing one or more hazardous substances, products containing a substance registered on list from the Danish Working Environment Authority (WEA) and if products/substances manufactured or imported in quantities over 100kg (58). Accordingly, exposures to relevant allergens used in products/substances in the work environment may be overlooked if only PROBAS is used in the exposure assessment.

Discussions

Additional discussion of the results presented in Manuscripts I–IV as well as a more general discussion.

An exposure assessment is essential for a correct diagnosis. The classification of irritant and allergic contact dermatitis depends upon defined, easily recognisable clinical signs with a temporal relation to the start and maintenance of the clinical disease, patch testing and exposure assessment (3).
The diagnosis OICD is the most frequently given diagnoses. In 2010, 70% (1054/1504) of the patients with occupational contact dermatitis recognised by the Board of Occupational Health received the diagnosis OICD, 15.1% (227/1504) received the diagnosis OACD, 10.3% received the combined diagnosis OICD/OACD, and 4.5% received the diagnosis occupational contact urticaria (97). We did not use the combined OICD/OACD diagnosis because no clear criteria exist (98) and therefore it would be subjected to major variations (97). At our department we have an equal number of OICD and OACD patients. This may be because the Gentofte department receives selected patients with severe dermatitis and because we patch test with an extended test series both for Type I and IV allergies and have extensive experience in using MSDS.

Exposure assessment

We developed a six-step systematic exposure assessment for occupational contact dermatitis. The 6 steps can be seen in Appendix 1 with a flowchart over the investigation in Appendix 2.
For 50.0% of the patients a conclusion was made at Step 1 (medical history); for 34.5% it was made at Step 2 (ingredient labelling or MSDS); and for 15.5% of the patients further steps had to be taken to reach a conclusion (chemical analysis, contact to manufacturer etc.).
At Step 2, patients were asked to provide the physician with all the MSDS and product labels from products at the workplace and from home. To identify the relevant exposure, the dermatologist needs to have special knowledge of the many different allergens and the corresponding legislation because concentration limits may differ for different allergens. If Step 2 is ignored, relevant allergens will be overlooked and patients will not receive the correct diagnosis, making the investigation ineffective.
We identified allergens of clinical relevance in the MSDS or product labelling in 34.5% (38/110) of the patients. In 42.4% (28/66) of the patients who provided MSDS (137), we found the MSDS were

insufficient and we had to contact the manufacturer to obtain the complete list of contents in the product. This was done at Step 3 and the procedure led us to identify relevant allergens in 2.7% (3/110) of the patients. Even if the procedure elicited only a small number of relevant allergens, it is, nevertheless, a valuable step that prevents certain allergens being overlooked.
Chemical analysis was done at Steps 4 and 5. If the patient was allergic to nickel, cobalt or formaldehyde a chemical analysis (a spot test) was carried out on the subjects of suspicion or if there was a suspicion that a product contained the allergen of interest the product was sent for chemical analysis.
The formaldehyde spot test was done nine times; in 8 patients there was an occupational relevance and in 1 patient a non-occupational relevance.
Step 6 (visiting the workplace) was not performed in our exposure assessment because the relevant patients were on sick leave, had changed job or had taken early retirement. In such cases it is crucial to gather as much detail information as possible about the patients' work tasks, for example, through drawings or photographs (42).
The systematic exposure assessment revealed additional relevant allergens in 36% (82/228) of the patients. Moreover, many more patients benefitted from the systematic exposure assessment because we identified allergens both in and out of the European baseline series in products from the workplace and the home. This is illustrated in the flowchart in Appendix 2.

Allergens

We found that even though the patients had different diagnoses, either OACD or OICD, they were in contact with the same allergens (Manuscripts I and II). The 110 patients with the diagnosis OACD were found to be allergic to a total of 132 different allergens. Of these allergens, 78.0% (103/132) were not included in the European baseline series but were found by additional testing based on the systematic exposure assessment.

The three most prevalent allergens of those included in the European baseline series were thiuram mix [N=17], a rubber chemical mixture; formaldehyde [N=12], which is a preservative used in industrial and cosmetic products; and MCI/MI [N=10], which is a preservative in the group of isothiazolinones.
Of those allergens not included in the European baseline series, we found MI, BIT, isophorone diisocyanate (IPDI) and bisphenol F. See Table 2 in Manuscript 1.

MI was a major additional allergen. It is a preservative used in industrial and consumer products. It is a well-known contact allergen (67) and can cause airborne contact dermatitis (63). The relevant exposures to MI were found to be from paint [N=5], products from hair salons [N=3], and a detergent [N=1]. These finding agree with those in the literature (67;99).
The preservative BIT is usually used in industrial products such as paints, metalworking fluids and rubber gloves (100;101). The exposures to BIT were found to be from paint [N=2] and a detergent [N=2]. These finding also agree with those in the literature (100;101). IPDI is an aliphatic isocyanate, usually used in varnishes, coatings, and paints (102). In our study, the exposures to IPDI were found to be from primers [N=2]. The last of the main additional allergens found was bisphenol F, which can act as both a contact and an airborne contact allergen (103). It is used in the manufacture of epoxy resins, which are used in adhesives, paints, insulating materials for electric components, and wind turbine rotor blades (104;105). Epoxy resin systems are among the most frequent causes of occupational allergic contact dermatitis (106). The exposures to bisphenol F were found to be from an epoxy resin [N=4], which agrees with the literature (105). Among the four most prevalent type I allergies are latex protein [N=5], cod [N=4], tomato [N=4] and potato [N=4].

Irritants

Allergies can be identified by a patch and/or prick test, but there is no such test for irritants. Accordingly, the dermatologist must exclude an allergy to give the diagnosis OICD. Therefore, OICD is based on the clinical picture, exposure assessment and the absence of positive patch test and momentary relationship. Because of the lack of clinical test, ICD is often based on contact to irritants, wet work and wet/dry cycles. As there is no international definition of wet work, wet-work criteria are often based on those set in Germany (36).

Based on the exposure assessment and the wet-work criteria, 118 patients received the diagnosis OICD. Patients with occupations where they were exposed to wet work and fresh food were most frequently diagnosed with OICD.
Based on the exposure assessment, we found that information from the MSDS could not directly be used in the diagnosis of OICD. The MSDS could give only qualitative information; consequently, the diagnosis often depended on the wet-work criteria. We did not find any new substances or products with irritant properties. Nevertheless, despite the MSDS not directly aiding in the diagnosis, they played a central role in identifying exposure to contact allergens.

The diagnosis OACD is based on systematic work in the search for type I and IV allergens where the MSDS and product labelling are central, leading to the individual patch testing. The diagnosis OICD necessitates the same meticulous exposure assessment despite the dermatitis appearing as a typical ICD.

A strength of this thesis is that all the patients were seen in the same department by the same staff, who all have extensive experience in exposure assessment and patch test readings. A weakness (Manuscript I and II) is that it was an open study with consecutive patients and that there was no control group. Another weakness is that Gentofte Hospital is a university hospital in the capital region where patients with severe dermatitis and patients with complex skin diseases are seen. Some patients included in the study were referred form other regions as a part of second opinion.

Shortcomings in MSDS

The MSDS provided by 66 patients were reviewed for chemicals known to be sensitizing. From a medical viewpoint, we found that 18.6% (137/738) of the MSDS contained shortcomings. The most frequent deficiency was "Missing R43/H317 while known contact allergen was present" in 61.3% (84/137) of the MSDS. A reason for these deficiencies could be that despite the "self-classification" being met, allergens do not appear on the MSDS because they are used in amounts under the SCL set at 1% for labelling the product as skin sensitizing and 0.1% for labelling the allergen in section 11, see all 16 sections required in an MSDS in Appendix 3. Another reason for these shortcomings could be that only few allergens are officially registered as skin sensitizers, which is a legally binding classification. If the substance is not on the official list in REACH, the manufacturer has an obligation to consider whether an ingredient fulfils the criteria for classification as a skin sensitizing substances. We asked the manufacturers about the ingredient list and not about the concentrations of the contents. Consequently, the MSDS we identified as insufficient from a medical viewpoint may have met the legislation. In some cases, the manufacturers informed us about the concentration of substances in these cases the law was met.

The concentration limit for a product to be classified as sensitizing and the concentration limit for listing the allergen in the MSDS tend to be insufficient to protect against sensitization and sensitized persons because sensitization and elicitation often occur at concentrations below the set limits (55;56).

According to the criteria, it requires toxicological insight to evaluate substances—something that is not always feasible in small companies. However, it is not appropriate that important information for workers to properly protect themselves is restricted.
It is the Danish Working Environment Authority that advises manufactures, importers and salespeople on meeting the legislation for MSDS given in REACH (107;108).

Because of inadequate MSDS, manufacturers had to be contacted to obtain information on the product ingredients. In 10 cases, the manufactures refused to provide the information because they viewed the information as confidential, despite the request often specifically concerning the use of preservatives in the product. It is difficult to understand why a preservative, for example used in water-based paint or cutting oil, can considered confidential when the information serves a medical purpose.

It should be mandatory for manufacturers to provide information on ingredients needed to investigate workers who have contact with the manufactured products. Because of the additional information the manufacturer provided, 31.8% (21/66) of patients were tested with supplementary allergens. This additional testing is time consuming for the patient. If all the ingredients or all known allergens were labelled, the exposure assessment would take less time and patients would need to undergo only one patch test. Occupational skin disease (OSD) is the most frequently recognized occupational disease and it is a major financial burden on society (108). If there were full labelling or allergen labelling, it would reduce the cost to both the patient and society.
Seen from a medical viewpoint, it is worrying that it is so difficult to obtain information about allergens in products. These disproportional difficulties are likely to lead to many dermatologist and patients abandoning their attempts to gather the relevant information. This will not only have repercussions for the patient's health, it will also be costly to society because of the time-consuming and ineffective procedures.

The Danish Product Registers database PROBAS

The Danish Product Registers database PROBAS is run by the Danish Working Environment Authority (WEA). In this thesis we show that many products registered in the database contain isothiazolinones.

The three most frequently registered isothiazolinone were BIT, MI and the mixture MCI/MI. They were registered in 985, 884 and 611 products respectively. As we found in Manuscript I, MI was the most frequent allergen found outside those included in the European baseline series. The largest group of the different product types containing the isothiazolinones was “paints and varnishes”, with 3567 products. Appendix 4 lists the different product types. The most frequently used isothiazolinones in these product types were BIT, MI and MCI/MI.
MI and BIT have been found to be airborne contact allergens (63;83) and have caused airborne contact dermatitis, systemic allergic contact dermatitis and respiratory symptoms including acute asthma. In a study of 19 paints, MI, MCI/MI and BIT were found, respectively, in 19, 4 and 16 different water-based paints bought on the Danish retail marked (75). Emission of MI, MCI/MI and BIT from paint has also been demonstrated, which shows they can act as airborne skin sensitizers (75).

The most frequent product type registered as containing isothiazolinones was car care products. BIT was registered in 21.9% of the products and MI in 18.8%. We found a similar pattern for polishing agents and floor products, but we have found no cases of contact allergy related to such products. BIT, MI and MCI/MI were also registered in product types for surface treatment of paper, other non-metals and cardboard, but these were not as frequently registered as those mentioned formerly. All the isothiazolinones were registered for use as biocide products. This product type may have multiple uses.
OIT was the only isothiazolinone registered as a cooling agent for metal, despite BIT and OIT having been reported as contact allergens in metal workers (73;74). This shows the importance of individual exposure assessment and of patch testing with these isothiazolinones in metal workers with suspected OACD.
One single accidental exposure to isothiazolinones used in high concentrations can cause chemical burns followed by contact sensitization (77-82). Such an exposure may also lead to systemic contact dermatitis and subjective symptoms (83).
The 6 isothiazolinones were registered in paint and varnishes, biocide and filling agents. All other product types had one or more isothiazolinones registered.
PROBAS can be used to supplement the MSDS, when these do not sum up to 100%. The information can be used to check the MSDS and for example it can be used for research of the exposures for different product types.

Conclusion

The thesis focuses on occupational contact dermatitis, the effect of a systematic stepwise exposure assessment and identifying the shortcomings in the exposure assessment based on the investigation of the allergens listed in the MSDS. It contributes to the research area with the following:

- We developed a systematic stepwise exposure assessment consisting of six steps. In 36% of patients, an additional allergy was found by testing based on the exposure assessment (Manuscript I)

- We identified 132 different allergens located in the work environment and relevant to the patients' dermatitis. Of these 132 allergens, 103 were not included in the European baseline series (Manuscript I)

- No new irritants were found through the MSDS, i.e. their role was limited. However, we found that patients with the diagnosis OICD were in contact with the same allergens as were patients with the diagnosis OACD. It is essential to exclude allergy in the diagnosis of OICD (Manuscript II)

- From a medical viewpoint, 18.6% of the MSDS contained errors or had missing information, which prevented a fast and complete allergy investigation. The most frequent shortcoming was missing information on which preservatives were used. Such shortcomings can be overcome only by improving legislation (Manuscript III)

- Seven different known allergenic isothiazolinones were found in many products registered for use in the work environment and possibly occurring in high concentrations. Benzisothiazolinone was the most frequently used isothiazolinone. It was found in 985 products with a concentration range of 0.01ppm to 45%. (Manuscript IV)

Taken together the results of Manuscript I and II show that a systematic exposure assessment is essential for a complete, in-depth investigation of OCD. The results of Manuscript III show that

improvements are needed, for example, full ingredient labelling or reducing the concentration limit for classifying the product as sensitizing and/or the SCL for listing the allergens on the product and in the MSDS. From the results of Manuscript IV, it can be concluded that isothiazolinones are used in many products registered for use in the work environment. The knowledge retrieved from the MSDS and PROBAS can be used in research and in the clinical work related to OCD. Moreover, the information registered in PROBAS can act as a control for the information given in the MSDS or vice versa.

Perspective and future studies

This thesis contributes with new, valuable knowledge on systematic exposure assessment and on which allergens and irritants patients are exposed to in their work environment. Only a few studies have been performed on the exposure assessment of allergens and irritants together with a review of MSDS. Studies on exposure assessment are clinically important because avoidance of these allergens is essential for the treatment and prognosis of the disease.

Based on the findings presented in this thesis, it is recommended that all patients be given the same individual stepwise systematic exposure assessment, irrespective of whether they work in a classic wet-work environment (e.g. hairdressing) or work with substances or products with irritant properties (e.g. blue-collar workers). This is based on the findings in Manuscript I and II showing that regardless of whether the final diagnosis is allergic contact dermatitis or irritant contact dermatitis, the patients are in contact with the same allergens.

Not all allergens are listed as skin sensitizing substances (R43/H317). Based on the findings in Manuscript III and in relation to the findings of the systematic stepwise exposure assessment (Manuscript I and II), the review of MSDS demonstrates that the legislation regarding MSDS must be reviewed. One aim could be lowering the concentration limits for classifying a product as skin sensitizing. Another could be lowering the concentration limit for listing the allergens in section 11 “toxicological information” with their chemical names.

The findings in Manuscripts I and IV show that isothiazolinones are one of the most frequent causes of contact dermatitis and airborne contact dermatitis. One way of reversing this increasing trend could be by regulating the use of isothiazolinones. Full declaration of preservatives used in industrial products by labelling and in MSDS would give more optimal conditions to prevent exposures of allergic individuals.

Future studies could be aimed at the atopic dermatitis and the filaggrin mutation to investigate how these parameters interact with occupational contact dermatitis. Another study could be a questionnaire follow-up on the cohort to examine how the patients use the knowledge on their allergies, how they prevent relapse of the dermatitis, for example, by change of routines, substitution of products/chemicals, use of protective clothing/gloves, or change of job. A more

detailed study on the MSDS could focus on comparing the concentrations of substances used in the products with the information in the MSDS to investigate how many meet the legislation and which allergens are most frequently not listed, despite the MSDS fulfilling the legislative requirements.

In an exposure assessment the dermatologist often uses the MSDS, but equally often well-known allergens are not listed. Products registered in PROBAS are registered with full ingredients. In the Danish legislation it is stated that only certain authorities and the Poison Control Hotline have full access to information in PROBAS. When a dermatologist sees a patient with suspected occupational contact dermatitis, he/she must first contact the Poison Control Hotline to obtain relevant the information. This delays the investigation. Accordingly, if the dermatologist had full access to PROBAS, it would greatly facilitate the exposure assessment.

References

(1) Kindt T.J., Goldsby R.A., Orsborne B.A. Innate Immunity. Kuby Immunology. Sixth edition ed. New York: W.H.Freeman and Company: 2007. p. 52-77.

(2) Rystemeyer T., van Hoogstraten I.M.W., von Blomberg B.M.E., Gibbs S., Scheper R.J. Mechanisms of Irritant and Allergic Contact Dermatitis. Contact Dermatitis Textbook. 5th edition ed. 2010. p. 43-90.

(3) Menne T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis 2011: 65(1):3-12.

(4) Diepgen TL, Elsner P, Schliemann S, Fartasch M, Kollner A, Skudlik C, John SM, Worm M. Guideline on the management of hand eczema ICD-10 Code: L20. L23. L24. L25. L30. J Dtsch Dermatol Ges 2009: 7 Suppl 3:S1-16.

(5) Frosch PJ, John S-M. Clinical Aspects of Irritant Contact Dermatitis. In: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. Contact Dermatitis Textbook. 5th edition ed. Berlin Heidelberg: Springer-Verlag: 2011. p. 305-45.

(6) Malten KE. Thoughts on irritant contact dermatitis. Contact Dermatitis 1981: 7(5):238-47.

(7) Cvetkovski RS, Rothman KJ, Olsen J, Mathiesen B, Iversen L, Johansen JD, Agner T. Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. Br J Dermatol 2005: 152(1):93-8.

(8) Meding B, Wrangsjo K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. Br J Dermatol 2005: 152(5):975-80.

(9) the Danish Health and Medicines Authority. Forebyggelse af kontakteksemer. the Danish Health and Medicines Authority;2001. Report No.: 2 udgave 1 oplag

(10) Kindt T.J., Goldsby R.A., Orsborne B.A. Hypersensitivity Reactions. Kuby Immunology. Sixth edition ed. New York: W.H.Freeman and Company: 2007. p. 371-400.

(11) Thyssen JP, Gimenez-Arnau E, Lepoittevin JP, Menne T, Boman A, Schnuch A. The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals. Part II. Contact Dermatitis 2012: 66 Suppl 1:25-52.

(12) Thyssen JP, Gimenez-Arnau E, Lepoittevin JP, Menne T, Boman A, Schnuch A. The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals. Part III. Contact Dermatitis 2012: 66 Suppl 1:53-70.

(13) Gerberick GF, Sikorski EE. In vitro and in vivo testing techniques for allergic contact dermatitis. Am J Contact Dermat 1998: 9(2):111-8.

(14) Magnusson B, Kligman AM. The identification of contact allergens by animal assay. The guinea pig maximization test. J Invest Dermatol 1969: 52(3):268-76.

(15) Thyssen JP, Linneberg A, Menne T, Nielsen NH, Johansen JD. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. Br J Dermatol 2009: 161(5):1124-9.

(16) Thyssen JP, Linneberg A, Ross-Hansen K, Carlsen BC, Meldgaard M, Szecsi PB, Stender S, Menne T, Johansen JD. Filaggrin mutations are strongly associated with contact sensitization in individuals with dermatitis. Contact Dermatitis 2013: 68(5):273-6.

(17) Bregnhoj A, Sosted H, Menne T, Johansen JD. Exposures and reactions to allergens among hairdressing apprentices and matched controls. Contact Dermatitis 2011: 64(2):85-9.

(18) Berndt U, Hinnen U, Iliev D, Elsner P. Hand eczema in metalworker trainees--an analysis of risk factors. Contact Dermatitis 2000: 43(6):327-32.

(19) Fischer T, Bohlin S, Edling C, Rystedt I, Wieslander G. Skin disease and contact sensitivity in house painters using water-based paints, glues and putties. Contact Dermatitis 1995: 32(1):39-45.

(20) Vester L, Thyssen JP, Menne T, Johansen JD. Occupational food-related hand dermatoses seen over a 10-year period. Contact Dermatitis 2012: 66(5):264-70.

(21) Christensson JB, Matura M, Gruvberger B, Bruze M, Karlberg AT. Linalool--a significant contact sensitizer after air exposure. Contact Dermatitis 2010: 62(1):32-41.

(22) Chu CY, Ponten A, Sun CC, Jee SH. Concomitant contact allergy to the resins, reactive diluents and hardener of a bisphenol A/F-based epoxy resin in subway construction workers. Contact Dermatitis 2006: 54(3):131-9.

(23) Bangsgaard N, Thyssen JP, Menne T, Andersen KE, Mortz CG, Paulsen E, Sommerlund M, Veien NK, Laurberg G, Kaaber K, Thormann J, Andersen BL, Danielsen A, Avnstorp C, Kristensen B, Kristensen O, Vissing S, Nielsen NH, Johansen JD. Contact allergy to epoxy resin: risk occupations and consequences. Contact Dermatitis 2012: 67(2):73-7.

(24) Amarasekera M, Rathnamalala N, Samaraweera S, Jinadasa M. Prevalence of latex allergy among healthcare workers. Int J Occup Med Environ Health 2010: 23(4):391-6.

(25) Wilkinson DS, Fregert S, Magnusson B, Bandmann HJ, Calnan CD, Cronin E, Hjorth N, Maibach HJ, Malalten KE, Meneghini CL, Pirila V. Terminology of contact dermatitis. Acta Derm Venereol 1970: 50(4):287-92.

(26) Cherry N. Recent advances: occupational disease. BMJ 1999: 318(7195):1397-9.

(27) Arbejdsskadestyrelsen. Arbejdsskadestatistik 2011. the National Board of Industrial Injuries in Denmark;2012 May 30. Available at: http://ask.dk/Statistik/~/~/media/30E79DCCC0F14AE1985453BF97A15E40.ashx

(28) Arbejdsskadestyrelsen. Arbejdsskadestatistik 2012. 2013. Available at: http://www.ask.dk/~/media/ASK/pdf/statistik/Arbejdsskadestatistik2012endelig%202pdf.ashx

(29) Skoet R., Olsen J., Mathiesen B., Iversen L., Johansen J.D., Agner T. A survey of occupational hand eczema in Denmark. Contact Dermatitis 2004: 51(4):159-66.

(30) Flyvholm M-A, Menne T. Allergic contact dermatitis from formaldehyde. A case study focussing on sources of formaldehyde exposure. Contact Dermatitis 1992: 27(1):27-36.

(31) Holness DL, Nethercott JR. Is a worker's understanding of their diagnosis an important determinant of outcome in occupational contact dermatitis? Contact Dermatitis 1991: 25(5):296-301.

(32) Kalimo K, Lammintausta K, Jalava J, Niskanen T. Is it possible to improve the prognosis in nickel contact dermatitis? Contact Dermatitis 1997: 37(3):121-4.

(33) Thyssen JP, Johansen JD, Menne T, Nielsen NH, Linneberg A. Nickel allergy in Danish women before and after nickel regulation. N Engl J Med 2009: 360(21):2259-60.

(34) Hald M, Agner T, Blands J, Johansen JD. Delay in medical attention to hand eczema: a follow-up study. Br J Dermatol 2009: 161(6):1294-300.

(35) Carlsen BC, Andersen KE, Menne T, Johansen JD. Patients with multiple contact allergies: a review. Contact Dermatitis 2008: 58(1):1-8.

(36) Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). Risks resulting from skin contact - identification, assessment, measures - TRGS 401. 2008. Available at: http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/TRGS-401.pdf?__blob=publicationFile&v=6 (last accessed 5-4-0014)

(37) Rustemeyer T, Elsner P, John S-M, Maibach H. Wet Work and Occlusion. Kanerva's Occupational Dermatology. 2nd ed. Berlin Heidelberg: Springer Verlag: 2012. p. 839-46.

(38) Thyssen JP, Skare L, Lundgren L, Menne T, Johansen JD, Maibach HI, Liden C. Sensitivity and specificity of the nickel spot (dimethylglyoxime) test. Contact Dermatitis 2010: 62(5):279-88.

(39) Thyssen JP, Menne T, Johansen JD, Liden C, Julander A, Moller P, Jellesen MS. A spot test for detection of cobalt release - early experience and findings. Contact Dermatitis 2010: 63(2):63-9.

(40) Baur X. Measurement of airborne latex allergens. Methods 2002: 27(1):59-62.

(41) Julander A, Skare L, Vahter M, Liden C. Nickel deposited on the skin-visualization by DMG test. Contact Dermatitis 2011: 64(3):151-7.

(42) Friis UF, Menne T, Thyssen JP, Johansen JD. A patient's drawing helped the physician to make the correct diagnosis: occupational contact allergy to isothiazolinone. Contact Dermatitis 2012: 67(3):174-6.

(43) Friis UF, Menne T, Jellesen MS, Moller P, Verdingovas V, Jensen TR, Thyssen JP, Johansen JD. Allergic nickel dermatitis caused by playing the guitar: case report and assessment of nickel release from guitar strings. Contact Dermatitis 2012: 67(2):101-3.

(44) Friis UF, Johansen JD, Krongaard T, Menne T. Quantitative assessment of diethylthiourea exposure in two cases of occupational allergic contact dermatitis. Contact Dermatitis 2011: 64(2):116-8.

(45) The European Parliament and the Council of the European Union. Regulation (EC) No 1223/2009 of the European Parliament and on the Council of 30 November 2009 on cosmetic products. 2009 Nov 30. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:EN:PDF (last accessed 2-1-2014)

(46) ECHA. Regulation on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. the European Parliament and the Council of the European Union;2010 Oct 29. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF (last accessed 2-1-2014)

(47) The European Parliament and the Council of the European Union. REGULATION (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. 2006 Dec 18. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:136:0003:0280:en:PDF

(48) The Commission of the European Communities. Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures. 2011 Mar 10.

(49) The Ministry of the Environment. More information on the Environmental Protection Agency's advisory list for self classification of chemicals. 2014. Available at: http://www.mst.dk/English/Chemicals/assessment_of_chemicals/The_advisory_list_for_selfclassification/more_information.htm. (Last accessed 26-2-2014).

(50) Loveless SE, Api AM, Crevel RW, Debruyne E, Gamer A, Jowsey IR, Kern P, Kimber I, Lea L, Lloyd P, Mehmood Z, Steiling W, Veenstra G, Woolhiser M, Hennes C. Potency values from the local lymph node assay: application to classification, labelling and risk assessment. Regul Toxicol Pharmacol 2010: 56(1):54-66.

(51) Nicol AM, Hurrell AC, Wahyuni D, McDowall W, Chu W. Accuracy, comprehensibility, and use of material safety data sheets: a review. Am J Ind Med 2008: 51(11):861-76.

(52) Keegel T, Saunders H, LaMontagne AD, Nixon R. Are material safety data sheets (MSDS) useful in the diagnosis and management of occupational contact dermatitis? Contact Dermatitis 2007: 57(5):331-6.

(53) Noiesen E., Munk M.D., Larsen K., Johansen J.D., Agner T. Difficulties in avoiding exposure to allergens in cosmetics. Contact Dermatitis 2007: 57(2):105-9.

(54) Friis UF, Dahlin J, Bruze M, Menne T, Johansen JD. Hidden exposure to formaldehyde in a swab caused allergic contact dermatitis. Contact Dermatitis 2014: 70(4):258-60.

(55) Fischer LA, Voelund A, Andersen KE, Menne T, Johansen JD. The dose-response relationship between the patch test and ROAT and the potential use for regulatory purposes. Contact Dermatitis 2009: 61(4):201-8.

(56) Friedmann PS. The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. Br J Dermatol 2007: 157(6):1093-102.

(57) Nixon RL. Material safety data sheets and allergic contact dermatitis: a misleading case. Australas J Dermatol 1997: 38(3):165.

(58) Danish Working Environment Authority. Substances and materials that must be notified to the Product Registry. 17-12-2013. Available at: http://arbejdstilsynet.dk/en/engelsk/produktregistret/produkter-der-skal-anmeldes.aspx. (Last accessed 17-12-2013).

(59) Substances in Products in the Nordic Countries. Use Categories Nordic (UCN). 12-9-2007. Available at: http://90.184.2.100/DotNetNuke/Portals/0/DNNPortal-Download/Funktionskoder-eng%20htm.htm.

(60) Thyssen JP, Johansen JD, Menne T. Contact allergy epidemics and their controls. Contact Dermatitis 2007: 56(4):185-95.

(61) Lepoittevin J-P, Le Coz C.J. Dictionary of Contact Allergens: Chemical Structures, Sources, and References. In: Rustemeyer T, Elsner P, John SM, Maibach H, editors. Kanerva´s Occupational Dermatology. 2 ed. Berlin Heidelberg: Springer-Verlag: 2012. p. 1737-848.

(62) Basketter DA, Rodford R, Kimber I, Smith I, Wahlberg JE. Skin sensitization risk assessment: a comparative evaluation of 3 isothiazolinone biocides. Contact Dermatitis 1999: 40(3):150-4.

(63) Lundov MD, Mosbech H, Thyssen JP, Menne T, Zachariae C. Two cases of airborne allergic contact dermatitis caused by methylisothiazolinone in paint. Contact Dermatitis 2011: 65(3):176-9.

(64) Schubert H. Airborne contact dermatitis due to methylchloro- and methylisothiazolinone (MCI/MI). Contact Dermatitis 1997: 36(5):274.

(65) Kaae J, Menne T, Thyssen JP. Presumed primary contact sensitization to methylisothiazolinone from paint: a chemical that became airborne. Contact Dermatitis 2012: 66(6):341-2.

(66) Gruvberger B, Bruze M, Almgren G. Occupational dermatoses in a plant producing binders for paints and glues. Contact Dermatitis 1998: 38(2):71-7.

(67) Thyssen JP, Sederberg-Olsen N, Thomsen JF, Menne T. Contact dermatitis from methylisothiazolinone in a paint factory. Contact Dermatitis 2006: 54(6):322-4.

(68) Mathias CG, Andersen KE, Hamann K. Allergic contact dermatitis from 2-n-octyl-4-isothiazolin-3-one, a paint mildewcide. Contact Dermatitis 1983: 9(6):507-9.

(69) Burden AD, O'Driscoll JB, Page FC, Beck MH. Contact hypersensitivity to a new isothiazolinone. Contact Dermatitis 1994: 30(3):179-80.

(70) Podmore P. An epidemic of isothiazolinone sensitization in a flax spinning mill. Contact Dermatitis 1998: 38(3):165-6.

(71) Estlander T, Jolanki R, Kanerva L. Occupational allergic contact dermatitis from 2,3-epoxypropyl trimethyl ammonium chloride (EPTMAC) and Kathon LX in a starch modification factory. Contact Dermatitis 1997: 36(4):191-4.

(72) Kawai K, Nakagawa M, Sasaki Y, Kawai K. Occupational contact dermatitis from Kathon 930. Contact Dermatitis 1993: 28(2):117-8.

(73) Geier J, Lessmann H, Dickel H, Frosch PJ, Koch P, Becker D, Jappe U, Aberer W, Schnuch A, Uter W. Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). Contact Dermatitis 2004: 51(3):118-30.

(74) Henriks-Eckerman ML, Suuronen K, Jolanki R. Analysis of allergens in metalworking fluids. Contact Dermatitis 2008: 59(5):261-7.

(75) Lundov MD, Kolarik B, Bossi R, Gunnarsen L, Johansen J. Emission of isothiazolinones from water-based paint (In Prep). 2013.

(76) Espasandin-Arias M, Goossens A. Natural rubber gloves might not protect against skin penetration of methylisothiazolinone. Contact Dermatitis 2014: 70(4):249-51.

(77) Bayraktar A, Ozcan M. An unusual case: burn following an accidental exposure to methylchloroisothiazolinone/methylisothiazolinone. J Burn Care Res 2007: 28(1):195-7.

(78) Monsalvez V, Fuertes L, Frutos JO, Vanaclocha F. Sensitization to methylchloroisothiazolinone-methylisothiazolinone after a burn caused by massive accidental occupational exposure. Actas Dermosifiliogr 2011: 102(3):224-6.

(79) Bruze M, Dahlquist I, Gruvberger B. Chemical Burns and Allergic Contact Dermatitis Due to Kathon WT. Am J Contact Dermatitis 1990: 1(2):91-3.

(80) O'Driscoll JB, Beck MH. Occupational allergic contact dermatitis from Kathon WT. Contact Dermatitis 1988: 19(1):63.

(81) Kujala V, Niinimaki A. Occupational induction of hypersensitivity after an accidental exposure to chloromethylisothiazolinone and methylisothiazolinone (CMI/MI) in an industrial worker. Occup Med (Lond) 1999: 49(1):51-3.

(82) Ng CK, Tay P. Two case reports of delayed skin burns from methylisothiazolines used in water treatment. Singapore Med J 1996: 37(6):577-8.

(83) Kaur-Knudsen D, Menne T, Carlsen B.C. Systemic allergic dermatitis following airborne exposure to 1,2-benzisothiazolin-3-one. Contact Dermatitis 2012: 67(5):310-2.

(84) Bregnbak D, Lundov MD, Zachariae C, Menne T, Johansen JD. Five cases of severe chronic dermatitis caused by isothiazolinones. Contact Dermatitis 2013: 69(1):57-9.

(85) alto-Korte K, Alanko K, Henriks-Eckerman ML, Kuuliala O, Jolanki R. Occupational allergic contact dermatitis from 2-N-octyl-4-isothiazolin-3-one. Contact Dermatitis 2007: 56(3):160-3.

(86) Mose AP, Frost S, Ohlund U, Andersen KE. Allergic contact dermatitis from octylisothiazolinone. Contact Dermatitis 2013: 69(1):49-52.

(87) Lundov MD, Zachariae C, Menne T, Johansen JD. Airborne exposure to preservative methylisothiazolinone causes severe allergic reactions. BMJ 2012: 345:e8221.

(88) Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy--growing epidemic. Contact Dermatitis 2013: 69(5):271-5.

(89) Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. Contact Dermatitis 2013: 69(4):231-8.

(90) Uter W, Gefeller O, Geier J, Schnuch A. Methylchloroisothiazolinone/methylisothiazolinone contact sensitization: diverging trends in subgroups of IVDK patients in a period of 19 years. Contact Dermatitis 2012: 67(3):125-9.

(91) Madsen JT, Andersen KE. Further evidence of the methylisothiazolinone epidemic. Contact Dermatitis 2014: 70(4):246-7.

(92) Johnston GA. The rise in prevalence of contact allergy to methylisothiazolinone in the British Isles. Contact Dermatitis 2014: 70(4):238-40.

(93) Gameiro A, Coutinho I, Ramos L, Goncalo M. Methylisothiazolinone: second 'epidemic' of isothiazolinone sensitization. Contact Dermatitis 2014: 70(4):242-3.

(94) Hosteing S, Meyer N, Waton J, Barbaud A, Bourrain JL, Raison-Peyron N, Felix B, Milpied-Homsi B, Ferrier Le Bouedec MC, Castelain M, Vital-Durand D, Debons M, Collet E, Avenel-Audran M, Mathelier-Fusade P, Vermeulen C, Assier H, Gener G, Lartigau-Sezary I, Catelain-Lamy A, Giordano-Labadie F. Outbreak of contact

sensitization to methylisothiazolinone: an analysis of French data from the REVIDAL-GERDA network. Contact Dermatitis 2014: 70(5):262-9.

(95) Lundov MD, Menne T. Airborne exposure to methylchloroisothiazolinone and methylisothiazolinone from a toilet cleaner. Contact Dermatitis 2013: 68(4):252-3.

(96) The National Allergy Research Centre. Annual report from the National Allergy Research Centre 2013. 2014.

(97) Caroe TK, Ebbehoj N, Agner T. A survey of exposures related to recognized occupational contact dermatitis in Denmark in 2010. Contact Dermatitis 2014: 70(1):56-62.

(98) Schwensen J.F., Menne T, Johansen J.D. The combined diagnosis of allergic and irritant contact dermatitis in a retrospective cohort of one thousands consecutive patients with occupational contact dermatitis (Submitted). Contact Dermatitis 2014:

(99) Flyvholm M-A. Contact allergens in registered chemical products. Contact Dermatitis 1991: 25(1):49-56.

(100) Flyvholm M-A. Preservatives in registered chemical products. Contact Dermatitis 2005: 53(1):27-32.

(101) Aalto-Korte K, Ackermann L, Henriks-Eckerman ML, Valimaa J, Reinikka-Railo H, Leppanen E, Jolanki R. 1,2-benzisothiazolin-3-one in disposable polyvinyl chloride gloves for medical use. Contact Dermatitis 2007: 57(6):365-70.

(102) Aalto-Korte K, Suuronen K, Kuuliala O, Henriks-Eckerman ML, Jolanki R. Occupational contact allergy to monomeric isocyanates. Contact Dermatitis 2012: 67(2):78-88.

(103) Lodi A, Mancini LL, Pozzi M, Chiarelli G, Crosti C. Occupational airborne allergic contact dermatitis in parquet layers. Contact Dermatitis 1993: 29(5):281-2.

(104) Ponten A, Carstensen O, Rasmussen K, Gruvberger B, Isaksson M, Bruze M. Epoxy-based production of wind turbine rotor blades: occupational dermatoses. Contact Dermatitis 2004: 50(6):329-38.

(105) O'Boyle NM, Delaine T, Luthman K, Natsch A, Karlberg AT. Analogues of the epoxy resin monomer diglycidyl ether of bisphenol f: effects on contact allergenic potency and cytotoxicity. Chem Res Toxicol 2012: 25(11):2469-78.

(106) Dickel H, Kuss O, Schmidt A, Diepgen TL. Occupational relevance of positive standard patch-test results in employed persons with an initial report of an occupational skin disease. Int Arch Occup Environ Health 2002: 75(6):423-34.

(107) The Ministry of Employment. The Working Environment Act (Arbejdsmiljøloven). 7-9-2010. Available at: https://www.retsinformation.dk/Forms/R0710.aspx?id=133159. (Last accessed 2-4-2014).

(108) Diepgen TL, Scheidt R, Weisshaar E, John SM, Hieke K. Cost of illness from occupational hand eczema in Germany. Contact Dermatitis 2013: 69(2):99-106.

Summaries

Summary in English

Nearly 2,600 new cases of occupational skin disease are reported annually to the National Board of Industrial Injuries in Denmark. The skin disease most often reported is hand dermatitis. It is often young persons under the age of 35 years who develop occupational hand dermatitis with twice as many women as men developing the disease. An exposure assessment is essential to classify dermatitis as work related, to give the correct information and for prevention.
The central information is the medical history combined with knowledge about workplace and work process product contents.
Material safety data sheets (MSDS) and ingredients labelling are important sources of information about ingredients in workplace products, but these sheets can be difficult to understand and studies indicate that they can be incorrect, have missing information and be insufficient.
How this affects the investigation of occupational allergic contact dermatitis among Danish patients in practice is unknown.

The aims of this thesis were to evaluate whether a systematic stepwise exposure assessment could aid in revealing patients with occupational allergy, to investigate whether MSDS contain information important to the diagnosis of irritant contact dermatitis, to detect whether there are any specific shortcomings linked to the use of MSDS and to map, by using the Danish Product Register, in which product types the potent allergens isothiazolinones are used.

We developed a stepwise exposure assessment where the products from the patient's home and workplace were analysed. In this process, MSDS, product information and ingredients labelling were analysed, workplaces were contacted and based on this information, individual allergy test panels were planned.
The systematic stepwise exposure assessment was performed in 228 patients with occupational dermatitis who during January 2010–August 2011 attended the department of Dermato-Allergology at Copenhagen University Hospital Gentofte, Denmark.

We found that such a stepwise exposure assessment combined with an individually designed allergy test increased the detection of allergies in 36% of the patients. Our assessment comprised 103

different extra allergens compared with testing with only the European baseline series, which contains 28 allergens.

We found that the three most frequent causes of occupational irritant contact dermatitis were wet work (n=64), use of rubber gloves (n=45) and mechanical traumas (n=19). The exposure assessment showed that the patients diagnosed with occupational irritant contact dermatitis had been in contact with the same types of allergens as those patients diagnosed with occupational contact allergy. This means that regardless of whether the patients are exposed to irritants, the investigation should be the same. Only then can the diagnosis of irritant contact dermatitis be qualified.

From a medical viewpoint, we found by investigating the MSDS that 18.6% (137/738) contained errors or had missing information, which prevented a fast and complete allergy investigation. The most frequent obstacle was missing information on the preservatives used. In 10 cases the manufacturer refused to provide information concerning the contents used in the products and referred to the information given in the MSDS. One way to avoid these shortcomings is to improve the legislation.

Isothiazolinones are a group of preservatives found to be causing an increasing number of allergies. We analysed product types registered in the Danish Product Register for occupational use containing one or more of the seven known and sensitizing isothiazolinones. We found that the three most frequently used isothiazolinones were benzisothiazolinone (n=985), methylisothiazolinone (n=884) and methylchloroisothiazolinone/methylisothiazolinone (n=611); the three most frequently used product types with one or more isothiazolinones were “paint and varnish”, “cleaning/washing agents” and “polishing agents”.

It can be concluded that a systematic exposure assessment has a significant, direct value for diagnosing occupational allergy and an indirect value for diagnosing irritant contact dermatitis by excluding allergy. The MSDS rarely contained information relevant for identifying irritants and were often insufficient in terms of medically relevant information regarding allergens. By using the Danish Product Register, it was documented that exposure to isothiazolinones was widespread in many work-related products.

Improving the quality of the MSDS and having more accessible information on ingredients in products used in the workplace is crucial for detecting an allergy. This will reflect on the diagnosis, prevention and prognosis of occupational dermatitis.

Summary in Danish

Der anmeldes ca.2.600 nye tilfælde af arbejdsbetinget hudsygdomme til arbejdsskadestyrelsen om året. Håndeksem er den hudsygdom der oftest anmeldes til Arbejdsskadestyrelsen. Det er ofte yngre personer under 35 år og dobbelt så mange kvinder som mænd der udvikler arbejdsbetinget håndeksem.
En eksponeringskortlægning er en forudsætning for at afgøre om et eksem er arbejdsbetinget, for at give den korrekte information samt for forebyggelse. Central information i denne sammenhæng er patientens sygehistorie, viden om indhold i de produkter, der arbejdes med og arbejdsprocesser. Sikkerhedsdatablade og ingredienslister er en vigtig kilde til viden om indhold i produkter på arbejdspladsen, imidlertid kan disse være svære at forstå og studier tyder på, at der kan være manglende eller forkerte informationer i sikkerhedsdatabladene. Hvor stor en rolle dette spiller i praksis ved udredning af arbejdsbetinget eksem blandt danske patienter vides ikke.

Formålet med denne afhandling var at evaluerer om en systematisk, trinvis eksponeringskortlægning giver anledning til påvisning af arbejdsbetinget allergi hos flere patienter, at undersøge om datablade indeholder information som er af betydning for diagnosen irritativt kontakteksem, at påvise om der er specielle forhindringer i forbindelse med at anvende informationen i datablade og at anvende det danske produktregister til at kortlægge, hvilke produkttyper de potente allergener isothiazolinoner anvendes i.

Vi udviklede en trinvis eksponeringsanalyse, hvor patienternes produkter fra hjemmet og fra arbejdspladsen blev gennemgået. Ved denne proces blev sikkerhedsdatablade, produktinformation samt ingredienslister gennemgået, producenter og arbejdspladser blev kontaktet og individuelle allergitest blev planlagt. Den systematiske eksponeringsanalyse blev foretaget hos 228 patienter med arbejdsbetinget eksem, som i en periode på januar 2010 til august 2011 blev udredt i Hud-og allergiafdelingen, Gentofte Hospital.
Vi fandt at en sådan trinvis eksponeringsanalyse efterfulgt af allergitestning med individuelt designede testpaneler medfører en forøget påvisning af relevante allergier hos 36% patienter og omfattede 103 forskellige ekstra allergener, sammenholdt med kun at teste med den europæiske basisserie, som indeholder 28 allergener.
De tre hyppigste årsager til et arbejdsbetinget irritativt kontakteksem var: vådt arbejde (n=64), brugen af gummihandsker (n=45) samt mekaniske traumer (n=19). eksponeringsanalysen viste at

patienterne, som endte med diagnosen irritativt kontakteksem, havde været i kontakt med de samme typer af allergener, som patienterne diagnosticeret med arbejdsbetinget kontaktallergi. Dette viser at udredningen bør være den samme uanset om patienterne i udgangspunktet er udsat for irritanter og kun herved kan diagnosen irritativt kontakteksem kvalificeres.

Vi fandt ved gennemgang af sikkerhedsdatabladene, at disse indeholdt fejl og mangler i 18,6% (137/738), fra et medicinsk synspunkt, det vil sige som forhindrer en hurtig og komplet allergiudredning. Den hyppigste mangel var at der ingen oplysninger var om de anvendte konserveringsmidler. I 10 tilfælde nægtede producenten at give information om indholdsstoffer ud over oplysningerne i sikkerhedsdatabladet. Disse forhindringer kan undgås ved fx at forbedre lovgivningen.

Isothiazolinoner er den gruppe af konserveringsmidler, der de sidste par år fundet værende årsag til et stigende antal tilfælde af allergi. Produkttyper registret i Produktregistret, til brug i erhvervslivet, indeholdende en eller flere af de syv kendte og allergifremkaldende isothiazolinoner blev analyseret. Her fandt vi at de tre hyppigste anvendte isothiazolinoner var: benzisothiazolinone (n=985), methylisothiazolinone (n=884) og methylchloroisothiazolinone/methylisothiazolinone (n=611) og at de tre hyppigste produkttyper med en eller flere isothiazolinoner i var ”maling og lakker”, ”rengørings- og vaskemidler” og ”polermidler”.

Det kan konkluderes at en systematisk eksponeringsanalyse har betydelig værdi for diagnosticering af arbejdsbetinget allergi og indirekte ved diagnosticering af irritativt kontakteksem ved at afkræfte allergi. Sikkerhedsdatablade indeholdt kun sjældent information af relevans for identifikation af irritanter og var ofte mangelfulde hvad angår medicinske relevante oplysninger om allergener. Ved hjælp af produktregistret dokumenteredes det at udsættelse for isothiazolinoner generelt var udbredt i mange arbejdsrelaterede produkter. En forbedring af kvaliteten af sikkerhedsdatablade og mere tilgængelighed af information om ingredienser i produkter på arbejdspladsen i det hele taget har stor betydning påvisning af allergi og dermed for diagnosen, forebyggelse og prognose af arbejdsbetinget eksem.

Appendix

Appendix 1 - The 6 steps in the exposure assessment

Appendix 2 - Flowchart

Appendix 3 – The 16 sections required in Material Safety Data Sheets (MSDS)

Appendix 4 – Results of the PROBAS analysis

Appendix 1

- The 6 steps in the exposure assessment

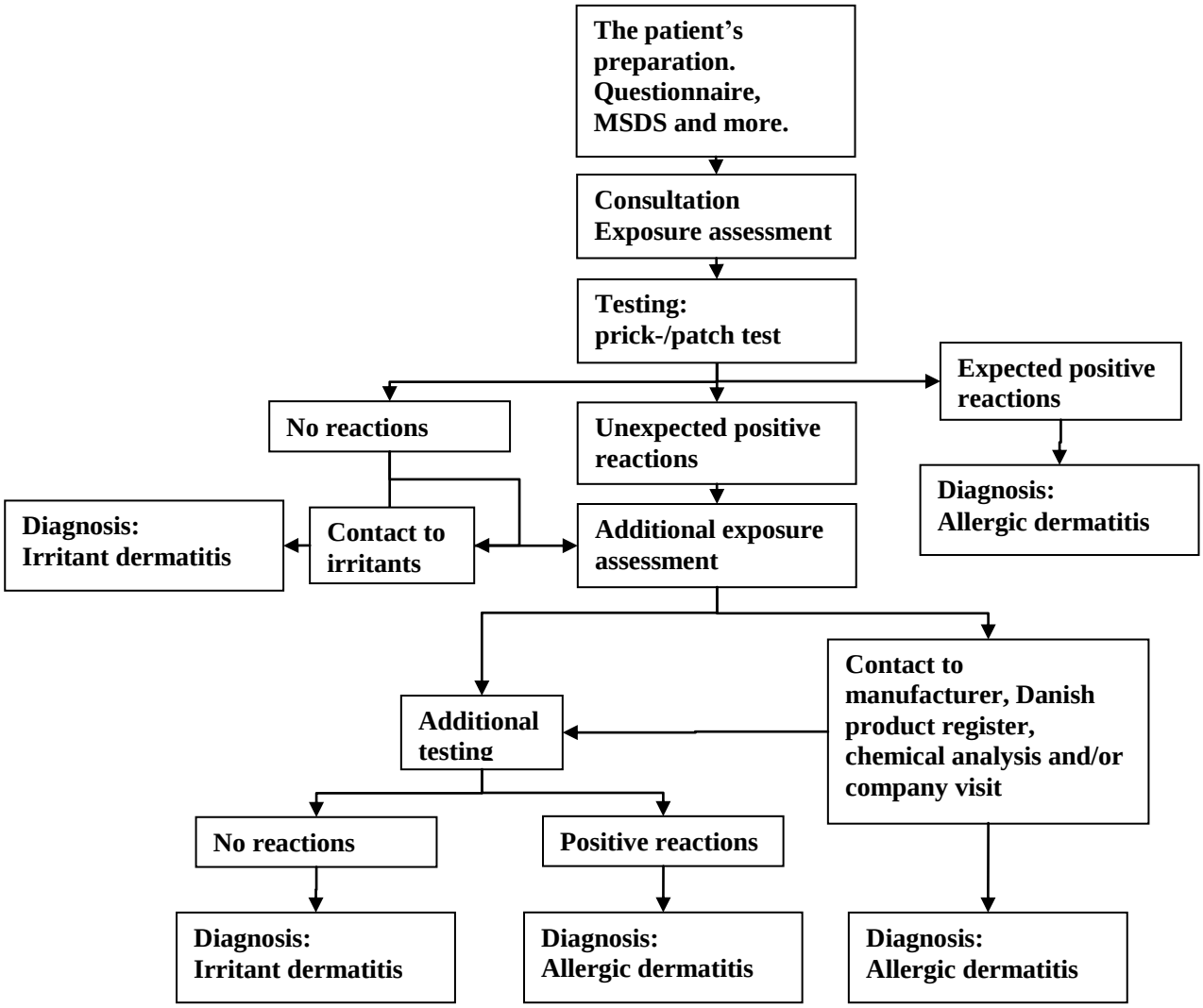
		Yes	Not relevant
Step 1:	Medical History		
	- Exposure assessment of irritants and allergens	☐	☐
	o Products from workplace	☐	☐
	o Products from home	☐	☐
	- Protective equipment (e.g. gloves)	☐	☐
	Interview of the patient by a chemist	☐	☐
Step 2:	Review of product ingredient lists	☐	☐
	Review of Material Safety Data Sheets	☐	☐
Step 3:	Contact with manufacturer	☐	☐
	Contact with workplace	☐	☐
	Contact with the Danish Product Register Database	☐	☐
	Patch testing		
Step 4:	Spot tests	☐	☐
	- Nickel test	☐	☐
	- Cobalt test	☐	☐
	- Formaldehyde test	☐	☐
Step 5:	Chemical analysis of material/product	☐	☐
Step 6:	Visiting the workplace	☐	☐

Results: Clinically relevant exposure identified	Yes	No
	☐	☐

If Yes, at which step:_____

Appendix 2

- Flowchart



Appendix 3

– The 16 sections required in Material Safety Data Sheets (MSDS)

1. Identification of the substance/preparation and of the company/undertaking
2. Hazards identification
3. Composition/information on ingredients
4. First-aid measures
5. Fire-fighting measures
6. Accidental release measures
7. Handling and storage
8. Exposure controls/personal protection
9. Physical and chemical properties
10. Stability and reactivity
11. Toxicological information
12. Ecological information
13. Disposal considerations
14. Transport information
15. Regulatory information
16. Other information

Appendix 4

– Results of the PROBAS analysis