



# Work-related Hand Dermatitis

Epidemiological studies in  
occupational dermatology



Jet Smit

RIJKSUNIVERSITEIT GRONINGEN

# WORK-RELATED HAND DERMATITIS

Epidemiological studies in occupational dermatology

## **Proefschrift**

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door

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## STELLINGEN

1. Het feit dat het merendeel van de buitenshuis werkende vrouwen ook regelmatig blootgesteld wordt aan water en zeep tijdens het verrichten van huishoudelijke arbeid, maakt het niet eenvoudig om bij vrouwen het effect van de beroepsmatige blootstelling aan irriterende stoffen te bepalen.  
dit proefschrift
2. Het regelmatig gebruik van ouderwetse zepen is niet minder schadelijk voor de huid dan regelmatig gebruik van moderne wasmiddelen.  
Naar: Nater JP. Contacteczeem. Leiden: Stafleu, 1974.
3. Om de rol van een atopische constitutie in het ontstaan van handeczeem te kunnen bestuderen in epidemiologisch onderzoek, is een eenduidige definitie van het begrip "atopische constitutie" noodzakelijk.  
dit proefschrift
4. De termen "beroepsziekte", "allergisch eczeem" en "stralingsleukemie" hebben gemeen dat het causale verband bij de individuele patiënt veelal niet aantoonbaar is.
5. Het is nooit te laat om het roken te laten.  
Naar: US Department of Health and Human Services. The Health Benefits of Smoking Cessation, US DHHS, PHS, 1990
6. De eisen die in wetenschappelijke publicaties gesteld worden aan de beschrijving van methoden voor biochemische bepalingen zouden evenzeer gesteld moeten worden aan de beschrijving van methoden voor het verzamelen van vragenlijstgegevens in epidemiologisch onderzoek.  
Naar: Gordis L. Am J Epidemiol 1979; 109: 21-24.

7. "There has never been an important epidemiologic observation which could not be clearly presented in a few tables of raw data with simple summary statistics."  
Walker AM. Am J Publ Health 1986; 76: 556-558.
8. Het toepassen van job-exposure matrices bij het schatten van blootstelling aan chemische stoffen maakt het mogelijk om gezondheidseffecten te bestuderen van blootstelling aan deze stoffen in verschillende beroepssituaties. Een classificatie op basis van het beroep als zodanig is echter meer geschikt om het effect van de gecombineerde blootstelling die typisch is voor een specifiek beroep, te bestuderen.
9. "Knowledge of causal associations that do not offer preventive possibilities, either because from a practical point of view the cause is unalterable or because the side effects are unacceptable, is nevertheless important. Such knowledge aids the study of other potentially causal associations, some of which may be alterable."  
MacMahon B, Pugh TF. Causes and Entities of Disease. In: Clark DW and MacMahon B (Eds). Preventive Medicine. Boston: Little, Brown, 1967.
9. De huid is het grootste menselijk orgaan; de epidemiologie trekt zich daar weinig van aan.
10. Als kranten even weinig gelezen zouden worden als proefschriften, was het met de dagbladjournalistiek snel gedaan.

Stellingen behorende bij het proefschrift van H.A. Smit: "Work-related hand dermatitis; epidemiological studies in occupational dermatology"

Groningen, 3 februari 1993

"Voor mij, het geluk van des morgens met een blij gelaat mijn lampet aan te grijpen en het heldere frissche water op mijne handen te gieten, heeft veel van zijne bekoorlijkheid verloren, sedert ik het klare vocht als het vehikel dier horreurs heb leeren beschouwen"

Hildebrand, *Camera Obscura*, 1884

*Aan mijn ouders  
Aan Bert en Joren*

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# 1. Introduction

Hand eczema or hand dermatitis<sup>1</sup> is a well-known problem in occupations with regular exposure to water and irritating agents ("wet work"). It is experienced frequently by nurses, hairdressers, housewives, food handlers and metal workers. Although hand dermatitis is a relatively infrequent cause of sick leave and medical care is sought by only a proportion of the cases, the symptoms are perceived as troublesome in daily occupational and social life. Moreover, once these symptoms have given rise to a period of sick leave, this period tends to be relatively long.

Eczema can be defined as a non-infectious inflammation of the skin. It is often thought to be an exclusively "allergic" phenomenon, but such a "classic" immunological process only plays a role in the causation of allergic contact dermatitis, which is one particular subtype of eczema. Other common diagnostic subtypes of eczema are irritant contact dermatitis, dishydrotic eczema, atopic eczema and nummular eczema. A combination of morphological, etiological and constitutional factors need to be considered in making a differential diagnosis. Often this requires additional diagnostic testing, for example patch tests or prick tests. In many instances, even when results of diagnostic tests are available, it is difficult to distinguish between subtypes, because symptoms are very similar and different subtypes of eczema may interact or be present simultaneously in one individual.

In epidemiological research where relatively large populations are investigated, it is usually not feasible to obtain sufficient information to make a reliable differential diagnosis for each subject. Therefore eczema must often be studied as an entity of morphological symptoms. Since the different subgroups have a partly different etiology, this may be an obstacle in the epidemiological study on risk factors for hand dermatitis. However, in occupations with frequent exposure to wet work, irritant contact dermatitis is by far the most important subtype of eczema.

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<sup>1</sup> In this thesis, the term dermatitis is used synonymously with the term eczema, although some authors prefer to reserve the term dermatitis for skin conditions with morphological aspects of eczema, and caused by external contact with toxic or irritant factors.

## *Chapter 1*

Irritant contact dermatitis is an inflammation of the skin resulting from repeated contact with weakly toxic agents. The sequence of events resulting in irritant contact dermatitis can be described as follows. Each contact with an irritating agent gives a reaction in the epidermis, which is usually not clinically visible. The severity of this invisible reaction depends on the duration, frequency and intensity of exposure, on the irritating potency of the agent and on the condition of the skin at the site of contact. The skin recovers after cessation of exposure, but it may take several days for complete recovery. In this situation, the subject has usually not experienced any discomfort. However, if renewed contact with the same or another irritant occurs within this recovery period, the effect will accumulate. Repeated contact within the recovery period may thus result in a clinically manifest reaction. Via this mechanism, contact with one or more weak irritants, either or not combined with physical influences (dry, cold weather, high humidity) may lead to clinically manifest symptoms. Therefore, it is often difficult to identify one single cause of irritant contact dermatitis. More often than not, the last exposure before the occurrence of symptoms is blamed to be the cause. Once the symptoms have occurred, it takes a long time for the skin to recover completely. Even in absence of visible symptoms the skin remains sensitive for several months. Within this recovery period even a weak irritant may provoke renewed flaring up of the symptoms.

As with many other diseases, not all individuals seem to be equally susceptible to the development of hand dermatitis under similar conditions of exposure. Some individual characteristics are known to be predisposing factors determining susceptibility. For example, a history of atopic eczema is generally recognized to be a risk factor for the development of contact dermatitis. Another more recent hypothesis concerns the role of the barrier function of the skin as a factor determining the individual susceptibility. It is hypothesized that transepidermal water loss may be an indicator of the performance of the barrier function of the skin against passage of chemicals. According to this hypothesis, a high trans-epidermal water loss would indicate impairment of the barrier function of the skin.

The application of epidemiological methods may contribute to the understanding of the multifactorial etiology of hand dermatitis. However, the

## *Introduction*

relatively limited number of publications in this field, may well reflect the difficulties that were experienced thus far in epidemiological studies of hand dermatitis.

The main objectives of this thesis were (1) to assess the prevalence and incidence of hand dermatitis in different occupational groups, using a standardized method for case ascertainment and (2) to investigate the role of endogenous risk factors for the development of hand dermatitis.

Chapters 2 and 3 contain a review of available literature on the descriptive epidemiology of hand dermatitis and discuss methodological aspects of designing epidemiological studies of hand dermatitis.

Firstly, a questionnaire-based method for the ascertainment of cases in relatively large study populations was developed and validated (Chapter 4). In a series of cross-sectional surveys, the validated questionnaire was used to estimate the prevalence of hand dermatitis in different occupational groups as compared with the general population (Chapter 5).

The prevalence of hand dermatitis may be a useful indicator of disease burden and it may provide information for the planning of preventive measures. However, the prevalence does not reflect the risk for the development of hand dermatitis and it is not adequate to study associations with occupational exposure. To investigate risk factors for hand dermatitis, a follow-up study in a disease-free population is necessary, such that the time sequence of events can be taken into account. A retrospective study using the validated questionnaire was performed as a pilot study to obtain a rough estimate of the incidence rate in newly employed nurses (Chapter 6). Also, it was investigated whether the measurement of transepidermal water loss could be used as an indicator for individual susceptibility to the development of hand dermatitis in epidemiological studies (Chapter 7). After gathering these experiences, a prospective cohort study on the role of individual susceptibility to acquiring hand dermatitis, was performed among apprentice nurses and apprentice hairdressers (Chapter 8). The thesis is concluded with a general discussion of the main findings (Chapter 9).

## 2. Epidemiology of contact dermatitis\*

H.A. Smit, P.J. Coenraads

### Definitions and methods

Contact dermatitis is an inflammation of the skin that may occur as a result of contact with external factors. Two etiologically different types can be distinguished: irritant and allergic contact dermatitis. Irritant contact dermatitis results from contact with irritant substances, while allergic contact dermatitis is a delayed-type immunological reaction in response to contact with an allergen in sensitized individuals. Usually the antigens are compounds of low molecular weight. After conjugation with protein in the skin the immunologically active hapten is formed, which interacts with the individual's immune system and may induce delayed hypersensitivity.

Several studies have been performed that contribute to the knowledge of the epidemiology of contact dermatitis. The majority of these studies is cross sectional, thus giving estimates of the prevalence. However, there is a lack of incidence figures for contact dermatitis. Routinely registered data are uninformative because contact dermatitis is a rare cause of death or hospitalization and prospective follow-up studies among the general population have not been performed yet. One retrospective cohort study on nickel allergy in women, was performed in Denmark using self-administered questionnaires.<sup>1</sup> The authors noted that the reporting of hand eczema by questionnaire was likely to contain errors and preferred to discuss the relative incidence figures rather than the absolute figures. Studies among patient populations from dermatology clinics are not adequate for estimating the incidence rate. The main reason for this is, that patient populations from different clinics often differ in demographic characteristics, while information on the distribution of demographic characteristics in the underlying population is usually unknown.

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\* In: Burr M (ed). *Monograph on Allergic Diseases*. Basel, Karger, (in press)

## Chapter 2

Six major population-based studies were performed in South Sweden, England (London), the United States, the Netherlands, Norway (Tromsø) and Gothenburg among a geographically defined population or a sample thereof.<sup>2-9</sup> The terms "dermatitis" and "eczema" in these studies are often used synonymously. The studies in England and the USA involved all skin disorders, the others focussed on eczema, including irritant and allergic contact dermatitis, nummular eczema, atopic eczema, seborrheic eczema, dyshidrotic eczema and unclassified eczema. An important difference in the study methods was the way in which persons with eczema/skin disorders were identified in the study population. In South Sweden, Gothenburg, Tromsø and London, an initial screening was performed by means of a self-administered questionnaire, resulting in an estimate of self-reported "skin disorders" (South Sweden), "hand eczema" (Gothenburg) or "allergic hand eczema" (Tromsø). In the Netherlands and in the USA the total study population was examined routinely (without patch testing or extensive history taking) by a dermatologist or a trained physician. Subsequently, in the studies in South Sweden, Gothenburg and the Netherlands, persons with skin disorders or dermatitis were invited for a clinical examination, during which patch testing with the standard series was performed and a medical and exposure history was taken. Based on that information, a differential diagnosis of allergic or irritant contact dermatitis was made. Evidently, not all persons who were invited attended the clinical examination. It was mentioned that persons who attended the examination suffered from more severe symptoms than those who did not attend. Hence, extrapolation would result in an overestimate of the prevalence. On the other hand, a proportion of persons with skin disorders was missed by the method of self-reporting. Other differences between the studies concerned the localization that was studied (hands versus all body localizations) and the period to which the prevalence estimate refers (12 months, 3 years or the time of the study only).

Indications on the role of specific allergens in the etiology of allergic contact dermatitis can be obtained from patch testing. Three types of populations in which patch testing has been performed can be distinguished: healthy populations or a sample of the general population, persons who were diagnosed with eczema in population-based studies and patients visiting dermatology clinics.

However, the relative importance of allergens is difficult to assess, because there is only a partial correspondence between a positive patch test and allergic contact dermatitis. Firstly, sensitization is not necessarily followed by symptoms of allergic contact dermatitis. A study on nickel sensitivity in the general population showed that only 45% of the nickel-sensitive individuals reported present or past hand eczema.<sup>10</sup> In other studies in which healthy individuals were patch tested, one or more positive reactions were observed in approximately 10% of the population.<sup>11,12</sup> Thus, patch testing studies among the general population can only provide information on the sensitization rates in that population, but they are unrelated to the prevalence of allergic contact dermatitis. Secondly, a positive patch test does not indicate that the substance is a sole or contributing cause of allergic contact dermatitis, since patients may react to multiple agents. The relevance of a positive patch test is indicated by the exposure history of the patient. Therefore, a high sensitization rate for a particular substance in persons with eczema does not necessarily imply that this substance is an important etiologic factor. Furthermore, an important limitation in the presentation and interpretation of studies among patients from dermatology clinics is, that patient populations may differ in many respects, such as criteria for referral of patients to the clinic, indications for patch testing (i.e. severity of the condition, type of skin disorder) and the distribution of age, gender, occupational and environmental exposure in the underlying population. Some authors therefore recommended that results be presented stratified for relevant factors like age and gender or that multivariate analyses be performed taking these factors into account.<sup>13</sup>

The epidemiology of contact sensitization is described by Menné et al.<sup>14</sup> In this chapter, the importance of a number of allergens will be discussed based on results from population-based studies in which patch testing of persons with eczema has been performed and on the reports of patch testing in several dermatology clinics in Western Europe, (former) Eastern Europe and North America, using standardized techniques.<sup>15-17</sup> Although the latter studies were performed among patient populations, the advantage of these studies in comparison to other similar reports is, that several clinics were involved in each study and that a large area was covered, reducing the chance of extreme distributions of popula-

tion characteristics. The study in North America involved 1,200 patients in 10 dermatology centers who were patch tested in 1971-1972.<sup>16</sup> The Eastern European study was performed during a 1-year period among 2,231 patients in several departments in Bulgaria, Czechoslovakia, GDR, Hungary and Poland.<sup>17</sup> The Western European study involved 4,825 patients from 8 dermatology clinics in 7 Western European countries, who were patch tested in 1967-1968.<sup>15</sup>

## Frequency

### *Incidence and prevalence*

The only estimate that is available on the incidence of eczema (including irritant and allergic contact dermatitis) is based upon two consecutive cross sectional studies among the same sample of the general population, which was 7.9 cases per 1,000 persons per year.<sup>6</sup> Based on six major population-based studies that were discussed before, it is estimated that the prevalence of contact dermatitis lies between 1 and 10% in the general population (table 1). The studies in South Sweden, Gothenburg and the Netherlands observed a prevalence of allergic contact dermatitis of approximately 1%. The estimates of the prevalence of irritant contact dermatitis varied between 1 and 4%.

### *Age and gender*

In most studies the prevalence among women was approximately twice as high as among men.<sup>2,6-8</sup> A predominance of females among dermatologic patients is reported frequently<sup>15-17</sup> and is often suggested to reflect a higher prevalence of contact dermatitis among women. In contrast, the prevalence of eczema in London was higher among males and in the USA no difference between men and women was observed.<sup>3,4</sup> The discrepancy with the results from the other studies may be related to the fact that the other studies involved the hands only, while the studies in London and the USA involved all body sites.



**Table 1** Prevalence of all hand dermatitis and allergic hand dermatitis in three crosssectional studies.

Place and year	Study population (n)	Site	Study method	Prevalence		
				period	definition	%
South Sweden, 1964-65 <sup>2</sup>	107,206	hands	questionnaire + patch testing of patients	point	hand eczema allergic CD irritant CD	1.2* 0.4* 0.5*
London, 1967-69 <sup>3</sup>	1,979	all sites	questionnaire + clinical evaluation of subsample	point	eczema	6.1
USA, 1971-74 <sup>4</sup>	20,749	all sites	clinical evaluation	point	contact dermatitis	1.4
Netherlands, 1979 <sup>5</sup>	3,140	hands	clinical evaluation	3-year	hand eczema	6.2
Netherlands, 1982 <sup>6</sup>	1,992	hands	clinical evaluation + patch testing of patients	3-year	hand eczema allergic CD irritant CD	7.1 1.0 4.0
Norway, 1979 <sup>7</sup>	14,667	hands	questionnaire	12 months	"all. hand eczema"	8.9
Gothenburg, 1982 <sup>8,9</sup>	16,584	hands	questionnaire + patch testing	12 months point	"hand eczema" "hand eczema" allergic eczema irritant eczema	10.6 5.4 1.0 1.9

\* Reported to be possibly underestimated by a factor 2

## Chapter 2

Table 2 gives age- and gender-specific estimates of the point prevalence of allergic and irritant contact dermatitis separately, as observed in the study in Gothenburg.<sup>8,9</sup> The prevalence of both types of contact dermatitis was higher among women in all age groups, but this difference was more pronounced for allergic than for irritant contact dermatitis. In women, the prevalence of irritant and allergic contact dermatitis was highest in the ages between 20 and 29 years. In men, no clear age trend in the prevalence of allergic dermatitis was observed. The prevalence of irritant contact dermatitis was higher in the age groups under 40 years.

Data on the prevalence of contact dermatitis in children are scarce, because most of the population-based studies were restricted to persons of 15 years and older<sup>2,3,5-9</sup> the study in the USA being an exception.<sup>4</sup> Hand eczema under 11 years of age was not observed in the USA, but the prevalence of contact dermatitis on other sites of the body was 1.4% in children 1-5 years and 0.5% in children 6-11 years, compared to an overall prevalence of 1.4%. It is generally believed that contact dermatitis in children is rare,<sup>18</sup> but some cases of allergic contact dermatitis are observed in dermatology clinics.<sup>19-22</sup>

Whether differences in prevalence between age groups and genders should be attributed to differences in susceptibility or to differences in exposure to irritants and sensitizing agents, will be discussed below.

**Table 2** Point prevalence of irritant (ICD) and allergic (ACD) contact dermatitis in Gothenburg by age and sex<sup>9</sup>

Age, years	Men		Women	
	ICD %	ACD %	ICD %	ACD %
20-29	1.1	0.25	3.3	2.3
30-39	1.5	0.35	2.1	1.6
40-49	0.9	0.49	2.2	1.7
50-59	0.6	0.38	1.9	1.5
60-69	1.1	0.40	2.3	1.8

*Occupational groups*

Large differences in the frequency of contact dermatitis between occupational groups may occur. Frequent contact with water, soaps, dyes and perfumes, rubber chemicals and metal working fluids are examples of occupational exposures that put the skin at risk of contact dermatitis.<sup>23</sup> Occupational dermatitis is one of the most frequent occupational diseases, accounting for 9 - 35% of all occupational diseases.<sup>24-28</sup> Its incidence is estimated to be 0.5 - 0.7 cases per 1,000 workers per year.<sup>29</sup> High risk industries include, among others, agriculture, the leather industry, rubber, chemical, metal and food industries and the health services.<sup>24,26,27</sup>

The age-adjusted 3-year prevalence of hand eczema in the population-based study in the Netherlands was 14.2% in the chemical industry, 11.6% in the metal industry, 7.8% in the construction industry and 6.5% in agriculture.<sup>5</sup> Using the same study method and definitions in a study among 1,691 construction workers the age-adjusted 3-year prevalence was 6.0% among carpenters, 12.1% among bricklayers and 6.9% among supervisors and administrative personnel.<sup>30</sup> In the population-based study in Gothenburg a relatively high 12-month prevalence of self-reported hand eczema was observed in medical and nursing occupations (15.9%) and in service occupations (15.4%).<sup>31</sup>

Irritant contact dermatitis is more prevalent in "wet work" occupations like cleaning, hairdressing, nursing and food handling while allergic contact dermatitis is reported to be predominant in for example the rubber, building and plastics industries.<sup>32</sup>

Incidence and prevalence figures from other studies among occupational groups are difficult to compare, because these studies usually involve one specific industry or one occupational group while different study methods and different criteria for the definition of contact dermatitis are used.

*Geographical distribution and time trends*

Although the population-based studies that were discussed before, took place in different geographical areas and in different time periods, the numerous differences in study methodology and diagnostic criteria do not allow to draw conclusions with regard to the geographical distribution or time trends in the preva-

## Chapter 2

lence of contact dermatitis. There are no indications for a changing trend in the number of persons visiting dermatology clinics, suggesting that no major changes in incidence have taken place in the last decades. Nevertheless, temporal patterns in sensitization in patients visiting dermatology clinics have been reported.<sup>33,34</sup> Edman and Möller<sup>33</sup> evaluated results from 12 years of patch testing (1969-1980) according to ICDRG guidelines in a dermatology clinic in Malmö. They observed an increase of nickel, cobalt and epoxy sensitivity in females, an increase in neomycin sensitivity in both genders, a decrease in paraphenylene diamine in males, a decrease of balsam of Peru, formaldehyde and colophony in females and a decrease of clioquinol sensitivity in both genders. They judged the increase of nickel allergy to be especially alarming. Gollhausen et al.<sup>34</sup> analyzed patch test results from one dermatology clinic in München according to ICDRG guidelines compiled over a period of 7 years (1977-1983). In agreement with the observations of Edman and Möller<sup>33</sup> were an increase in nickel sensitivity and neomycin sensitivity and a decrease in clioquinol sensitivity. As opposed to Edman and Möller<sup>33</sup> they observed a significant increase in sensitivity to potassium dichromate and balsam of Peru in both genders and to formaldehyde in females.

An increase in nickel sensitization is reported frequently.<sup>1,33,35,36</sup> Menné et al.<sup>1</sup> found that the incidence density of nickel allergy had doubled in all age groups between 1948 and 1973, based on a retrospective cohort study among women in Denmark. Romaguera et al.<sup>36</sup> noted an increase in the nickel sensitivity rate in patients visiting a dermatology clinic, from 13.8 to 26.1% over the last 10 years. Similarly, Lunder<sup>35</sup> reported a sensitization rate for nickel of 6.7% in the period 1972-1976 and of 9.1% in 1982-1986. The increase in nickel sensitivity was especially pronounced in younger women and is generally attributed to an increase in wearing fashion jewelry and the habit of ear piercing.<sup>33,35-37</sup> The observation in one study, that 72% of the schoolgirls 8-15 years of age had their ears pierced and that nickel sensitivity was present in 13% of the girls with pierced ears against 1% of the girls without pierced ears, illustrates the potential threat of nickel sensitivity in the future.<sup>38</sup>

Observations from several occupational dermatologists in Europe suggest that the number of cases of allergic chromate eczema in their patient populations is

decreasing. In Northern Ireland the number of disability claims related to chromate allergy decreased over the period 1965-1975.<sup>39</sup> In Sweden, a decrease of the number of positive patch test reactions to potassium dichromate was observed before the introduction of ferro-sulfate.<sup>40</sup>

Geographical differences in the incidence or prevalence of allergic contact dermatitis and irritant contact dermatitis are not obvious from the available studies, but geographical differences in sensitization rates to certain substances in patient populations have been observed repeatedly. Although part of these differences are accounted for by differences in the criteria for patch testing in different areas, it is well known that differences in exposure to allergens between geographical areas exist. These differences will probably be reflected in a geographical pattern of contact dermatitis. A clear example of this is the frequently observed contact allergy to poison ivy in the USA and the absence of this type of contact allergy in Europe.<sup>19,41</sup> Other differences in sensitization rates in patient populations in North America, and Eastern and Western Europe will be discussed in the next paragraph.

## **Clinical picture**

Morphological symptoms of contact dermatitis are erythema, papules, pustules, vesicles, exudation and itching. In chronic cases, fissuring and lichenification develop. Primary lesions of contact dermatitis are usually found at the site of contact with the irritant or allergen. The symptoms of irritant contact dermatitis remain restricted to the site of contact. In case of allergic contact dermatitis, secondary lesions may occur subsequently on other sites of the body, also on those sites that have never been in contact with the allergen. In the general population and in patients visiting dermatology clinics, the majority of contact dermatitis is localized on the hands, alone or in combination with other localizations.<sup>2,4,15,17,32</sup> Occupational dermatitis in particular, shows high proportions of hand involvement. Meneghini and Angelini<sup>42</sup> reported that in 90% of all occupational allergic contact dermatitis was found on the dorsum of the hands and forearms. Also in women who frequently suffer from irritant contact dermatitis,

contact dermatitis occurs predominantly on the hands.<sup>32</sup> Hand eczema in housewives occurred in nearly half the cases on the palms of the hands, while in 15% the dorsa combined with the fingers were involved.<sup>43</sup>

The morphological patterns of irritant and allergic contact dermatitis are very similar. Additional patch testing and thorough history taking is necessary to make a differential diagnosis of irritant contact dermatitis or allergic contact dermatitis. The diagnosis allergic contact dermatitis is indicated by an exposure history of previous contact with a substance that also showed a positive test result. A diagnosis of irritant contact dermatitis is more likely in the absence of positive patch tests and when contact with irritants is indicated in the exposure history. Occasionally, a combination of irritant and allergic contact dermatitis may occur, because the presence of irritant contact dermatitis facilitates the passage of sensitizing agents through the skin, thus stimulating the development of allergic contact dermatitis.<sup>15</sup>

In the general population, irritant contact dermatitis is more common than allergic contact dermatitis, the ratio of allergic versus irritant contact dermatitis being under 1 in these populations.<sup>2,6,9</sup> As was mentioned before, in occupational groups the ratio of allergic versus irritant contact dermatitis will depend largely on the exposure characteristics of specific occupational tasks. Persons with allergic contact dermatitis tend to seek medical care more often than persons with irritant contact dermatitis, because symptoms in allergic dermatitis are generally more severe and more persistent.<sup>2,9,32</sup> Probably for that reason, the ratio of allergic versus irritant contact dermatitis among patients visiting dermatology clinics is higher than in the general population. For example, in a study in seven European countries, allergic contact dermatitis was diagnosed twice as often as irritant contact dermatitis. Veien et al.<sup>44</sup> found that allergic contact dermatitis was 1.6 times more common than irritant contact dermatitis among 3,164 patients of one clinic, who were patch tested with the standard series of substances. Consistent with this picture is the observation by Menné and Bachmann<sup>45</sup> that allergic contact dermatitis was approximately 7 times more common among persons who applied for permanent disability pension in Denmark than irritant contact dermatitis.

## *Descriptive epidemiology*

### *Provoking factors*

Low humidity, high temperatures, occlusion and sweating may damage the surface of the skin and facilitate penetration of irritants and allergens, thus provoking the occurrence of contact dermatitis. Especially in occupational settings, these factors may contribute to the occurrence of contact dermatitis.<sup>46</sup> Seasonal variations in relation to these factors are known to occur,<sup>18</sup> but no epidemiologic data are available to quantify this variation.

### *Patch testing*

The technique of patch testing is now widely used to detect sensitivity to specific substances in patients with suspected contact allergy. Patch tests results may vary substantially, depending on the concentration and vehicle that was used for testing and on criteria for evaluation of patch tests. To improve comparability of patch test results between different clinics, standard patch test series and guidelines for evaluation of patch tests have been recommended by the International Contact Dermatitis Research Group.<sup>15</sup> The standard series of substances consists of the most commonly encountered allergens and is updated regularly.<sup>47</sup> Prick tests and other tests for immediate type allergy (like scratch/chamber tests, RAST tests for determination of specific IgE antibodies) are less useful as diagnostic tests for allergic contact dermatitis.<sup>44</sup>

Nickel, chromium and (to a lesser extent) cobalt, were the highest ranking sensitizers in the population-based studies and in the patient-based studies in North America, Western Europe and Eastern Europe.<sup>2,6,8,15-17</sup> Sensitivity to chromium was most common in men, while nickel was a typically female sensitizer. The sensitization rate was highest for nickel, except in Eastern Europe where chromium was the most common sensitizer. Table 3 shows the sensitization rates for some substances as observed in these studies. The frequency of positive reactions to chromium among males varied substantially between the studies.

**Table 3** Sensitization rates for some common allergens in different studies (in percentages)

Reference	Nickel women	Cobalt women	Chromium men	Balsam of Peru both genders	Neomycin both genders
(9)	21.9	9.4	0.9	4.9	1.8
(6)	26.3	1.1	4.3	1.4	NA
(2)	12.1	8.9	9.6	9.0	1.7
(16)	14.9	NA	9.8	NA	6.0
(15)	9.9	6.6	10.6	6.3	3.7
(17)	NA	NA	NA	5.6	NA

NA = not available

This can possibly be ascribed to differences in the chromate content of cement.<sup>17,18,33</sup> Sensitization to balsam of Peru among both genders was common in all studies, except in the Netherlands and sensitization to rubber chemicals was most common in Eastern Europe, followed by North America. A relatively low frequency of positive reactions was observed in Western Europe and in the population-based studies in Sweden and in the Netherlands. These differences are likely to be due to differences in (occupational) exposure.

Sensitization rates to neomycin show an interesting pattern. Firstly, the rates were higher in North America than in Western Europe, which was attributed to the more widespread availability of topical medicaments, containing neomycin in North America.<sup>16</sup> Secondly, the population-based studies had clearly lower sensitization rates than studies among patient populations. This may reflect the greater use of medicaments among the patient populations than among the general population.



## **Natural history**

### *Course and prognosis*

Contact dermatitis is recognized as a disease with an unfavorable prognosis<sup>2,32,48-50</sup> Agrup<sup>2</sup> found that approximately 10% of the persons who were diagnosed with hand eczema was completely healed while 56% had improved and in 34% the condition was unchanged or had worsened. The percentage of eczema patients with recurring symptoms of contact dermatitis in working populations varied between 35 and 80% depending on the severity of the symptoms, the period of follow-up and the intensity of exposure.<sup>49</sup> Fregert<sup>32</sup> reported that only in one quarter of the patients was the hand eczema cured within a period of 2-3 years after diagnosis.

The prognosis for allergic contact dermatitis is thought to be worse than that for irritant contact dermatitis. Driessen et al.<sup>48</sup> followed eczema patients 4-7 years after they had visited the dermatology clinic and found that 56% of the patients with irritant contact dermatitis were healed versus 37% of the patients with allergic contact dermatitis. A greater tendency for medical consultation, sick leave and permanent disability in persons with allergic contact dermatitis is consistent with the observation that symptoms in these patients are generally more persistent than in patients with irritant dermatitis. In the population-based study in Gothenburg, 35% of the patients with allergic contact dermatitis reported 5 or more medical consultations versus 12% of the patients with irritant contact dermatitis<sup>50</sup>. Sick leave in relation to hand dermatitis was reported by 37% of the patients with allergic dermatitis and by 14% of the persons with irritant dermatitis. Also, the mean duration of sick leave was longer in persons with allergic than with irritant dermatitis (29 vs 13 days on average). Several studies found that the prognosis for eczema patients was not better after a change of occupation or retirement.<sup>32,45</sup> Rystedt<sup>51</sup> found that 65-70% of the patients with hand eczema and severe or moderate atopic dermatitis had improved significantly after a change of job. Schubert et al.<sup>52</sup> also reported better results of a change of occupation. Out of 42 patients who had changed occupation, 36 persons who had mostly changed to a white collar occupation, were successfully healed. The fact that 6 persons were still suffering from contact

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dermatitis, was ascribed to continuing nickel exposure in their new jobs. This supports the view that lack of improvement may be due to the fact that even occasional contact with the allergen in the home or in the working environment is sufficient to maintain the condition.

Fregert<sup>32</sup> found that the prognosis was especially bad in women with nickel allergy, since all of the 29 nickel sensitive females still suffered permanent or periodic symptoms 2-3 years after diagnosis. Wet work, which is frequently performed by women, helps maintain the eczema. Fregert<sup>32</sup> therefore argues that persons with nickel allergy and pronounced hand eczema are often unable to continue work in an occupation with exposure to wet work. Christensen<sup>53</sup> observed a better prognosis in 63 female patients with nickel allergy and hand eczema. They were reinvestigated 6 years after diagnosis and 30% of them were healed. When a differentiation was made between types of hand eczema it appeared that the prognosis for nickel sensitive patients with non-pompholytic eczema (including contact dermatitis) was better than for patients with nickel allergy and hand eczema of pompholytic type (healing in 77% vs 18%). Other factors that were suggested to worsen the prognosis of hand eczema in females with nickel allergy were a combination of immediate and delayed-type hypersensitivity, and combined nickel and cobalt allergy.

### *Predictive factors*

The development of contact dermatitis is determined by a combination of individual susceptibility and exposure characteristics. Individual susceptibility may be related to personal characteristics like age, gender, genetic factors, the condition of the skin and the presence of other diseases. Environmental factors may play a role in this process by influencing the individual susceptibility (condition of the skin) and/or the characteristics of exposure.

**Gender.** Some physiologic and anatomic differences between the skin of men and women exist, which may cause gender related differences in susceptibility to irritants or sensitizers (dryness of the skin, subcutaneous fat etc). As was mentioned before, the prevalence of irritant contact dermatitis is higher among women but gender related differences in irritability of the skin have not been observed.<sup>54</sup> It is more likely that the high exposure to irritating agents, especially

### *Descriptive epidemiology*

of younger women in household duties, child care and occupations involving "wet work" (nursing, hairdressing, cleaning) is responsible for the higher prevalence. Also, the differences between men and women in sensitization rates to nickel and chromium that were discussed before, are more likely to be caused by differences in exposure than by gender related differences in susceptibility. One study reported that women were more easily sensitized than men,<sup>55</sup> but this finding was contradicted by the results of other studies showing no gender related differences in susceptibility.<sup>56,57</sup>

**Age.** Clear differences in sensitization rates between age groups were noted in the patch test studies in Eastern and Western Europe. The sensitivity was highest between 20 and 59 years of age (appr. 20% in Western Europe and 35% in Eastern Europe). In the ages below 20 years and 60 years or older, the frequency of positive reactions was around or under 10%. It has been a topic of debate whether children have a decreased susceptibility to sensitization or whether their limited exposure to allergens was responsible for the low prevalence of allergic contact dermatitis. Positive patch tests in children were observed, but the validity of the results was questioned by some authors who argued that patch test concentrations as used for adults caused irritant reactions in children.<sup>58</sup> In more recent investigations however, no irritant reactions were observed to standard patch test concentrations and the positive reactions were considered valid.<sup>20-22</sup> The most common allergens in children were found to be the Rhus allergen, nickel, cobalt, rubber and topical medicaments.<sup>19-22,41</sup> In older age groups, the properties of the skin (permeability, dryness, ability to recover from damage) may have changed, such that it is more susceptible to irritants and allergens. On the other hand, the reactivity of the immune system may have decreased, resulting in a lower susceptibility. No clear evidence from experimental studies exist with regard to this issue. However, it is obvious that the type and intensity of exposure to allergens changes significantly with increasing age. For example, occupational exposure tends to decrease with age and exposure to medicaments tends to increase with age. This is consistent with the findings in the patch testing studies in Western Europe that patients with sensitivity to chromium, nickel, cobalt and rubber were generally younger than those with sensitivity to medicaments (neomycin, vioform, wool alcohols and sterosan) and balsams

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(colophony, wood tars, balsam of Peru, turpentine). Also, Coenraads et al.<sup>59</sup> showed that the association between age and eczema prevalence disappeared when occupation was accounted for in the analysis. They concluded that occupation and not age was a major factor associated with eczema prevalence.

The role of genetic factors in the causation of contact dermatitis has not been fully clarified. Evidence derived from animal models and epidemiologic studies shows that the immune response to antigens, which includes contact allergy, is under direct genetic control.<sup>57,60</sup>

### *Exposure*

Skin contact with external factors (irritant or allergic) is a necessary condition for the development of contact dermatitis. No symptoms will occur without previous contact, but once that contact with an allergen has occurred, the probability and severity of a reaction depend on the type and intensity of exposure. Whether or not sensitization occurs after contact with an allergen, depends on the sensitizing potential of the allergen, its concentration, the nature of the vehicle and the presence of surface active agents. In addition, the frequency and intensity of skin contact determines the probability to become sensitized and to develop symptoms of allergic contact dermatitis. Overall, it is the combination of the sensitizing potential of the allergen and the intensity of exposure to the allergen that determines the sensitization rate in a population. Strong sensitizers with low intensity of exposure or exposure among a small proportion of the population, will have less impact on the prevalence of allergic contact dermatitis than a mild or medium sensitizer with widespread exposure in the general population. An example of the latter situation is nickel exposure among women, resulting in high sensitization rates for nickel in comparison with men.

### *Relation with other diseases*

In recent years, evidence has accumulated that atopic dermatitis is a risk factor for contact dermatitis. Earlier studies indicated that the proportion of atopic individuals among patients with hand eczema was almost three times as high as among the general population or a healthy control group.<sup>61,62</sup> Later it appeared that an atopic history was especially associated with irritant dermatitis.<sup>2,32</sup> This

### *Descriptive epidemiology*

was ascribed to a reduced resistance of the atopic skin.<sup>63</sup> The proportion of persons with sporadic or continuous hand eczema was significantly elevated in the groups with moderate and severe atopic dermatitis in childhood (60 and 48% respectively) as compared to the groups with respiratory allergy only and a group of non-atopics (14 and 11% respectively).<sup>51</sup> Rystedt<sup>63</sup> provided evidence that exogenous factors like exposure to irritant factors were less important in the development of hand eczema than constitutional factors like severe eczema in childhood, persistent eczema on other parts of the body and dry and itchy skin. A family history of eczema, female gender and concurrent asthma and rhinitis were of limited importance as well.

The role of atopy in the development of allergic contact dermatitis is still being discussed.<sup>64-66</sup> Some studies indicated that atopics were not more susceptible to sensitization than non-atopics.<sup>67</sup> Other studies even showed a decreased sensitivity among atopics to specific sensitizers like dinitrochlorobenzene (DNCB).<sup>68,69</sup> Jones et al.<sup>69</sup> performed a study among 40 patients with atopic dermatitis and 44 controls free of dermatitis, in which they were patch tested with Rhus allergen. They found that only 15% of the patients with atopic dermatitis had a positive patch test to Rhus Oleoresin, compared to 61% of the controls. They argued that this could not be explained by differences in exposure, but that atopics were less susceptible to sensitization than non-atopics. De Groot<sup>66</sup> determined the sensitization rate among 214 atopic patients and 285 non-atopics, both with dermatitis. Positive reactions to one or more substances of the European standard series were observed in 52% of the non-atopics and in 37% of the atopics, a difference that was statistically significant. Also in other studies it was shown that the sensitization rates to different substances were lower in atopics than in non-atopics. The sensitization rates varied between 26 and 40% in atopics and between 39 and 51% in non-atopics, depending on the selection of patients and criteria for atopy.<sup>66</sup> The mechanism that is responsible for the hyporeactivity in atopics is not fully clarified. Jones et al.<sup>69</sup> suggested that this hyporeactivity was genetically determined and that this was associated with atopic disease as well. However, a recent study provided evidence for the hypothesis that decreased sensitivity occurs secondary to atopic dermatitis.<sup>64</sup> Uehara and Sawai<sup>64</sup> showed that decreased sensitivity was only present in persons with severe atopic derma-

titis and not in persons with mild or moderate dermatitis. Moreover, it was demonstrated that decreased sensitivity was a reversible phenomenon, because after improvement of the condition in patients with previously severe atopic dermatitis the sensitization rate was not different from that in patients with mild or moderate symptoms or in non-atopics. These results would imply that only active atopic dermatitis with severe symptoms has a "protective effect" on the risk of sensitization and that other atopics are equally at risk for sensitization as non-atopics.

The relative importance of the risk factors that were mentioned in this paragraph is difficult to assess due to an almost complete lack of epidemiologic studies where the effect of these factors has been analyzed simultaneously. A recent publication on the population-based study in Gothenburg in which a multivariate analysis was performed, may shed some light on the relative importance of a number of risk factors.<sup>70</sup> It was concluded that a history of childhood eczema was the most important predictive factor for hand eczema. Second was female gender, followed by occupational exposure, a history of asthma and/or hay fever, and a service occupation.

In summary, contact dermatitis is an inflammation of the skin that may occur as a result of contact with external factors. Irritant contact dermatitis results from contact with irritant substances, while allergic contact dermatitis is a delayed-type immunological reaction in response to contact with an allergen in sensitized individuals. It is estimated that the prevalence of contact dermatitis lies between 1 and 10% in the general population. In most studies the prevalence among women was approximately twice as high as among men. Occupational dermatitis is one of the most frequent occupational diseases and its incidence is estimated to be 0.5-0.7 cases per 1,000 workers per year. High risk industries include for example agriculture, the leather, rubber, chemical, metal and food industries and the health services. Nickel, chromium and cobalt are among the highest ranking sensitizers. The incidence of nickel sensitivity has increased in younger women probably attributable to wearing fashion jewelry and ear piercing.

The development of contact dermatitis is determined by a combination of individual susceptibility and exposure characteristics. Individual susceptibility may be related to personal characteristics like age, gender, genetic factors, the condition of the skin and the presence of other diseases. Environmental factors may play a role in this process by influencing the individual susceptibility (condition of the skin) and/or the characteristics of exposure.

Evidence has accumulated that atopic dermatitis is a risk factor for irritant contact dermatitis due to a reduced resistance of the atopic skin. In contrast, atopics are thought to be less susceptible to sensitization than non-atopics, but the mechanism that is responsible for this, is not fully clarified. A recent study provided evidence for the hypothesis that decreased sensitivity occurs secondary to atopic dermatitis implying that only active atopic dermatitis with severe symptoms has a "protective effect" on the risk of sensitization and that other atopics are equally at risk for sensitization as non-atopics.

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### 3. Methodological aspects of epidemiologic studies of contact dermatitis\*

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The epidemiology of contact dermatitis is concerned with the description of the distribution of contact dermatitis in human populations, and with the identification of factors that affect this distribution. A basic activity in epidemiology involves counting the number of diseased persons (cases) in a specified population and recording relevant characteristics of these diseased persons and of the study population. From this information, the frequency of disease among the study population can be calculated. Associations between the disease frequency and the presence or absence of relevant characteristics suggest whether these characteristics may cause contact dermatitis.

In the first part of this chapter, some general epidemiologic concepts are applied to the study of contact dermatitis. In the context of these concepts, several sources of available data on the distribution of contact dermatitis in population groups will be discussed. Subsequently, the prevalence and incidence of contact dermatitis among the general population and the working population will be discussed. Very few "truly" epidemiological studies have been published which were aimed at the identification of risk factors for the development of contact dermatitis. Therefore, this chapter concludes with some methodological considerations for the design of such epidemiologic studies.

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\* In: Rycroft RJG, Menné T, Frosch PJ Benezra (eds). *Textbook of Contact Dermatitis*. Berlin, Springer, 1992, pp133-150.

### **Basic concepts in the epidemiology of contact dermatitis**

The epidemiologic concepts discussed in this paragraph are important for the interpretation and comparison of results from epidemiologic studies and from routinely registered data.

#### *Measures of disease frequency*

Measures of disease frequency consist of the number of cases in the numerator, and the size of the population under study in the denominator. Measures of disease frequency that are commonly used in epidemiology are "incidence" and "prevalence". The "incidence" of contact dermatitis refers to the number of new cases of contact dermatitis during a defined period in a specified population. Commonly, the "incidence rate" is defined as the number of non-diseased persons who become diseased within a certain period of time, divided by the number of person-years in the population. Person-years are contributed only by those who are not ill at the beginning of the study. From the point in time a person becomes diseased, he or she also no longer contributes to the total number of person-years in the denominator. Even when a subject becomes non-diseased again, person-years are no longer contributed. The "cumulative incidence" is the proportion of a fixed population that becomes ill in a specific period of time. The difference between the two measures of incidence is small when the proportion of people that becomes ill in a specific period is small, but it can be sizable when many people become ill in a short period of time. The incidence of contact dermatitis can be measured by periodic screening of the population to detect all new cases in the study population over a certain period of time.

The "prevalence" of contact dermatitis is the number of persons with contact dermatitis at a certain point in time or during a certain (usually short) period of time. The "point prevalence" refers to the proportion of subjects having active contact dermatitis at the time of data collection and the "period prevalence" includes, in addition to these active cases, also those cases that have occurred during a specified short period of time prior to the investigation. When comparing prevalences between studies, the time period to which the prevalence

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refers should be taken into account. It is likely that the point prevalence of contact dermatitis is lower than a period prevalence because symptoms are not continuously present in patients. In theory, the period prevalence of contact dermatitis over a period of several years should be higher than the period prevalence over a period of several months. However, the difference may be small due to the fact that in many patients contact dermatitis is a condition with an unfavourable prognosis and a high rate of recurrence. In addition, the accuracy of recall will decrease with time, and it is conceivable that those persons who did not have symptoms recently will more often forget to report their earlier symptoms.

#### *Case definition*

Counting the number of diseased persons in a population requires the explicit statement of diagnostic criteria to judge whether a person is considered to have contact dermatitis or not. In many publications, diagnostic criteria for the definition of contact dermatitis are not explicitly stated and several authors reserve this term to denote allergic contact dermatitis. Since contact dermatitis refers to eczematous symptoms due to exposure of the skin to irritant or sensitizing agents, it can be considered as a subcategory of eczema. Other categories of eczema are, for example, dyshidrotic eczema, nummular eczema and atopic eczema. In practice, the distinction in categories of eczema is often difficult because of the fact that the classifications are based upon a combination of morphological, etiological, constitutional and other factors. This leads to inconsistent terminology and overlapping categories. In some publications the terms "contact dermatitis" and "eczema" (especially of the hands), are used interchangeably, assuming that irritant or sensitizing agents often play a role in the causation of (hand) eczema. The descriptive epidemiology of contact dermatitis presented in this chapter mostly refers to "eczema", unless contact dermatitis is mentioned explicitly by the authors.

Another aspect of case definition, apart from diagnostic criteria, is the localization of eczema. In theory, the prevalence of contact dermatitis on one site should be lower than the prevalence on all sites. When restricted to the

hands and forearms, the difference is often minimal because contact dermatitis occurs on the hands in the majority of patients.<sup>1</sup>

The ambiguity in diagnostic criteria also plays a role in the further distinction between allergic and irritant contact dermatitis. Detailed investigation (for example patch testing) is necessary to determine whether sensitization to certain agents has occurred, but even then it is sometimes not certain whether the contact dermatitis is of allergic origin. In many instances, simultaneous exposure to irritant factors plays an essential role in the development of allergic contact dermatitis. Therefore, the distinction between allergic and irritant contact dermatitis should be interpreted with care in those publications where this distinction is made.

#### *Source population*

The population from which the cases arise (source population) is the denominator of the measure of disease frequency (incidence or prevalence). A common feature of observational studies is the occurrence of non-response in the population that was invited to participate in the study. The denominator then refers to the respondents only. Whether generalizations can be made to the source population as a whole depends on the extent to which the non-responders were different in relevant characteristics from the source population.

To describe patterns in the distribution of contact dermatitis in the population according to characteristics like age, gender and occupation, these characteristics should be recorded not only among cases, but also among the population from which the cases originated.

#### *Case ascertainment*

The method of case ascertainment refers to the methods used to let cases come to the attention of the investigator. It depends largely on the sources of data that are used, like mortality statistics, morbidity statistics or observational studies. It may have major consequences for the magnitude of the disease frequency which one obtains. In mortality or morbidity statistics, case ascertainment usually involves registration of persons with eczema/dermatitis who fulfil additional criteria for registration, like hospital admission or sick leave. This restriction in

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the definition of a "case" will probably result in a selective inclusion of the more severe cases, since a large proportion of individuals suffering from contact dermatitis does not come to medical attention.<sup>2-5</sup> In general, the diagnostic criteria for eczema are not clear in these morbidity statistics, since the information is compiled from diagnoses made by many different physicians who were not usually instructed to use a standardized set of criteria.

In observational studies, active case ascertainment usually involves screening of the study population by clinical examination, by questionnaire or by a combination of both. The advantage in observational studies is that case ascertainment can be performed using uniform criteria (chosen by the investigators) for the definition of cases. However, the frequency of cases obtained by questionnaire may be quite different from those ascertained by clinical examination. Problems in defining diagnostic criteria in a clinical examination were mentioned before. The case definition in questionnaire surveys depends on the phrasing of the questions and on the responders' perception of the disease. For example, the question "Have you had hand eczema in the past 12 months?" requires that the responders compose their own criteria for judging whether they have (had) hand eczema or not. The comparison of results of questionnaire surveys is hampered by the lack of standardized and adequately validated questionnaires.

#### *Observational studies*

The three most important types of observational studies in the epidemiology of contact dermatitis are follow-up studies, case-control studies and cross-sectional studies. Important measures of association are the "relative risk", the "rate ratio", the "rate difference" and the "odds ratio".

In follow-up studies, selection of subjects is based upon exposure to the factor of interest. For example, the "relative risk" of having an atopic constitution (relative to not having it) for the development of contact dermatitis can be studied in a follow-up study. This implies that a population of atopics and non-atopics is selected before the disease has developed and that they are followed over a certain period of time. The "rate ratio" (RR) is a basic measure of association between exposure and disease. This is the ratio of the incidence rates in exposed and unexposed persons. Another measure of association is the "rate



difference" (RD), being the difference between the incidence rates in exposed and unexposed subjects.

In case-control studies, the subjects are selected according to their disease status. Information is collected on the past exposure of the diseased persons (cases) and the non-diseased persons (controls). The odds of exposure among cases is compared to the odds of exposure among controls. This can be expressed in an odds ratio (OR): when 40 cases (out of 100 cases) are exposed and 60 are not exposed, the exposure odds is 40:60. When the exposure odds among controls is 20:80, the odds ratio is 2.7. A case-control study can be seen as a study among a defined population, in which all diseased persons, and only a sample of the non-diseased persons are studied. This design is especially efficient in the study of a rare disease. In this situation, the majority of the population does not have the disease, and it is not necessary to study all non-diseased persons. For reasons of interpretability, it is necessary to make an effort to select a population of controls in such a way that they reflect the exposure distribution among the non-diseased part of the source population from which the cases originated. Case-control studies can be based on incident cases or on prevalent cases. A study of incident cases includes as cases only those who develop the illness during a specified time period. In a case-control study of prevalent cases all existing cases at a point in time are selected.

In cross-sectional studies, a study population is selected regardless of exposure status or disease status (in contrast with case-control and follow-up studies). Usually, the information on exposure and disease in cross-sectional studies refers to the time of data collection. In cross-sectional studies, it is not possible to draw conclusions with regard to the relationship between previous exposure and disease, because current exposure may be different from the exposure in the past which caused the disease.

Cross-sectional studies are especially suitable to study the prevalence of a disease in a population in relation to characteristics that do not change much over time.

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#### *Examples of use and misuse of terms*

Suppose a publication in which the authors state that "the incidence of nickel contact dermatitis at Saint XY Hospital was  $18/120 = 15\%$ ". They imply that out of 120 patients seen 18 were found to have this disease. In this common example the use of the term "incidence" is wrong and term "prevalence" should be used. If the authors had followed a group of 120 healthy nurses without contact dermatitis in their hospital over a certain time period, and at the end of that period had found 18 to have developed nickel dermatitis during that period, then they could use the term "cumulative incidence".

The term "incidence rate" (often abbreviated to "incidence") can only be used if this group of 120 nurses was examined at the beginning of the study, to ascertain that nobody has nickel dermatitis, and if this group was continuously monitored during follow-up (e.g. 5 years) This design will yield exact information about the point in time that anybody becomes diseased and will allow calculation of the number of person-months that each person contributes. A person no longer contributes until he or she becomes diseased. The number of months of follow-up until he or she shows dermatitis, or the total amount of months of follow-up (5 x 12 months) if no dermatitis appears, will be known at the end of the study. Suppose that the 18 persons who became diseased had a total of 300 months of follow-up without disease (e.g. one person 10 months until dermatitis appeared, another 14 months etc.). The remaining 102 were followed for the total period of 5 years, contributing  $102 \times 5 \times 12 = 6120$  months of follow-up. Thus for the whole group we have  $300 + 6120 = 6420$  months of follow-up. This implies an "incidence rate" of  $18/6420 = 0.0028$  cases per person-month of follow-up. If necessary, this can be converted to 0.034 cases per person-year of follow-up and often this can be regarded as 0.034 cases per person-year exposure to nursing work.

Unfortunately in contact dermatitis research, there are very few publications based on this more sophisticated design. The advantage of such a design is that it permits comparison with a different, unexposed group, provided it is followed-up in the same way (e.g. clerical staff). The comparison can be expressed as a ratio of the two incidence rates, the "rate ratio" (RR) or as a difference

between the two incidence rates, the "rate difference" (RD), which tells us about the association between exposure and dermatitis risk.

Suppose the incidence rate of dermatitis was 0.017 per person-year of follow-up in clerical staff, then the rate ratio, RR (sometimes called "relative risk") of  $0.034/0.017 = 2$  would quickly tell us that the risk to develop dermatitis during nursing work is twice as high compared to low-risk clerical work. The "RR" and the "RD" are also amenable to further statistical elaboration, which could tell us more about, for example, the importance of soaps or gloves as specific exposure factors, or the role of nickel allergy.

### Sources of data on contact dermatitis

#### *Mortality statistics*

Mortality statistics give information on the number of cases of contact dermatitis and eczema which resulted in death of the person. Contact dermatitis as a primary cause of death is extremely rare, as illustrated by the following figures. The death rate for all diseases of the skin in the United States was 3.6 per 100,000 persons in 1973 (0.38% of deaths from all causes).<sup>6</sup> The death rate for contact dermatitis is not mentioned. In the Netherlands, the death rate of all skin diseases in 1987 was 2.7 per 100,000 persons and the number of deaths due to contact dermatitis as a primary cause was zero in a population of over 14 million inhabitants in the same year.<sup>7</sup> From these figures it follows that mortality statistics cannot contribute any valuable information in the descriptive epidemiology of contact dermatitis.

#### *Morbidity statistics*

Morbidity statistics which provide information on the occurrence of skin diseases, eczema or contact dermatitis specifically are, for example, hospitalization records, case records from dermatology clinics, and data on sick leave and occupational diseases. As mentioned before, it is likely that morbidity statistics include mainly the more severe cases of skin disease.

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Data on hospital admissions show that contact dermatitis is a rare cause of hospitalization. Johnson<sup>6</sup> estimated that 1-2% of patients admitted to hospitals in the US were admitted for conditions of the skin. In the Netherlands, the hospital admission rate for contact dermatitis as a primary diagnosis was approximately 9 persons per 100,000 inhabitants per year, which is 6% of the rate for all skin diseases, and less than 1% of all hospital admissions 1988.<sup>8</sup>

There are several publications on the number and characteristics of patients visiting dermatology clinics and/or patch testing units.<sup>9-11</sup> However, no information on the incidence or prevalence of contact dermatitis can be derived from these publications, because information on the size of the source population from which the cases originated is usually lacking. It is difficult to interpret the distribution of occupations, age or sex in a patient population without knowing the distribution of characteristics among the source population. Also, information on type and severity of skin disease in patient populations is difficult to interpret, because of selection mechanisms that play a role before a dermatology clinic is consulted.

Occupational disease statistics provide useful information on the incidence of occupational skin diseases among the working population. Registers of occupational diseases are kept in several European countries and in the USA.<sup>12-17</sup> Although most of these registers concern all types of skin disease and no distinction is made with regard to eczema or contact dermatitis, it is estimated that eczema or contact dermatitis accounts for 85-98% of all occupational skin diseases.<sup>18,19</sup> The registration of occupational diseases in Sweden, West Germany and Finland is based upon the notification of diseases caused by exposure to factors associated with employment. Usually only those cases are notified for which compensation is payable. Criteria for compensation, and thus criteria for notification of occupational diseases, depend on the legislation on occupational diseases in each country. Evidently, this influences the comparability of the incidence figures between countries. In the US the occupational disease statistics are based upon annual surveys by the Bureau of Labor Statistics (BLS) among a random sample of approximately 280,000 employers in private industry.<sup>17</sup> All illnesses should be reported, whether or not time is lost from work. Consequently, the less severe cases should be included in the incidence figures.

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However, it has been suggested that the incidence of occupational skin diseases in the USA is being underestimated by 10 to 50 times,<sup>19</sup> the milder cases of skin disease not being registered at all. Some of the occupational disease statistics give a breakdown by sex and occupation or branch of industry (usually not by age). Depending on whether these distributions are known in the working population as a whole, the occupation or industry specific figures can be calculated. Unfortunately, information on the actual cause of contact dermatitis and pre-disposing factors is not available in most statistics.

#### *Observational studies*

Publications of true follow-up studies are virtually absent, with a retrospectively designed study among Danish women<sup>20</sup> as one of the exceptions. Thus, incidence figures are hard to obtain. An eczema incidence of 7.9 new cases per 1000 persons per year has been derived from 2 consecutive cross-sectional studies.<sup>21</sup>

Information on the prevalence of eczema in the general population can be obtained from 6 major cross-sectional studies that were performed in the last 20 years in The Netherlands,<sup>4</sup> Sweden,<sup>2,22</sup> England,<sup>3</sup> The United States<sup>5</sup> and Norway.<sup>23</sup> In all studies, a geographically defined population or a sample thereof was screened. In some of the studies all skin disorders were recorded, other focussed on eczema only. In this chapter, only the data on eczema will be discussed. In most of the studies the term "eczema" included allergic contact dermatitis, irritant contact dermatitis, seborrhoeic eczema, nummular eczema, atopic eczema, dyshydrotic eczema and unclassified eczema. In the Dutch study,<sup>4</sup> "eczema" referred to the presence of eczematous symptoms for a period longer than 3 weeks, or to recurrent eczematous symptoms. The American<sup>5</sup> and the Dutch<sup>4</sup> study provide information on contact dermatitis explicitly. Relevant characteristics of the studies, like the method of case ascertainment, localization of eczema and the period to which the prevalence refers, are summarized in Table 1. Four of the studies allow calculation of age and sex specific prevalence figures. Because Rea et al.<sup>3</sup> do not present the distribution of eczema by age, and Agrup<sup>2</sup> does not provide the age and sex distribution of the source population in the denominator, it is not possible to calculate age and sex specific rates

in those two studies. Occupation specific rates can be obtained from the Dutch cross-sectional study.<sup>4</sup>

### **Prevalence in the general population**

Table 1 summarizes the results of the prevalence studies. The estimated point prevalence of eczema varied from 1.7 to 6.1%. The estimated prevalence over a period of one to three years varied from 6.2 to 10.6%. As was to be expected, the estimated point prevalence was lower, on average, than the period prevalence. However, it is difficult to interpret the differences in point prevalence or period prevalence between studies. They may arise from a combination of true differences in prevalence between the studies, but also from differences in diagnostic criteria and aspects of methodology, like the method of case ascertainment. As mentioned before, the clinical examination of the study population is probably a more reliable method for case ascertainment than the use of a self-administered questionnaire. In the American<sup>5</sup> and the Dutch<sup>4</sup> study, the complete study populations underwent medical examination. In contrast, cases in the study in Norway<sup>23</sup> were ascertained by a self-administered mail questionnaire. The validity of the questionnaire is unknown. The other studies used combinations of these methods, where a first screening by questionnaire was followed by a clinical examination of a subpopulation. Agrup<sup>2</sup> performed a clinical examination on a subsample of her study population, consisting of 1,819 persons. 1.8% had responded affirmatively to the question: "Do you have any skin changes on the hands (apart from common warts)?". In the clinical examination of the positive and negative responders, the diagnosis of skin disease was confirmed in 32 out of 33 positive responders and in addition, another 33 persons (1.8%) among the negative responders were found to have skin disorders. Consequently the prevalence of skin disorders by clinical examination was almost twice as high due to false-negative answers in the questionnaire.

**Table 1** Prevalence of all skin disorders, eczema and contact dermatitis in the general population.

author(s)	area and population	year of study	n of responders	method of case ascertainment	localization	measure of prevalence	prevalence(%) of eczema
Agrup <sup>2</sup>	South-Sweden 10 years and older	1964-1965	107,206	questionnaire + clin. exam. subsample	hands	point	1.7*
Rea et al. <sup>3</sup>	London, England 15-74 years	1967-1969	1,979	questionnaire + clin. exam. subsample	all sites	point	6.1
Johnson & Roberts <sup>5</sup>	USA 1-74 years	1971-1974	20,749	clin. exam.	all sites	point	2.0
Coenraads <sup>4</sup>	urban and rural Netherlands, 28-71 yrs	1979,1981	3,140	clin. exam.	hands	3 yrs	6.2
Kavli et al. <sup>23</sup>	Tromsø Norway, 20-54 yrs	1979	14,667	questionnaire	hands	12 mnths	8.9
Meding & Swanbeck <sup>22</sup>	Gothenburg Sweden, 28-63 yrs	1982	16,587	questionnaire verified by clin. exam.	hands	12 mnths point	10.6 5.4

\* prevalence based on subsample

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A comparable result was obtained for eczema: 15 of the positive responders were diagnosed as eczema, while another 16 persons among the negative responders were found to have eczema. The prevalence of eczema in the subsample was thus estimated to be 1.7% (31 out of 1,819 persons).

Rea et al.<sup>3</sup> examined a stratified subsample of the study population consisting of 3/4 of the positive responders to a question on the presence of any skin disorder and 1/5 of the negative responders. They found that 86 percent of the positive responders had skin disorder and that another 13 percent of the negative responders had skin disorders. The estimate of the prevalence rate of eczema made by the authors was based on the findings in the stratified sample and took into account the distribution of age, sex and occupation and the disproportionate sampling fraction in the subsample. Meding and Swanbeck<sup>22</sup> performed a clinical examination on 70.7 percent of the positive responders to a question about symptoms of eczema in the previous twelve months. The diagnosis of eczema was confirmed in 89.4 percent of the positive responders. Based on these results they estimated that the prevalence of eczema was 10.6 percent in the study population. However, since negative responders were not examined, this may be an underestimate due to false-negative answers in the questionnaire.

Table 2 shows the prevalences of eczema for men and women separately. In The Netherlands, Norway and Sweden, the prevalence was higher among women, in London the prevalence was higher among men, while there was no difference between sexes in the US. No unanimous conclusion can be drawn from these data. It is possible that the differences are obscured by differences in age-distribution of the populations. Figures 1a and b show the age-specific prevalence of hand eczema in men and women (on the same scale). There was no clear trend in age distribution in men. The prevalence in women was especially high in the younger age groups (under 30 years). One possible explanation is that many of the women have high exposure to "wet work" in household activities and child care.<sup>4,23</sup> Figure 2 represents the age-specific prevalence of contact dermatitis by sex in the study by Johnson and Roberts.<sup>5</sup>



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**Table 2** Prevalence of eczema among males and females.

Country	Study population n	<u>Prevalence of eczema (%)</u>	
		males	females
UK (3)	1,979	8.0	4.3
USA (5)	20,749	1.9	1.9
Netherlands (4)	3,140	4.6	8.0
Sweden (22)	16,587	8.8	14.6
Norway (23)	14,667	4.9	13.2

In the US, the prevalence seems to increase with age, while according to the publication from the Netherlands, in Sweden and in Norway, the prevalence seems to decrease slightly in the age groups above 50 years. The Dutch study<sup>4</sup> analyzed the relative contribution of age and occupation to the prevalence of eczema and found that the relationship with age disappeared after controlling for occupation. The same phenomenon was described in a population of Australian rubber and cement industry workers: the prevalence of dermatitis was relatively high in workers under 45 years, but the age effect disappeared also after controlling for job classification.<sup>24</sup>

The only study reporting on socio-economic status of the population in relation to the prevalence of skin disorders is the community study in London.<sup>3</sup> No significant trend was seen, but the prevalence in the socio-economic class III M (skilled occupations, manual) was relatively high. The authors suggest that persons in this socio-economic class are more frequently occupationally exposed to industrial chemicals. So, again the suggestion is that there are underlying factors responsible for higher prevalences of contact dermatitis found in some subgroups in these studies.

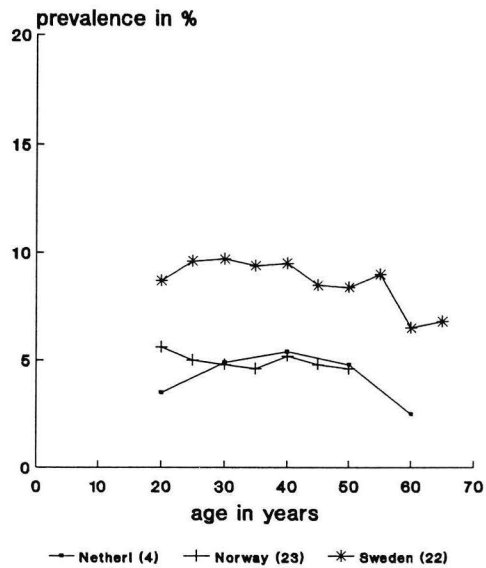


Figure 1a Prevalence of hand eczema by age  
Men

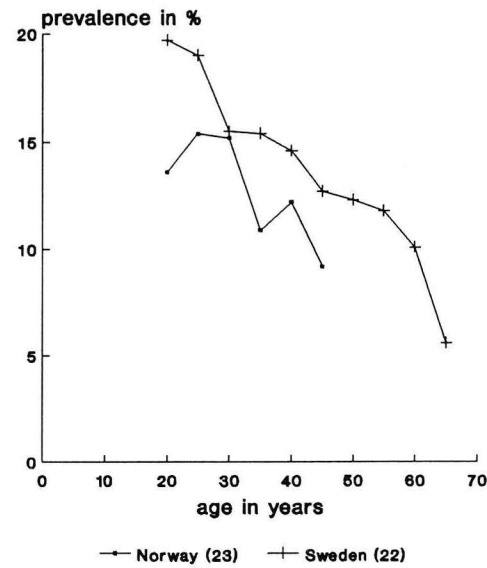
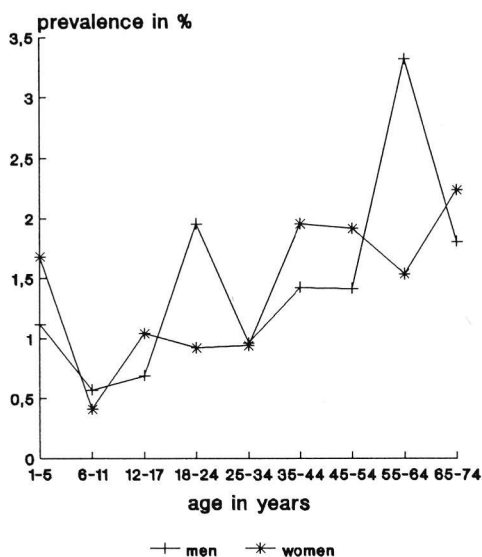


Figure 1b Prevalence of hand eczema by age  
Women

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**Figure 2** Prevalence of contact dermatitis by age and sex, USA<sup>5</sup>

The major risk factor for contact dermatitis is considered to be exposure to irritant or sensitizing factors. This exposure is common during household activities and in certain occupations. Several cross-sectional studies have been performed among specific occupational groups, for example metal industry,<sup>25</sup> construction,<sup>26</sup> hospital work<sup>27</sup> and painters.<sup>28</sup> These studies will not be reviewed in this chapter.

In conclusion, the prevalence studies strongly suggest that age and sex are not risk factors for contact dermatitis by itself, but that these characteristics are associated with exposure in occupational and household activities. In a review of the epidemiology of allergic contact sensitization, where similar phenomena were seen, Menné et al.<sup>29</sup> concluded that the age-dependent immunological reactivity was less important than differences in exposure between age groups, and that differences in sensitization pattern between sexes seem to be caused by different exposures. The dissimilarity was considered to be so obvious that patch tests results were always given for men and women separately.

### Incidence in the working population

Table 3 shows the incidence of occupational skin diseases in 5 European countries and the US.<sup>12-17</sup> As mentioned earlier, eczema or contact dermatitis accounts for 85-98% of all causes of occupational skin diseases.<sup>18,19</sup> In spite of the differences between legal criteria for the registration of occupational diseases in the 4 countries, it appears that the incidence of occupational skin disease in these countries is in the same order of magnitude with 0.5-0.7 cases per 1,000 workers per year. In these figures, occupational skin diseases constitute 13 to 34% of all occupational diseases. Occupational skin diseases either take the first rank among all occupational diseases, or they follow musculo-skeletal disorders and/or hearing damage closely. An even higher proportion was mentioned in many older publications. However, the proportion of occupational skin diseases has declined in recent years, although the incidence rates remained approximately the same. This can be explained by the fact that the criteria for the definition of occupational diseases in some countries were broadened in the last few years. As a consequence, the total number of notified occupational diseases has increased, and the proportion of occupational skin diseases has decreased.

**Table 3** Occupational skin diseases as a percentage of all registered occupational diseases in six countries.

Country	Year	Total number of occupational diseases	of which: <u>skin diseases</u> number	%	Rank order among all occupational diseases
The Netherlands <sup>12</sup>	1984	527	159	30.2	1
Finland <sup>13</sup>	1982	5,365	1,132	21.1	3
Sweden <sup>14</sup>	1981	17,107	2,271	13.0	2
FRG <sup>15</sup>	1971-76	81,255	NA	24.6	2
GDR <sup>16</sup>	1971-75	NA	NA	20.3	2
USA <sup>17</sup>	1984	NA	42,500	34.0	?

NA not available

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Table 4 shows the incidence of occupational diseases in the highest ranking branches of industry in Finland,<sup>13</sup> the US<sup>17</sup> and West Germany.<sup>30</sup> The Swedish publication<sup>14</sup> presents a breakdown by occupation only of the occupational diseases. The distribution of occupations among the total working population is not mentioned. The incidence in the construction industry was 0.7 cases per 1,000 workers per year in all three countries.

**Table 4** Incidence of occupational skin diseases by division of industry per 1,000 workers per year (13, 17, 30).

United States		Finland		West-Germany	
Construction	0.7	Construction	0.7	Construction	0.7
Manufacturing	1.2	Manufacturing	1.0		
- leather	2.7	- textile and leather	0.6		
- metal prod.	1.8	- metal and machinery	1.0	- iron and steel	0.6
- machinery	1.4				
- electr.prod.	1.4				
- rubber	1.9	- rubber and chemical	1.3	- chemical	0.6
- chemical	1.3				
- food	1.7	- food	1.1	- food	0.6
- miscellaneous	2.6	- miscellaneous	1.9		
Health services	0.8	Sanitary services	1.3	Health services	2.8
Agriculture	2.8	Agriculture	0.4		
Total	0.6	Total	0.5	Total	0.5

The incidence of occupational skin diseases by sector of industry is hard to compare because of the differences in classification of industries. The highest incidence rates were recorded in the leather industry, the metal industry, the food industry, the chemical industry and the rubber industry.

## **Methodological considerations in the design of epidemiologic studies on contact dermatitis**

The following characteristics of contact dermatitis may affect the choice of study design in the planning of an epidemiologic study:

1. Contact dermatitis is a multifactorial disease. Apart from exposure to irritating or sensitizing agents there are many factors that may influence the development of contact dermatitis, like weather conditions, humidity, psychologic factors and atopic constitution. These factors may act as confounders in studies, when they are not properly controlled for either in the design of the study or in the analysis. In the design of the study these factors can be controlled for by matching cases and controls (or exposed and unexposed) so that they are equal with respect to the distribution of confounders, or by restriction to subjects within certain confounder categories only. In the analysis of the study, several statistical methods (e.g., multivariate analysis) can be used to adjust for the influence of confounders on the estimated "rate ratios", "rate differences" or "odds ratios".
2. Persons suffering from contact dermatitis do not necessarily exhibit symptoms continuously, although these are often recurrent. In follow-up studies, where the incidence is measured, this implies that cases are only those persons who exhibit symptoms for the first time. In case-control studies and cross-sectional studies different definitions of a "case" may be used, as long as it is clear which definition was used. Thus, a prevalent case may be defined as a person exhibiting symptoms at the time of the examination, or as a person who has had symptoms during a specified period of time prior to the investigation.
3. The exposure of interest may vary over time. In some situations the change of exposure status will be determined by the fact that the person has contact dermatitis. Persons who are susceptible to the development of eczematous symptoms are often aware of this. So they may change their habits or use medication to suppress symptoms. In that case, when current exposure (as opposed to past exposure) is recorded in a case-control study or a cross-sectional study, the results will show that cases use medication more often

than controls. Obviously the use of medication is a result of being a case and not a cause. In many situations this type of distortion is less obvious. It is therefore preferable to record exposure with reference to the time prior to the first occurrence of eczematous symptoms. However, in practice it may be difficult to obtain reliable information on past exposure. In follow-up studies this poses less of a problem, because exposure is recorded before the symptoms of eczema become manifest.

4. Contact dermatitis is not extremely rare among the general population. The incidence of contact dermatitis in the general population is not known. In follow-up studies a rough idea about the incidence of contact dermatitis in the population to be studied is necessary to determine the size of the exposed and unexposed populations. The prevalence figures suggest that a relatively large population needs to be followed to obtain enough cases at the end of follow-up. However, the majority of the population remains free of contact dermatitis, contributing little information to the study. A follow-up study will in this respect be less efficient than a case-control study. In situations where the effect of a factor is studied that changes over time, and cannot be determined in retrospect, it may be necessary to perform a follow-up study.
5. Not many people stop working because of skin disease. This suggests that in studies of occupational populations selection bias (in case-control studies and cross-sectional studies) and bias due to loss-to-follow-up (in follow-up studies) is small.
6. The time interval between exposure and onset of contact dermatitis (induction period) is virtually unknown. This average period of time elapsed from the start of exposure until the disease becomes manifest is a result of a cumulative toxic damage in irritant contact dermatitis. The time course of this process is different from the induction of sensitization in allergic contact dermatitis,<sup>31</sup> but little information is available on the exact duration of the induction period. Rothman<sup>32</sup> stresses that the issue of induction period must nevertheless be addressed, because inaccurate assumptions cause a type of misclassification that tends to reduce the magnitude of associations and underestimate effects.

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*Methodologic aspects*

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## 4. Evaluation of a self-administered questionnaire on hand dermatitis\*

H.A.Smit, P.J. Coenraads, A.P.M. Lavrijsen, J.P. Nater

### Summary

The purpose of the study was to evaluate a self-administered questionnaire on hand dermatitis that was developed to identify persons with hand dermatitis in epidemiological studies. A total of 109 nurses were subject to dermatological examination of the hands within 1 month of returning the questionnaire. Two types of questionnaire diagnoses were made: a "symptom-based" diagnosis and a "self-reported diagnosis". These were compared to the medical diagnosis of hand dermatitis. The prevalence of hand dermatitis in the 12 months before the study, based on the medical diagnosis was 18.3%. The prevalence according to the symptom-based diagnosis and the self-reported diagnosis was 47.7% and 17.4% respectively. The sensitivity and specificity of the symptom-based diagnosis were 100% and 64% respectively. It is concluded that the symptom-based diagnosis can be used as screening instrument for the detection of cases in large study populations, if followed by dermatological examination of persons with a positive diagnosis. The sensitivity and specificity of the self-reported diagnosis were 65% and 93% respectively. It is concluded that the self-reported diagnosis can be used to obtain a rough estimate of the prevalence, although comparison of prevalence figures between study populations may be distorted due to a difference in reporting of hand dermatitis. The results of the study illustrate the size of the differences in prevalence estimates that may arise as a result of differences in the definition and method of diagnosing hand dermatitis.

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\* Contact Dermatitis 1992; 26: 11-16.

## Introduction

Although contact dermatitis of the hands is one of the most common occupational diseases,<sup>1-3</sup> epidemiologic studies for the identification of risk factors are rare. Studies among relatively large study populations are hampered by the lack of cost-effective methods for case ascertainment. Dermatological examination of the total study population has been performed in some studies,<sup>4-5</sup> but when a large study population is involved, dermatological examination is often not feasible. Therefore, several studies have used self-administered questionnaires for the ascertainment of cases of contact dermatitis.<sup>6-9</sup> In some of these studies, a subsample of the population was subject to medical examination. However, the validity of these questionnaires was often not assessed, making the study results difficult to compare. Recently, the validity of a self-administered questionnaire on facial skin complaints has been evaluated, that was developed for use in an epidemiological study on the relationship between work with visual display units and skin disease.<sup>10-12</sup>

We developed a short, self-administered questionnaire to identify persons with hand dermatitis in epidemiological studies. A study was undertaken to evaluate the performance of the self-administered questionnaire among nurses. Firstly, we report on the prevalence of hand dermatitis as estimated by the questionnaire diagnosis and by the medical diagnosis. Secondly, we report on the validity of the questionnaire diagnosis compared to the medical diagnosis.

## Material and Methods

### *Study population and data collection*

The study was conducted from May through July 1989, among nurses in the surgical department of one hospital. A self-administered questionnaire to identify nurses with hand dermatitis was distributed among all 207 nurses. 187 nurses (90.3%) responded to the questionnaire. Dermatological examination of the hands took place on 6 working days in a period of one month. A total of 109

## *Evaluation of questionnaire*

nurses (60% of the responders to the questionnaire) available on one of those 6 days, were subject to dermatological examination.

### *Hand dermatitis*

Hand dermatitis is characterized by the presence of morphological signs and symptoms such as erythema, papules, pustules, vesicles, exudation and itching. In chronic cases, fissuring and lichenification develop. Rycroft<sup>13</sup> used an operational definition requiring the presence of either vesicles, papules, pustules or exudation, or the presence of 2 or more of the following symptoms: erythema, scaling, oedema, fissuring and lichenification. Coenraads et al.<sup>4</sup> required additionally that the symptoms should be recurrent or should have lasted for more than 3 weeks.

Three questions to determine whether these conditions are satisfied, are given in Appendix A. A person with a positive symptom-based diagnosis of hand dermatitis is defined as "a person who answered positively to one or more of the questions [1a] through [1e] (symptoms) and who answered positively to either question [2] (symptoms for more than three weeks) or question [3] (symptoms recurrent)". Since this definition is broad, persons with other skin disorders or persons with minor symptoms of hand dermatitis may be diagnosed as "cases". Many additional questions would have to be included in the questionnaire to exclude those persons, which is not feasible. Therefore the questions were designed to identify as many potential cases as possible and to exclude only persons definitely free of hand dermatitis, such that subsequent dermatological examination could be restricted to persons with a positive symptom-based diagnosis, without missing cases of hand dermatitis.

A 4th question was added to the questionnaire, to make a self-reported diagnosis of hand dermatitis: "According to your own opinion, have you suffered from hand dermatitis in the past 12 months?". Thus, 2 types of questionnaire diagnoses were evaluated, a symptom-based diagnosis and a self-reported diagnosis of hand dermatitis.

A medical diagnosis of hand dermatitis was made by a dermatologist. This was based upon anamnestic information and an examination of the hands using the same criteria as for the symptom-based diagnosis. However, morphological

characteristics and, if necessary, constitutional factors were taken into account to exclude persons with other skin disorders. No attempt was made to differentiate between irritant and allergic contact dermatitis, because morphological characteristics are similar and additional clinical tests are often required to make this distinction.

The dermatologist was not informed of the answers to the questionnaire; also, the responder was unaware of his or her symptom-based diagnosis of hand dermatitis.

#### *Data analysis*

The prevalence of hand dermatitis in the 12 months before the study, was assessed using the medical diagnosis and both questionnaire diagnoses.

To assess the validity of both questionnaire diagnoses, the sensitivity, specificity and predictive values were computed (Appendix B). The medical diagnosis served as a reference. The sensitivity indicates what proportion of all persons with a medical diagnosis of hand dermatitis, is identified by a positive questionnaire diagnosis. The specificity indicates what proportion of persons without hand dermatitis according to the medical diagnosis, also had a negative questionnaire diagnosis.

Other measures to evaluate the questionnaire diagnosis are the positive and negative predictive value. The positive predictive value represents the proportion of all persons with a questionnaire diagnosis of hand dermatitis, who had a positive medical diagnosis. A high positive predictive value is important when the questionnaire is to be used for the identification of persons with hand dermatitis in a study population. The negative predictive value indicates what proportion of persons without hand dermatitis according to the questionnaire diagnosis, had a negative medical diagnosis. A high negative predictive value is important when the questionnaire is used to exclude persons without hand dermatitis from further dermatological examination or to include them in a study as disease-free controls.

Validity statistics were computed not only for the symptom-based diagnosis that was defined a priori, but also for alternative symptom-based diagnoses. These were defined as respectively 2 or more, 3 or more and 4 or more positive

answers to questions [1a] through [1e], combined with a positive answer to questions [2] or [3].

## **Results**

The study population of 109 nurses who were subject to dermatological examination consisted predominantly of women. The age ranged from 18 to 54 years, the majority of the population being under 35 years. Approximately 2/3 of the population worked for more than 32 h per week. There were no significant differences in personal characteristics (age, gender, working schedule) between all responders and the sample that underwent dermatological examination.

### *Prevalence*

Table 1 shows that different estimates of the prevalence were obtained, depending on the type of diagnosis that was used. The highest prevalence was found for the symptom-based diagnosis. The prevalence of the medical diagnosis and the self-reported diagnosis of hand dermatitis were comparable.

**Table 1** 12-month prevalence of hand dermatitis as estimated using different methods.

Type of diagnosis of hand dermatitis	Period prevalence % (nos)
medical diagnosis (dermatological evaluation)	18.3 (20/109)
symptom-based questionnaire diagnosis	47.7 (52/109)
self-reported questionnaire diagnosis	17.4 (19/109)

### *Validity*

Table 2 shows that the sensitivity and negative predictive value of the symptom-based diagnosis were high, while the specificity and positive predictive value were relatively low. The positive predictive value of 38% implies that 62% of

the persons with a positive symptom-based diagnosis of hand dermatitis, had a negative medical diagnosis (false-positives). However, only 1 person was diagnosed as having another skin disorder (psoriasis). The other "false positives" consisted predominantly of persons with less severe symptoms of hand dermatitis.

**Table 2** Validity statistics of the questionnaire diagnoses of hand dermatitis compared with a medical diagnosis of hand dermatitis.

Validity statistics for two questionnaire diagnoses	% (nos)
<b>Symptom-based diagnosis</b>	
sensitivity	100 (20/20)
specificity	64 (57/89)
positive predictive value	38 (20/52)
negative predictive value	100 (57/57)
<b>Self-reported diagnosis</b>	
sensitivity	65 (13/20)
specificity	93 (83/89)
positive predictive value	68 (13/19)
negative predictive value	92 (83/90)

The sensitivity and negative predictive value of the self-reported diagnosis were lower than of the symptom-based diagnosis, but the specificity and the positive predictive value were higher.

When one of the alternative symptom-based diagnoses was used, that is 2 or more positive answers to questions [1a] through [1e] in combination with positive answers to either question [2] or [3], the sensitivity remained high (80%) while the specificity increased to 89%, resulting in a relatively high positive predictive value of 62%. However, this requires subsequent formal validation since the alternative diagnosis was not defined before this validation study.



## **Discussion and conclusions**

The results show that different estimates of the prevalence of hand dermatitis are obtained depending on whether the medical diagnosis or one of the questionnaire diagnoses was used. The results of the validation study are useful in interpreting these differences. The symptom-based diagnosis of hand dermatitis, overestimated the prevalence of hand dermatitis according to the medical diagnosis as a result of its high sensitivity and its low positive predictive value. The false positives consisted predominantly of persons with less severe symptoms of hand dermatitis suggesting that the criteria for a medical diagnosis were more stringent than the questionnaire-based diagnosis. Taking this into consideration, the symptom-based questionnaire diagnosis, being a relatively objective measure, may be useful in comparing prevalence figures in different study populations. Because of its high sensitivity, the symptom-based questionnaire diagnosis can be used as a screening instrument for the detection of cases in large study populations. Subsequent dermatological examination of persons with a positive questionnaire diagnosis is necessary, to exclude persons with other skin disorders or minor symptoms of hand dermatitis. Since a negative symptom-based diagnosis is highly predictive for the absence of hand dermatitis, it seems justified to restrict dermatological examination to persons with a positive symptom-based diagnosis. This may reduce the expense and time needed for data collection, depending on the size of the study population and the prevalence of hand dermatitis in that population. It is noted that a high sensitivity and a low specificity were also found in the evaluation of a self-administered questionnaire on facial skin complaints in visual display unit work, and that similar conclusions with regard to the usefulness of that questionnaire were drawn.<sup>10</sup>

The prevalence figures according to the medical diagnosis and the self-reported diagnosis were comparable, suggesting that the self-reported diagnosis is a good indicator of the presence of hand dermatitis. However, in quite a number of cases the medical diagnosis and the self-reported diagnosis did not agree. 32% of the self-reported diagnoses were incorrect compared to the medical diagnosis and 7.7% of the persons without self-reported hand dermatitis, were in fact diagnosed as having hand dermatitis on dermatological examination. This

## Chapter 4

suggests that self-reported hand dermatitis is not adequate to identify cases of hand eczema for further study, but that it may be suitable to obtain a rough estimate of the prevalence of hand dermatitis in a large study population. Nevertheless, the self-reported diagnosis is a subjective measure and it is unclear on which criteria the responders have based their diagnosis. Whether a responder will be able correctly to diagnose hand dermatitis will depend largely on his or her medical knowledge, on the level and type of education, on earlier diagnosis or treatments and on responder's tendency to report this in a questionnaire. Therefore, the comparison of prevalence figures between study populations (e.g. occupational groups) may be distorted when the self-reported questionnaire diagnosis is used.

The results of this study illustrate that the comparison of prevalence figures from different studies should always take into account which method and which definition was used to identify persons with hand dermatitis. For example, several studies on the prevalence of hand dermatitis among hospital personnel were performed showing rather large differences in prevalence figures ranging from 17 to 41 percent.<sup>14-16</sup> The study in Tromsø (Norway), showed a prevalence of self-reported hand dermatitis over a 12-month period of 17% among nurses.<sup>14</sup> This figure is comparable to the prevalence of self-reported hand dermatitis in this study of 17%. Lammintausta<sup>15</sup> found a prevalence of hand dermatitis among assistant nurses of 33% over a period of approximately 6 months. Nilsson et al.<sup>16</sup> found a prevalence of hand dermatitis among nurses of 41% over a period of 20 months on average. Both estimates were based on a complex of symptoms comparable to the definition of the symptom-based diagnosis in this study resulting in an estimate of the prevalence of almost 48% over 12 months. Again, these results show reasonable agreement.

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## 5. The prevalence of hand dermatitis in different occupations\*

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### Summary

The prevalence of hand dermatitis in different occupational groups was estimated using a standardized questionnaire in a series of surveys among workers of a chemical company, a municipal electricity company, municipal public works, nurses and surgical assistants. A survey in a sample of the general population was performed to obtain a reference estimate of the prevalence.

The prevalence of hand dermatitis in the general population was 5.2% in men and 10.6% in women. The prevalence of hand dermatitis among the occupational groups ranged from 2.9% in office workers to approximately 30% in nurses.

The age-adjusted prevalence ratio of hand dermatitis in office workers was not significantly elevated compared with the general population. In nurses, the age-adjusted prevalence ratio was 9.3 among men (95% CI: 3.6-23.9) and 2.3 among women (95% CI: 1.5-3.5). The prevalence ratio in surgical assistants was not significantly elevated (PR 1.4; 95% CI: 0.7-2.6). This suggests that exposure in nurses (frequent washing of the hands), is more harmful to the skin than the less frequent but more intensive exposure in surgical assistants. The age-adjusted prevalence ratios were also significantly elevated in male manual workers of the chemical company, the electricity company and public works and varied from 2.4 to 2.8. Occasional or regular occupational exposure to a variety of irritants in combination with mechanical stress (as occurs frequently in manual work) may be responsible for this observation.

It is concluded that nurses (heavy exposure) as well as manual workers (low to moderate exposure to irritants in combination with mechanical stress) have an elevated prevalence of hand dermatitis in comparison with the general popula-

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tion, whereas the prevalence in office workers (no exposure) is comparable to that of the general population. To put the findings into perspective, it is noted that the symptoms probably are relatively mild in the majority of cases, judged from the proportion of cases that resulted in sick leave (3-9%) and the proportion of cases that required medical attention (15-36%).

## Introduction

Hand dermatitis accounts for 9 to 35% of all occupational diseases.<sup>1-4</sup> However, the prevalence of hand dermatitis as determined from medical records underestimates the true prevalence since many of the workers with hand dermatitis do not consult a doctor for their symptoms.

Hand dermatitis is characterized by the presence of visible symptoms such as erythema, papules, pustules, vesicles, exudation and itching. In chronic cases, fissuring and lichenification develop. Usually these symptoms are persistent for several weeks and have a recurrent character. Occupational exposures, such as frequent contact with water, dyes, perfumes, metal working fluids and other irritants or allergens, put the skin at risk of contact dermatitis.<sup>5</sup>

In the period 1989-1991, several surveys were conducted in The Netherlands, to determine and compare the prevalence of hand dermatitis in nurses, surgical assistants and workers in a chemical company, a municipal electricity company and municipal public works. A reference estimate of the prevalence of hand dermatitis was obtained in a sample of the general population. A validated questionnaire was used in all surveys, which allowed us to compare the prevalence figures between occupational groups and to estimate the prevalence ratio in comparison with the general population.

## **Materials and methods**

### *Study population*

Five cross-sectional surveys among occupational groups were performed in the period 1989-1991. A sixth survey among a sample of the general population was conducted in January 1992. Data were collected among the following study groups:

- a. nurses working in the surgical department of a university hospital. Occupational exposure in nurses is often referred to as "wet work", involving frequent exposure to water and detergents. Questionnaires were distributed and collected via mailboxes at the workplace in May/June 1989.
- b. surgical assistants of a university hospital working under sterile conditions. Typical exposure in surgical assistants consists of regular preoperative disinfection of the hands, which involves scrubbing after application of abrasive agents. Sterile gloves are usually worn during the major part of the working time. The questionnaire was sent by mail to the home addresses in November/December 1991.
- c. employees of a large chemical company, consisting of process operators, office workers and supervising personnel in two refinery departments, a polyvinyl chloride production plant and a pesticide plant and of maintenance engineers in the maintenance department. The process operators and maintenance engineers perform mainly manual work with regular, moderate occupational exposure to miscellaneous irritant and sensitizing agents (such as vinyl chloride, solvents and decreasing agents). Office employees and supervising personnel have negligible or no occupational exposure to irritants or allergens. The questionnaire was distributed within the framework of a periodical occupational health survey among all workers of the plants between January and April 1990.
- d. employees in a municipal electricity company; the questionnaire was sent by mail to all employees in January and February 1991.
- e. employees of municipal public works; the questionnaire was sent by mail to all workers in the period January and February 1991.

Surveys in groups d) and e) were performed to obtain an estimate of the prevalence of hand dermatitis in manual workers with occasional exposure to irritants (for example decreasing agents). A small proportion of these study groups consisted of office workers without occupational exposure.

- f. a sample of the general population stratified according to age and gender in three Dutch cities, located in different parts of the Netherlands. Data were collected within the framework of the Monitoring Project on Risk Factors for Cardiovascular Diseases, which takes place among a stratified random sample of the general population between 20 and 60 years of age. In January and February 1992, participants of the Monitoring Project were invited to complete the questionnaire on symptoms of hand dermatitis.

#### *Data collection*

A short, self-administered questionnaire was distributed among the populations under study. The questionnaire included questions on age, gender, history of atopic dermatitis (a known risk factor for hand dermatitis) and the presence of symptoms of hand dermatitis (see Appendix A). To assess whether occupational exposure contributed to the symptoms, those who reported one or more symptoms were asked if symptoms improved or disappeared after a weekend or holiday. To assess severity of the symptoms it was asked whether respondents had sought medical attention for these symptoms and whether the symptoms had resulted in sick leave.

Based on the questions in appendix A, a person with hand dermatitis was defined as "a person who answered positively to two or more of the questions 1a through 1e (symptoms) and who answered positively to either question 2 (symptoms for more than three consecutive weeks) or question 3 (recurrence of symptoms)". The definition is broad, allowing for persons with other skin disorders or persons with minor symptoms of hand dermatitis to be diagnosed as 'cases'. This could not be avoided because many additional questions would have to be included in the questionnaire to exclude those persons, which would severely limit the feasibility of the questionnaire. The questionnaire-based diagnosis of hand dermatitis was validated in comparison with a medical



## *Prevalence*

diagnosis.<sup>6</sup> The positive predictive value of the questionnaire-based diagnosis was 62%, indicating that a relatively large number of false-positives were generated by the questionnaire. However, it was found that less than 1% of the false-positives consisted of persons with other diseases such as psoriasis, while the remaining false-positives usually had mild or reversible symptoms of hand dermatitis. The criteria for a medical diagnosis of hand dermatitis appeared to be more stringent than the questionnaire-based diagnosis. It was concluded that the questionnaire-based diagnosis of hand dermatitis was adequate to provide an objective estimate of the prevalence of hand dermatitis, allowing a comparison of prevalence figures between occupational groups. However, it should be taken into account that the prevalence as measured by the questionnaire may overestimate the true prevalence.

### *Data analysis*

Crude prevalence figures were calculated for each occupational group. Prevalence ratios with the general population as a reference group were calculated as a measure of the relative risk.

Adjustment for age was performed, since age was a confounding factor in these data. Age-adjusted prevalence ratios were calculated using the pooled Mantel Haenszel estimator for relative risks, which pools stratum-specific estimates of the prevalence ratio assigning weights which are inversely proportional to the variance of the logarithm of the prevalence ratio under the null hypothesis ( $PR=1$ ).<sup>7</sup> The reference group did not contain persons younger than 20 and older than 60 years, whereas some of the occupational groups had a small number of individuals in these age groups. In those occupational groups, the individuals under 20 years and over 60 years were grouped in the age category of 20-30 year and 50-60 years old respectively, thus assuming that the age-specific prevalence figures in these age groups are comparable under the null hypothesis. The number of male surgical assistants and the number of women in the chemical company, the electricity company and public works was too small to produce stable estimates of the prevalence ratio. Therefore prevalence ratios for these groups are not presented.

**Table 1** Characteristics of the study populations in each survey

Characteristic	Nurses		Surgical assistants		Chemical industry		Electricity company		Public works		General population	
	n	%	n	%	n	%	n	%	n	%	n	%
<b>Total number</b>	187		67		550		439		272		670	
<b>gender</b>												
male	34	18.2	11	28.0	530	96.4	425	96.8	271	99.6	290	43.3
female	153	81.8	56	72.0	20	3.6	14	3.2	1	0.4	380	56.7
<b>age (yrs)</b>												
15-20	3	1.7	-	-	-	-	2	0.5	11	4.1	-	-
20-29	102	58.3	18	26.9	93	16.9	108	25.2	67	24.7	103	15.8
30-39	57	32.6	32	47.8	163	29.6	133	31.1	68	25.1	148	22.7
40-49	12	6.9	14	20.9	177	32.2	102	23.8	85	31.4	197	30.3
50-59	1	0.6	3	4.5	113	20.5	79	18.5	37	13.7	203	31.2
60-65	-	-	-	-	4	0.7	4	0.9	3	1.1	-	-
<b>history of atopic dermatitis</b>	14	7.5	5	7.5	22	4.0	15	3.4	14	5.0	31	4.6

## Results

A total of 2,185 persons participated in the surveys. The response rate among the five occupational groups was 81% on average and ranged from 71% to 90% per survey. Due to practical circumstances, the response rate in the general population can only be estimated over a full year and was 53% in 1990.

The distribution of age, gender and history of atopic dermatitis differed between study groups (table 1).

Nurses and surgical assistants consisted predominantly of women, whereas the proportion of women in the other occupational groups was negligible. Also, the nurses and surgical assistants were younger on average than the other occupational groups and the general population. The proportion of participants who reported a positive history of atopic hand dermatitis was higher among nurses and surgical assistants than among the other occupational groups.

The prevalence of hand dermatitis in the general population was twice as high among women as among men (table 2). With respect to the occupational groups, the highest prevalence was found among nurses (both genders), the lowest prevalence was observed among office workers.

**Table 2** Prevalence of hand dermatitis for each survey

Occupational groups	Men		Women	
	n	Prevalence (%)	n	Prevalence (%)
General population	290	5.2	380	10.6
Nurses	34	29.4	153	32.0
Surgical assistants	11	7.7	56	19.6
Chemical company				
- manual workers	359	13.6	-	
- office and supervisor	171	2.9	20	5.0
Electricity company				
- manual workers	321	13.4	9	22.2
- office and supervisor	104	6.7	5	20.0
Public works				
- manual workers	239	12.6	-	
- office and supervisor	32	6.3	1	0.0

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Table 3 shows crude and age-adjusted prevalence ratios. Adjustment for history of atopic dermatitis did not alter the estimates of the prevalence ratio, since hand dermatitis was not related to a positive history of atopic dermatitis in these data.

**Table 3** Prevalence ratio of hand dermatitis in each occupational group

Occupational groups	Men				Women			
	PR	95% CI	PR <sup>a</sup>	95% CI	PR	95% CI	PR <sup>a</sup>	95% CI
General population	1.0		1.0		1.0		1.0	
Nurses	5.7	2.9-11.2	9.3	3.6-23.9	3.0	2.1-4.2	2.3	1.5-3.5
Surgical assistants	-		-		1.8	0.98-3.4	1.4	0.7-2.6
Chemical company								
- manual workers	2.6	1.6-4.5	2.8	1.6-4.8	-		-	
- office & supervisor	0.6	0.2-1.5	0.5	0.1-1.4	-		-	
Electricity company								
- manual workers	2.6	1.5-4.4	2.7	1.4-4.9	-		-	
- office & supervisor	1.3	0.5-3.1	1.3	0.5-3.5	-		-	
Public works								
- manual workers	2.4	1.4-4.3	2.4	1.3-4.5	-		-	
- office & supervisor	1.2	0.3-5.1	1.1	0.3-4.7	-		-	

<sup>a</sup> Mantel-Haenszel Prevalence ratio adjusted for age in 10-years categories

The age-adjusted prevalence ratio of hand dermatitis was significantly elevated in nurses, but not in surgical assistants. In male nurses the age-adjusted prevalence ratio was approximately 4 times as high as in female nurses (PR of 9.3 and 2.3 respectively). The prevalence ratio of hand dermatitis among male manual workers in the chemical company, the electricity company and public works varied from 2.4 to 2.8, whereas no elevated prevalence ratio was observed among office workers in these occupational groups.

Table 4 shows that the majority of persons with hand dermatitis in all occupational groups, except for the chemical company, reported improvement of their

## Prevalence

symptoms after weekends or holidays. One third of the cases or less (15-36%), had consulted a physician for treatment of their symptoms. A small proportion of persons with hand dermatitis (3-9%) experienced a period of sick leave due to their symptoms.

**Table 4** Possible work-relatedness of hand dermatitis and sick leave or medical consultation due to hand dermatitis

Occupational group	Total number of persons with hand dermatitis n	Improvement after cessation of work		Sick leave		Medical consultation	
		n	%	n	%	n	%
Nurses	59	58	98.3	2	3.4	9	15.3
Surgical assistants	12	12	100.0	1	8.3	3	25.0
Chemical company	55	31	58.5	2	3.6	19	35.2
Electricity company	55	46	85.2	3	5.5	19	35.8
Municipal public works	32	25	80.6	3	9.4	8	25.0

## Discussion and conclusions

The response rates in the surveys of occupational groups were sufficiently high to allow a reliable estimate of the prevalence. The response rate of 53% among the sample of the general population raises concern with regard to the reliability of the prevalence estimate. However, the questionnaire on hand dermatitis was distributed at the municipal health service among participants who had responded to the invitation for screening on cardiovascular risk factors. Selective response may have occurred with respect to cardiovascular risk factors, but since these factors are unrelated to hand dermatitis, it is less likely that significant bias has occurred in the prevalence estimates of hand dermatitis.

The prevalence figures that were observed among the general population in this study are consistent with results of five major population-based studies, where the prevalence of hand dermatitis in the general population was estimated between 2% and 10%.<sup>8-12</sup> Similarly, the two-fold difference in the prevalence of

hand dermatitis in women as compared with men was observed in most of these studies, which supports the assumption that significant bias due to selective response was less likely.<sup>7,9,11</sup> A higher prevalence of hand dermatitis among women in the general population is believed to be due to higher background exposure of women in household activities. For the interpretation of the prevalence ratios this implies that the female reference group is to some extent exposed, which is generally not the case for the male reference group.

The prevalence of hand dermatitis among male office workers and supervising personnel was not significantly different from that in the general population (men), which points to a similar background prevalence in occupations without occupational exposure to irritants or allergens and in the general population, as would be expected.

The prevalence of hand dermatitis among nurses in this study (approximately 30%), was comparable to the results of two Scandinavian studies where prevalence figures of 33% and 41% were found among nurses.<sup>13,14</sup> The prevalence of hand dermatitis in the chemical company also compares well with the prevalence of 14.5% that was found in a previously reported study.<sup>15</sup> In that study, the same criteria for the definition of hand dermatitis were used as in the current study. However, the source of information was a dermatological inspection of the hands and symptoms in the past 3 years, as reported in a face-to-face interview. No studies are available to compare the prevalence of hand dermatitis in the electricity company and public works.

The elevated prevalence of hand dermatitis in nurses as compared with the general population is likely to be due to heavy exposure in wet work, in particular to the frequency of hand cleaning which is practised 40-60 times per shift on average. This type of exposure seems to affect men as much as women, given the similar prevalence figures in both genders. The crude prevalence ratio in men was approximately twice as high in men as in women as a result of the higher background prevalence among women in the general population. It is reasonable to assume that the prevalence ratio in women would be higher if the reference population consisted of unexposed women.

The prevalence ratio in female surgical assistants was not significantly elevated as compared with the women in the general population. This is contrary to what

## *Prevalence*

was expected. Although no objective data are available, it was assumed that the hand disinfection protocol as practised by surgical assistants, which involves scrubbing of the hands for at least 2 minutes, is more harmful to the skin than the more frequent, but less intensive hand washing habits of nurses.

Another interesting result is that the prevalence ratio of hand dermatitis in male manual workers in the chemical company, electricity company and public works seemed to be independent of the type of exposure that occurs in these occupational groups. An explanation may be that mechanical stress as occurs frequently in manual work, in combination with low or moderate exposure to irritants contributes to the symptoms of hand dermatitis.

The high proportion of persons with hand dermatitis, reporting improvement after weekends or holidays, suggests that occupational exposure contributes to the occurrence or aggravation of the symptoms. It is not directly evident why this proportion among chemical workers is substantially lower than in other study groups. The observation that 3-9% of the cases resulted in sick leave and 15-36% of the cases sought medical attention for their condition is consistent with results from other studies among occupational groups.<sup>13,15,16</sup> Although the relatively high prevalence of hand dermatitis among the occupational groups in this study emphasizes the need for preventive measures, the proportion requiring medical attention or resulting in sick leave suggests that the symptoms were relatively mild in the majority of cases.

It is concluded that nurses (heavy exposure) as well as manual workers (low to moderate exposure to irritants in combination with mechanical stress) have an elevated prevalence of hand dermatitis in comparison with the general population although the symptoms probably are relatively mild in the majority of cases. The prevalence in office workers (no exposure) is comparable to that in the general population.

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## 6. A retrospective cohort study on the incidence of hand dermatitis in nurses\*

H.A. Smit, P.J. Coenraads

### Summary

Data on the incidence rate and induction time of hand dermatitis are not available from the literature. To assist the planning of a prospective study on risk factors for hand dermatitis, a retrospective cohort study was performed in nurses and office employees to obtain a rough estimate of the incidence rate and induction time of hand dermatitis in these occupational groups.

Data were collected by means of a self-administered questionnaire with validated questions on symptoms of hand dermatitis. The cohort consisted of 371 nurses and 111 office employees who were newly employed by a University Hospital between January 1, 1987 and December 31, 1988. Follow-up ended on September 30, 1989. Subjects who reported that symptoms had already occurred before entering the study were excluded for analysis on the incidence rate, leaving 298 nurses and 101 office employees for further analysis. Due to limitations of the retrospective study design, only half of the cases was able to report the exact month of incidence. Therefore only a rough estimate could be made of the incidence rate and induction period, assuming that the distribution of person-months of observation in cases with known incidence date was equal to that of cases with unknown incidence dates. Thus, it was estimated that the overall incidence rate was 6.5 cases/1000 person-months in nurses and 1 case/1000 person-months in office employees. In nurses, 72% of the cases occurred within 3 months of follow-up. However, in the interpretation of these figures it should be taken into account that 83% of the nurses had been working as a nurse before start of employment by the University Hospital. Since these nurses may represent a less susceptible group with a lower incidence rate,

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\* submitted

it should be considered to focus on apprentice nurses who have not been occupationally exposed as a nurse before entering the study.

## **Introduction**

Hand dermatitis is a common disease in occupational groups with exposure to wet work. Although not life threatening, it is also known to be a disease with an unfavorable prognosis.<sup>1,2,6</sup> It may take months or even years for the skin to heal completely, particularly when exposure continues to exist. In that situation, a cross-sectional study does not allow to distinguish between factors contributing to the development of hand dermatitis and factors contributing to maintaining the symptoms. Therefore, a prospective study was planned to study individual risk factors (in particular atopic constitution and transepidermal water loss) and occupational risk factors for hand dermatitis. Nurses, known to be at high risk for hand dermatitis, were envisaged as a study population in the prospective study. The prevalence of hand dermatitis in nurses is estimated to be 30-40%.<sup>3,7,9</sup> However, figures on the incidence rate which was to be expected, were completely absent for nurses or any other occupational group. This information was particularly important in the planning phase, since a disease with a long duration may still have a low incidence in spite of a high prevalence. To obtain a rough estimate of the incidence rate and induction time, a (less expensive) retrospective cohort study was carried out among nurses who were newly employed by a University Hospital.

## **Methods**

Nurses formed the population of interest in this study. To obtain an estimate of the incidence in an unexposed occupational group, office employees were chosen as a reference group. Nurses and office employees who were newly hired by the University Hospital of Groningen between January 1, 1987 and December 31, 1988, were eligible for the study. A cohort of 428 nurses and 154 office employees was

### *Retrospective study*

assembled from the computerized personnel files of the hospital. Follow-up ended on September 30, 1989. Thus, the maximum duration of follow-up was 33 months.

A self-administered questionnaire was sent to the study population in the last week of September 1989. A reminder was sent after three weeks. The occurrence of hand dermatitis during employment was determined by the investigators from a set of validated questions (Appendix A).<sup>10</sup> Based on these questions, a person with hand dermatitis was defined as "a person who answered positively to two or more of the questions 1a through 1e (symptoms) and who answered positively to either question 2 (symptoms for more than three consecutive weeks) or question 3 (recurrence of symptoms)". The sensitivity and specificity of a diagnosis of hand dermatitis in comparison with the medical diagnosis were 80% and 89% respectively.<sup>10</sup> All subjects reporting one or more of the symptoms, were asked to indicate the month of first occurrence of the symptoms and whether the symptoms had already occurred before employment by the University Hospital. Subjects who satisfied the criteria for hand dermatitis and who reported presence of symptoms before employment, were excluded for estimation of the incidence rate and induction period. Study subjects who remained free of hand dermatitis during employment contributed person-time from the date of hire until September 30, 1989 or to the date of termination of employment if this was earlier than September 30, 1989. Incident cases contributed person-time from the date of hire until the month of first symptoms of hand dermatitis. An implication of the retrospective study design was that the validity of the estimates of incidence rate would rely heavily on the ability of participants to recall the exact month in which symptoms had first occurred.

The incidence rate was defined as the number of incident cases of hand dermatitis per 1000 person-months of observation. The induction time was defined as the period between date of hire and month of first symptoms of hand dermatitis.

## **Results**

87.8% of the nurses (376/428) and 74.7% of the office employees (115/154) returned the questionnaire. Nine responders who did not fulfil eligibility criteria, as it appeared from the questionnaire, were excluded from the study population. Thus, the study

## Chapter 6

population consisted of 371 nurses and 111 office employees (82.8% of the source population). The study population was similar to the source population with respect to the distribution of age, gender, marital status, number of working hours per month, termination of employment and reasons for termination of employment.

Nurses and office employees were similar with respect to age (27.0 years  $\pm$  6.2 and 30.8 years  $\pm$  8.1 respectively). The proportion of men was higher among office employees than among nurses (30.6% and 13.7%). The proportion of office employees who had terminated employment was larger than in nurses (30.6% and 11.3%), but the distribution of reasons for termination of employment was similar in both groups. None of the nurses had terminated employment because of hand dermatitis.

The proportion of nurses with hand dermatitis during employment was 28.8% (107/371). In office employees this was 10.8% (12/111). In 68.2% of the nurses with hand dermatitis (73/107) and in 83.3% of the office employees with hand dermatitis (10/12), one or more symptoms had already occurred before employment by the University Hospital. These subjects were excluded, leaving 298 nurses and 101 office employees for analysis on incidence rate and induction period. 83.2% of those nurses reported that they had been working as a nurse before employment at the University Hospital.

Between January 1, 1987 and September 30, 1989, 34 incident cases occurred among nurses and 2 incident cases occurred among office employees. Information on the month of first symptoms, which is necessary to estimate the induction time and incidence rate, was reported by 18 out of 34 incident cases among nurses and by 1 out of 2 incident cases among office employees. The induction time in nurses varied from 1 to 24 months. In the office employee who reported the month of incidence, the induction time was 24 months. Duration of employment and the date of hire were equally distributed among those who did and those who did not report the month of incidence.

Table 1 shows the incidence of hand dermatitis for nurses according to the time since first employment. Results in the first 3 columns are based on cases with known incidence dates only. In the last 3 columns of table 1, extrapolated estimates are given, under the assumption that the distribution of person-months over the intervals of follow-up was equal in cases who reported the month of incidence and the cases who failed to do so. The extrapolated estimate of the incidence rate in nurses in

*Retrospective study*

the first 3 months after start of employment was approximately 29 cases/1000 person-months. The incidence rate declined rapidly after 3 months of follow-up: 72% of the cases had occurred within this period. The extrapolated incidence rate in nurses over the first 12 months was 9.4 cases per 1000 person-months. The extrapolated estimate of the overall incidence rate over the total study period of 18.5 months in nurses was 6.5 cases/1000 person-months. The overall incidence rate in office employees was approximately 1 case/1000 person-months of observation (1947 months by 99 disease-free subjects + 24 months by the case reporting month of incidence + 20 months estimated for the case who failed to report incidence date = 2 cases/1971 person-months).

**Table 1** Incidence of hand dermatitis and time since first employment in nurses, based on cases with known month of incidence

Time since first employment (months)	Effective sample size (N)	Observed			Extrapolated*		
		Incident cases (n)	Person-months (pm)	Incidence rate per 1000 pm	Incident cases (n*)	Person-months *	Incid. rate per 1000 pm**
0 - 3	282	13	825	15.8	24.5	854	28.7
4 - 6	265	1	799	1.3	1.9	812	2.3
7 - 12	241	2	1530	1.3	3.8	1550	2.5
13 - 18	181.5	1	1087	0.9	1.9	1096	1.7
19 or more	71.5	1	906	1.1	1.9	911	2.1
Overall		18	5147	3.5	34	5223	6.5

\* 16 cases with unknown incidence date are assigned to each time interval, proportional to the distribution of that in the 18 cases with known incidence date. These 18 cases contributed 86 person-months. 16/18 of these 86 person-months were assumed to be equally distributed over each time interval.

\*\* the extrapolated incidence rate over the first 12 months of follow-up is 9.4 cases per 1000 person-months (30.2 cases/3216 person-months).

## Discussion

The proportion of all nurses having suffered from hand dermatitis during employment at the University Hospital, was 28.8% in this study, which is similar to estimates of 30-40% that were found in other studies among nurses.<sup>3,7,9</sup> The proportion of office workers having suffered from hand dermatitis during employment (10.8%) is comparable to prevalence figures of 5 to 10% that were observed in the general population.<sup>4,5,8,9</sup> The period over which the prevalence figures in these other studies were estimated, varied from 12 months to 3 years. Apparently this does not influence the estimates of the prevalence to a large extent, which can probably be explained by the long duration of the disease.

However, the potential of the current study to produce an estimate of the incidence rate and the induction period was limited, since almost half of the subjects failed to report the month of incidence. To obtain a rough estimate of the incidence rate and induction period for the planning of a prospective study among nurses, it was assumed that the distribution of person-months of follow-up in cases who reported the month of incidence (average induction period of 4.8 months), was equal to that in cases who failed to report the incidence date. This seemed reasonable because reporting of the month of incidence was not related to the duration of employment or to the date of hire.

Thus, in nurses who are occupationally exposed to wet work, the overall incidence rate over the total study period was estimated to be 6.5 cases per 1000 months of follow-up. The incidence rate of 1 case per 1000 person-months of follow-up in office workers gives an indication on the background incidence rate of hand dermatitis, that may be expected in populations without occupational exposure. The 95% confidence interval around the overall incidence rate in nurses was 4.3 - 8.7 cases/1000 person-months, under the assumption that the extrapolated number of person-months were truly observed. The estimate of the incidence rate in nurses is not strongly biased by the missing information on the month of onset, because it involved only 16 cases. These cases would contribute between 1 and 326 person-months (assuming the average induction time of 20.4 months in non-diseased nurses), leading to a range of estimates for the incidence rate between 6.2 and 6.6 cases/1000

### *Retrospective study*

person-months. Selective non-respons of nurses without hand dermatitis would result in a decrease of the overall incidence rate to 5.3 cases/1000 person-months.

For the planning of a prospective study, it is important that the incidence rate declined rapidly with longer time period elapsed after start of employment. The results of this preliminary study suggest that a follow-up period of approximately 1 year in a prospective study would be reasonable. From the extrapolated incidence rate of 9.4 cases per 1000 person-months over the first 12 months of follow-up, it can be calculated that the 1-year cumulative incidence was 9.0%. However, it should be taken into account that 83% of the disease-free nurses in this study had been working as a nurse before employment at the University Hospital. These nurses who have been occupationally exposed before entering the study without developing symptoms of hand dermatitis may form a selection of less susceptible subjects. On average, they may therefore have a lower incidence rate than a population of firstly exposed nurses, which contains an (unknown) proportion of susceptible individuals. The current study did not allow to compare incidence rates between previously exposed and firstly exposed nurses, because of the small numbers of firstly employed nurses.

The high proportion of previously employed nurses as observed in this study, may well reflect the situation in other hospitals as well. Therefore, in the planning of a prospective study among nurses it should be considered to focus on apprentice nurses who have not been occupationally exposed as a nurse before entering the study.

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## 7. Variability in transepidermal water loss of the skin: evaluation of a method to assess susceptibility to contact dermatitis in epidemiological studies\*

H.A. Smit, J. Pinnagoda, R.A. Tupker, J. Burema, P.J. Coenraads, J.P. Nater

### Summary

Transepidermal water loss (TEWL) has been suggested to be a measure which can be used to identify subjects at risk for the development of contact dermatitis. Transepidermal water loss is high when the barrier function of the skin is impaired. It is assumed that subjects with a high TEWL have skin which is more permeable to substances causing contact dermatitis.

The inter-individual and intra-individual variability of simultaneous TEWL measurements and TEWL measurements over a period of three weeks were estimated in healthy individuals. The intra-individual coefficient of variation (CV) of simultaneous measurements was 13.5%. The intra-individual coefficient of variation of the measurements on consecutive days was somewhat higher (15.1%). The intra-individual coefficients of variation were low compared to the inter-individual coefficients of variation.

The results indicate that transepidermal water loss is a stable personal characteristic, which can be studied as a risk factor in epidemiologic studies on contact dermatitis.

### Introduction

Transepidermal water loss (TEWL) has been suggested as a predictor of the irritant response of the skin to surfactants.<sup>3</sup> TEWL is a measure of the effectiveness of the stratum corneum of the skin. An impaired barrier function of the

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stratum corneum facilitates penetration of irritating and sensitizing agents through the skin. Contact dermatitis may occur as a result of exposure to irritating or sensitizing agents. Therefore, TEWL may serve as a risk indicator in epidemiologic studies on contact dermatitis.

A method of measuring transepidermal water loss through the skin was developed by Nilsson.<sup>8</sup> This non-invasive method is based on the estimation of the vapor-pressure gradient immediately adjacent to the surface of the skin. Since the original development, the accuracy of the method has been improved and the measurement conditions are standardized.<sup>9</sup> The instrument is easy to handle and it is convenient of use in field studies. An increase in transepidermal water loss after exposure has been shown in experimental studies<sup>1,2,5,7,11,13</sup> and in one occupational field study.<sup>3</sup> Since random error in the measurement of a risk factor is known to introduce bias in the estimate of the relative risk, it is important to obtain information on the variability of transepidermal water loss prior to the planning of an epidemiologic study. Here we report on the variability of TEWL values on eight different sites of the forearm and on the variability of TEWL values over a period of three consecutive weeks. The estimate of the intra-individual variance can be used to estimate the probability of misclassification of individuals into categories of high and low transepidermal water loss, for different cut-off values of TEWL.

## Materials and methods

### *Design of the experiment*

TEWL measurements were performed on 30 healthy individuals. The measurements took place on Monday through Friday on 3 consecutive weeks. On the first day, a total of eight TEWL measurements were carried out simultaneously on four unexposed sites of each forearm. On the following days, six sites were exposed to surfactants, one site to water and one site remained unexposed. To determine whether it is useful to study TEWL as a risk factor for contact dermatitis, information is needed on the inter-individual and intra-individual variability in TEWL values of the unexposed skin. Therefore, we report in this

article on the variability of TEWL-values on the unexposed sites: (1) for the measurements on eight sites taken simultaneously on the first day and (2) for the measurements taken on the site closest to the wrist on consecutive days. The effects of exposure on TEWL values have been reported elsewhere.<sup>11</sup> All 30 individuals had a complete set of eight measurements on the first day. However, in the analysis of the day-to-day variation, five days were excluded from the analysis, because TEWL values of four or more individuals were missing. On the remaining 10 days, a total of 18 observations were missing.

The study population consisted of 30 students, 14 men and 16 women aged 21-49 years (mean age 31 yrs). None of them reported prior skin diseases or had skin disorders during the investigation. None of the students had relevant occupational exposure of the skin. Data on personal characteristics such as type of skin, sensitivity to soap and history of atopy, were obtained. None of those characteristics was related to transepidermal water loss in these data.

#### *Transepidermal water loss measurements*

The measurements were performed with the ServoMed Evaporimeter (ServoMed, Stockholm, Sweden). This method was developed and described by Nilsson.<sup>8</sup> The measurements took place in an air-conditioned room at a constant temperature of 20°C and a relative humidity of  $45 \pm 5\%$ . Temperature and humidity were constantly monitored during the measurements.

On the first day, the TEWL measurements were performed on four locations on the volar side of each forearm between the wrist and the elbow (R1-R4 on the right arm and L1-L4 on the left arm). Control measurements on the following days were performed on one unexposed site on the left arm (L1), closest to the wrist (75 mm from the wrist joint). In order to prevent the influence of air current on the TEWL measurements, the forearm was placed in a measuring box with an open top, constructed for this purpose. Digital readings were taken 30 sec after the start of the recording to obtain a stable TEWL value.<sup>9</sup>

*Statistical analysis*

An analysis of variance was conducted to estimate the inter-individual and intra-individual variation in transepidermal water loss on eight sites of the forearm and over a period of 3 weeks.

The underlying random effects model for the variation in the eight measurements on the first day can be written as:<sup>10</sup>

$$X_{ij} = \mu + A_i + e_{ij} \quad (1)$$

where:  $X_{ij}$  = TEWL value ( $\text{g}/\text{m}^2\cdot\text{h}$ ) of the  $j^{\text{th}}$  measurement in the  $i^{\text{th}}$  individual

$i$  denotes the  $i^{\text{th}}$  individual (1,2,...,a)

$j$  denotes the  $j^{\text{th}}$  measurement (1,2,...,n)

$\mu$  = the overall mean TEWL value ( $\text{g}/\text{m}^2\cdot\text{h}$ ) of the population

$A_i$  = difference between the mean TEWL in the  $i^{\text{th}}$  individual and the overall mean TEWL in the population.  $A_i$  is assumed to be a normally distributed random variable with mean 0 and variance  $\sigma_A^2$ :  $A_i \sim N(0, \sigma_A^2)$ .

$e_{ij}$  = error in the individual values:  $e_{ij} \sim N(0, \sigma^2)$ .

The intra-individual and the inter-individual variations in the random effects model can be estimated from the Mean Squares (MS) in an analysis of variance, i.e. the intra-individual variance ( $\sigma^2$ ) from the error MS:

$$\hat{\sigma}^2 = MS_{\text{error}} \quad (2)$$

and the inter-individual variance ( $\sigma_A^2$ ) from the formula for the expectation of the MS of the model:

$$E(MS_{\text{model}}) = n\sigma_A^2 + \sigma^2 \quad (3)$$

### Variability TEWL

thus:

$$\hat{\sigma}_A^2 = (MS_{\text{model}} - MS_{\text{error}})/n \quad (4)$$

For the first day, a complete set of eight observations was available for each of the 30 study persons. However, since the data on the following days contained some missing observations on TEWL, the design for the day-to-day analysis was unbalanced. In this case, the number of measurements ( $n$ ) in the estimate of the inter-individual variance was replaced by the following expression for  $n_0$ :<sup>10</sup>

$$n_0 = [N - \Sigma(n_i^2)/N]/(a-1) \quad (5)$$

where:  $N$  = total number of measurements  
 $n_i$  = number of measurements on the  $i^{\text{th}}$  individual  
 $a$  = number of individuals in the experiment

The underlying assumption of the model is that the intra-individual variance is independent of the level of TEWL. However, preliminary analyses showed that there was a strong linear relationship between an individual's mean TEWL and standard deviation. Thus, the data were fitted better by a model with constant coefficient of variation. Therefore, the analysis was performed on the log<sub>e</sub>-transformed data.<sup>4,12</sup> The variance components  $\sigma^2$  and  $\sigma_A^2$  now denote the intra-individual and inter-individual variances of the logarithm of TEWL. The square root of the variance is approximately equal to the coefficient of variation of TEWL, which now is independent of the level of TEWL. For each value of TEWL, an intra-individual standard deviation can be calculated as the product of the coefficient of variation and the level of TEWL.

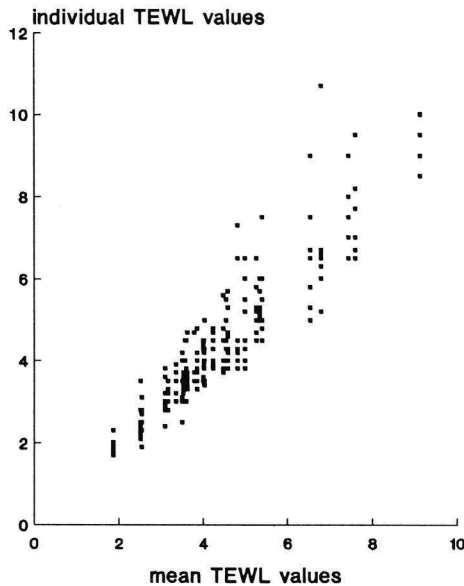
The estimated intra-individual variation can be used to calculate the probability of misclassification of individuals into categories of high and low TEWL values, for a given value of the cut-off point. This probability depends on the magnitude of the difference between the true mean TEWL of an individual and the TEWL value of the cut-off point, on the number of repeated measurements and on the intra-individual standard deviation:<sup>6</sup>

$$Z_p = \frac{b}{\sigma/\sqrt{n}} \quad (6)$$

- where:  $Z_p$  = the percentage point of the standard normal distribution  
 $b$  = distance between the true mean TEWL of an individual and the cut-off value  
 $\sigma$  = intra-individual standard deviation  
 $n$  = number of measurements per individual

## Results

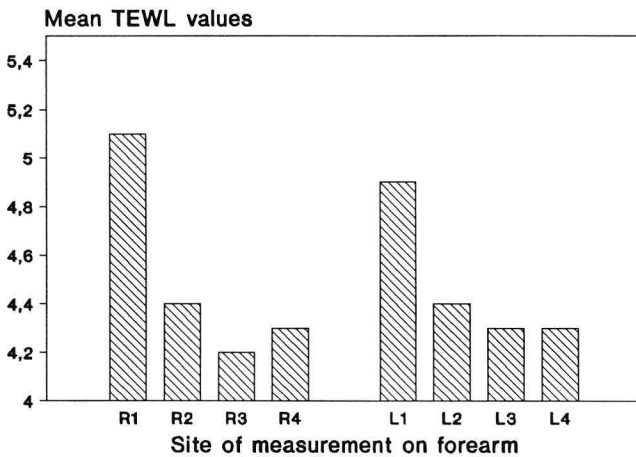
The overall mean TEWL of the measurements taken on the first day was  $4.5 \pm 1.7$  g per  $m^2$ .hour. Figure 1 shows the individual TEWL values as a function of each individual's mean TEWL value.



**Figure 1** Individual TEWL values as a function of each individual's mean TEWL value (measurements on the first day in 30 individuals), Groningen, The Netherlands, 1987. TEWL transepidermal water loss in g per  $m^2$ .hour

### Variability TEWL

It can be seen that the standard deviation increases with an increasing mean TEWL value. Therefore, the analysis of variance was performed on the log<sub>e</sub>-transformed data. Figure 2 shows the mean TEWL on each site of the forearms (R1-R4 and L1-L4). The mean TEWL values on the sites closest to the wrist (R1 and L1) were slightly higher than the values on the other sites of the forearm.



**Figure 2** Frequency distribution of mean TEWL values on eight sites of the forearm (measurements on the first day in 30 individuals), Groningen, The Netherlands, 1987. TEWL transepidermal water loss in g per m<sup>2</sup>.hour

Table 1 shows the ANOVA table for the eight measurements taken on the first day, from which the intra-individual and the inter-individual coefficients of variation were calculated. The intra-individual coefficient of variation of TEWL, as estimated from  $\sqrt{MS_{\text{error}}}$  was 13.5%. Thus, for individuals with a true mean TEWL value of 4.5 g per m<sup>2</sup> hour, the intra-individual standard deviation was estimated as 0.61. The inter-individual coefficient of variation, estimated from equation (4) was 34.3%. Although the effect of measurement site on the variance in TEWL values was significant, the intra-individual coefficient of



variation declined only slightly from 13.5 to 12.4%, after allowing for the effect of measurement site in the analysis.

The overall mean TEWL of measurements on different days was  $4.9 \pm 1.7$  g per m<sup>2</sup> hour. Again, the analysis of variance was performed on the log<sub>e</sub>-transformed data, because of heteroscedasticity in the data.

**Table 1** ANOVA table for the logarithm of TEWL<sup>a</sup> measurements in 30 individuals (measurements on the first day on 8 sites of the forearm)

Source	d.f. <sup>b</sup>	Sum of Squares	Mean Square	Expected Value
Model	29	27.8867	0.962	$\sigma^2 + n\sigma_A^2$
Error	210	3.8404	0.0183	$\sigma^2$
Total	239	31.7271		

<sup>a</sup> TEWL transepidermal water loss in g per m<sup>2</sup>.hour

<sup>b</sup> d.f. degrees of freedom

The ANOVA table for the measurements on consecutive days is shown in table 2. The value of  $n_0$  (equation 5) was computed as 9.4. For the TEWL measurements on ten consecutive days the intra-individual and inter-individual coefficient of variation were estimated as 15.1 and 32.6%, respectively.

## Discussion

TEWL measurements with the ServoMed Evaporimeter have been performed in other studies mostly to determine the effects of exposure to irritants on TEWL values.<sup>1,2,3,5,7,11,13</sup> Some of these studies reported or allowed calculation of the mean TEWL and its standard deviation in unexposed persons. However, none of the studies reported on the inter-individual and intra-individual variance components as estimated by means of analysis of variance.

*Variability TEWL*

**Table 2** ANOVA table for the logarithm of TEWL<sup>a</sup> measurements in 30 individuals on 10 consecutive days

Source	d.f. <sup>b</sup>	Sum of Squares	Mean Square	Expected Value
Model	29	29.5574	1.0192	$\sigma^2 + n_0\sigma_A^2$
Error	252	5.7246	0.0227	$\sigma^2$
<b>Total</b>	<b>281</b>	<b>35.2820</b>		

<sup>a</sup> TEWL values in g per m<sup>2</sup>.hour

<sup>b</sup> d.f. degrees of freedom

The intra-individual coefficient of variation of the measurements on eight sites (13.5%) was small compared to the interindividual coefficient of variation (34.3%), suggesting that individuals can be distinguished based on their TEWL values. It should be noted that the study population is not a representative sample of the general population, but a relatively young and well-educated sample thereof. However, there are no indications that these factors will greatly affect the inter- and intra-individual variability in TEWL values.

The mean TEWL values on the two sites closest to the wrist were slightly higher than on the other sites. Allowing for the effect of the measurement site would reduce the intra-individual variance only slightly from 13.5 to 12.4%. The implications of the difference between sites, for the choice of a site to perform TEWL measurements in future studies, depend largely on the study design. If TEWL is to be studied as a risk factor for the occurrence of contact dermatitis on one specific site, the intra-individual coefficient of variation could be reduced by repeated measurements on only one specific site of the forearm. On the other hand, it may be more useful in epidemiologic studies, to characterize an individual by the average TEWL value of several sites on the forearm.

The probability of misclassification of individuals with a given true mean TEWL of the forearm, can be estimated from the intra-individual coefficient of variation (equation 6). If, for example a cut-off value of 5.0 g per m<sup>2</sup> hour is

chosen, the probability of misclassification of individuals with a true mean TEWL value of 4.5 g per m<sup>2</sup> hour, based on one measurement on the forearm, would be 20.6%. By increasing the number of measurements per individual to 2 or 3, the probability of misclassification would be reduced to 12.3 and 7.8%, respectively.

The overall mean TEWL over 10 days was slightly higher than the overall mean TEWL of eight simultaneous measurements due to the fact that the measurements on different days were performed on the site closest to the wrist, which was relatively high compared to the other sites of the forearm.

The intra-individual coefficient of variation of the measurements taken on ten consecutive days, was 15.1%. This was slightly higher than the intra-individual coefficient of variation of the simultaneous measurements on eight sites. Slight changes in TEWL values over the days may have contributed to the higher intra-individual variation. As an example, we chose 5.4 g per m<sup>2</sup> hour as a cut-off point for classification of the average TEWL over a period of 3 weeks, which is 0.5 g per m<sup>2</sup> hour above the overall mean TEWL of 4.9 g per m<sup>2</sup> hour. The probability of misclassification of an individual with an average TEWL value of 4.9 g per m<sup>2</sup> hour, based on a measurement on one single day, is estimated to be 24.8%. Repeated measurements on 2 or 3 days would reduce the probability of misclassification to 16.8 or 12.1%, respectively.

These results suggest that measurement of TEWL on the forearm can be considered a relatively stable personal characteristic over a period of three weeks that may be studied as a risk factor in epidemiologic studies on contact dermatitis. However, if TEWL is to be studied as a risk factor over a longer period, further studies of the variability are necessary, since seasonal influences may affect TEWL values.<sup>9</sup>

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## 8. Individual susceptibility and the incidence of hand dermatitis in a cohort of apprentice hairdressers and nurses\*

H.A. Smit, A. van Rijssen, J.P. Vandenbroucke, P.J. Coenraads

### Summary

Several endogenous factors are known to determine the development of hand dermatitis during occupational exposure: atopic constitution, contact sensitization and a dry skin. More recently, transepidermal water loss through the skin has been suggested to be an indicator of individual susceptibility in the development of hand dermatitis. The authors investigated the role of these endogenous factors in the development of hand dermatitis in a prospective study among 74 apprentice hairdressers and 111 apprentice nurses in Groningen, The Netherlands, from September 1990 to July 1992.

The average incidence rate of hand dermatitis was 32.8 cases/100 person-years in hairdressers and 14.5 cases/100 person-years in nurses. The relative risk of having a dry versus normal skin type was 7.3 in hairdressers (95% confidence interval: 2.2-24.3) and 1.7 in nurses (95% confidence interval: 0.5-6.4). Apprentice nurses with a history of (atopic) mucosal symptoms had a 3.4-fold increased risk of hand dermatitis (95% confidence interval 1.05-11.2). The risk of mucosal atopy in apprentice hairdressers was 2.2 (95% confidence interval: 0.7-6.7). The results suggested an increased risk of hand dermatitis in apprentice hairdressers with transepidermal water loss on the hand greater than 15 g/m<sup>2</sup>.h; but, no statistically significant relative risk was observed.

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\* submitted

## Introduction

Under the same working conditions, some persons will develop hand dermatitis and others will not. This is not just a matter of chance. Individual susceptibility plays an important role in the causation of hand dermatitis. Characteristics known to be associated with hand eczema are atopic background (in particular, atopic dermatitis),<sup>1-5</sup> contact allergy (especially nickel allergy)<sup>2,6,7</sup> and skin dryness.<sup>8,9</sup> Over the last decade, several authors have suggested that baseline pre-exposure transepidermal water loss can serve as an indicator of individual susceptibility to the development of contact dermatitis.<sup>10-13</sup> The biologic mechanism underlying this hypothesis is that a diminished barrier function of the skin, reflected by increased transepidermal water loss, allows harmful agents to pass through the stratum corneum more easily and cause damage in the underlying layers of the skin. However, the predictive value of an increased baseline transepidermal water loss for the risk of hand dermatitis, has not yet been evaluated in epidemiologic studies.

A prospective study was performed among apprentice hairdressers and nurses with two objectives. One objective was to obtain quantitative estimates of the relationship between hand dermatitis and known risk factors such as atopic background, contact allergy and type of skin. The other was to investigate the hypothesis that individuals with increased baseline transepidermal water loss as a personal characteristic are more susceptible to developing hand dermatitis during occupational exposure than those with low transepidermal water loss and similar exposure. Hairdressers and nurses were chosen as study populations because they are known to be at high risk for the development of hand dermatitis.<sup>2,14-17</sup>

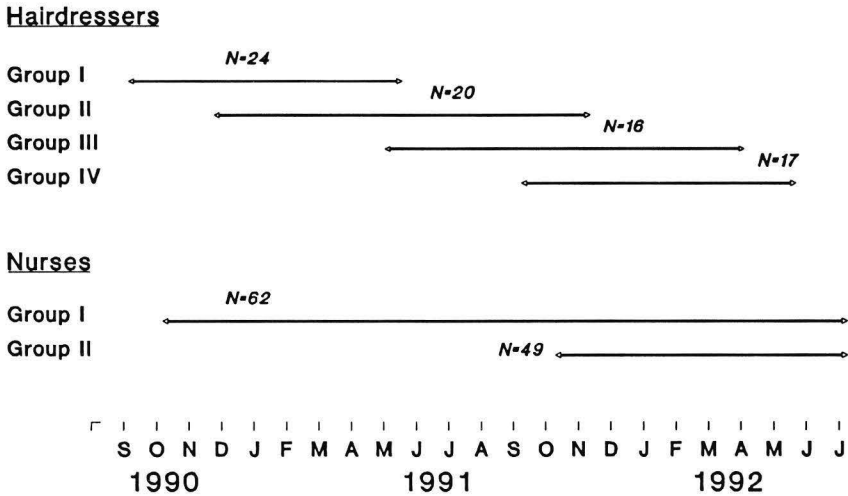
## Material and methods

### *Study design and population under study*

The study group consisted of 111 apprentice nurses and 74 apprentice hairdressers who were free of hand dermatitis at the start of the investigation. The

*Individual susceptibility*

apprentices were under observation during their training. They were examined at regular intervals to identify new cases of hand dermatitis and to record changes in occupational exposure. Figure 1 summarizes the design of the study.



**Figure 1** Design of the prospective study among apprentice hairdressers and apprentice nurses, Groningen, the Netherlands, 1990-1992

Four groups of apprentice hairdressers, a total of 77 persons, were recruited at the start of their training in September 1990, December 1990, May 1991 and September 1991 respectively. Three apprentices left school before the first follow-up measurement was made. Therefore, 74 apprentice hairdressers were included in the study. The duration of the hairdressers' training was 10 months on the average. Eight subjects who failed their final examination, remained under observation until they were successful at one to four months later. The study in hairdressers ended in May 1992, when the last determination was made in the fourth group.

Two groups of apprentice nurses, a total of 126 persons, were recruited in the third year of their training, which included the first period of practical training. The first group was enrolled in October 1990. They were under observation for

two years until the end of their training (July 1992). The second group was enrolled in October 1991 and was under observation until July 1992 (one school year). Four individuals who suffered from hand dermatitis at the start of the study were not included in the analysis. Eleven apprentice nurses dropped out before the first follow-up determination was made, for reasons unrelated to hand dermatitis. Therefore, 111 apprentice nurses were included in the study. The first year of follow-up included two periods of practical work of 12 weeks each, with an interval of eight weeks of classes without occupational exposure. The second year of follow-up consisted of 12 weeks of classes followed by 20 weeks of practical work.

### *Data collection*

#### Baseline measurements.

Data collection took place in an office at the hairdressers' and nurses' schools. At the time of entry into the study, the following protocol was adhered to:

1. A questionnaire was completed to determine relevant baseline characteristics such as age, gender, history of asthma or hay fever, history of childhood eczema, history of past skin disease and prior exposure to hairdressing or nursing activities.
2. An examination of the skin of the hands was performed by a trained physician and positive skin findings (one "A-sign" or two "B-signs") were recorded. A-signs were: grouped papules, grouped pustules, grouped vesicles, exudation; B-signs were erythema, scaling, edema, fissures and lichenification.<sup>18</sup> The type of skin of the hands was recorded and graded as dry, normal or oily.
3. Baseline measurements of transepidermal water loss (expressed as g/m<sup>2</sup>.h) were performed on the forearm and the back of the dominant hand as indicators of the susceptibility of the skin. Measurements on the forearm were made on the volar side, eight centimeters from the wrist. Transepidermal water loss measurements were performed on the dominant hand, since this hand was assumed to have a similar probability of occupational exposure in all subjects.



### *Individual susceptibility*

The Evaporimeter EP1C (ServoMed AB, Kinna, Sweden) was used for the measurement of transepidermal water loss. The operating principle of the instrument is based upon measuring the vapor pressure gradient through the skin.<sup>19</sup> The transepidermal water loss measurements were performed according to the guidelines proposed by the Standardization Group of the European Society of Contact Dermatitis.<sup>20</sup> The exception was that the temperature and relative humidity ranged more widely in this study than what was proposed in the recommendations (20°C; 40% relative humidity). On the six occasions that baseline measurements were performed, the ambient air temperature varied between 16 and 24°C. The range in the relative humidity of the ambient air was 27-62%. Fluctuations in measurement conditions were due mainly to the fact that the measurements were performed in the schools, where no air conditioned rooms were present. Ambient air temperature and humidity were recorded before each measurement. The transepidermal water loss measurements were recorded continuously, using a chart strip recorder. All measurements were made in duplicate.

4. A thin layer rapid use epicutaneous test (TRUE test) was performed to determine the existence of cell-mediated allergy to common contact allergens at the start of the study.<sup>21</sup> Patch testing was performed by using the European Standard Series, which included 23 of the most common allergens and one negative control. The patches were applied on the subjects' back and removed after 48 h. The patch tests were read by a dermatologist after 48 and 72 h. They were graded according to the recommendations of the ICDRG.<sup>22</sup>
5. Prick tests were carried out on the forearm to determine the existence of immediate type allergy. Test substances were pollen of birch, alder, timothy grass, dander of cat, dog, guinea pig and house dust mite. Histamine was used as a positive control. Prick tests were read after 20 min by an experienced dermatologist.

Follow-up measurements.

The follow-up measurements in apprentice hairdressers took place at intervals of about six weeks. Those in apprentice nurses were performed in the week before and after each period of practical work. The following protocol was applied in each follow-up measurement.

1. a questionnaire was completed by all subjects to determine the incidence of symptoms of hand dermatitis over the preceding period and the date of occurrence of first symptoms. For this purpose, a set of validated questions on symptoms of hand dermatitis (vesicles, scaling, itching, redness, swelling and fissures) and their frequency and duration was used.<sup>23</sup> The type and intensity of exposure during the preceding period was also assessed.
2. An examination of the hands was performed by a physician who recorded the presence of signs of (recent) hand dermatitis.
3. Transepidermal water loss measurements were performed on the forearm and the back of the dominant hand following the same protocol as used for the baseline measurements. Results of the repeated transepidermal water loss measurements over time will be reported elsewhere.

#### *Definition of relevant variables*

The identification of cases of hand dermatitis was performed by one experienced dermatologist (PJC) without knowledge of the baseline characteristics. The diagnosis was based upon the occurrence of symptoms of hand dermatitis during the previous follow-up period as reported in the validated questionnaire. The skin findings as recorded by the physician were evaluated to exclude mild or doubtful cases or subjects with other skin diseases. A subject was diagnosed as having hand dermatitis if one or more combinations of symptoms, as reported in the questionnaire, had occurred during the previous follow-up period, if the symptoms were recurrent or had lasted for at least three weeks and if this was supported by the skin findings recorded during the examination of the hands. The date of the onset of symptoms reported in the questionnaire was taken as the incidence date of hand dermatitis.

### *Individual susceptibility*

Information on the history of (atopic) mucosal symptoms was based upon the question: "Have you ever suffered from asthma or hay fever?" A history of childhood dermatitis was based upon the question: "Did you suffer from eczema or dermatitis as a child?"

Patch test readings with a grading of 2+ or more after 72 h were interpreted as positive patch tests. A positive prick test was defined as a reaction (in mm) to a test substance that was greater than or equal to the reaction to histamine. Any reaction less than the one to histamine was defined as negative. One or more positive reactions to any of these substances versus all negative tests was used as an indicator of the presence of immediate type allergy in the analysis.

Transepidermal water loss values (TEWL). The average value of the duplicate TEWL measurements was taken as an individual's baseline transepidermal water loss value for the hand and forearm. For comparison of the relative risk of high versus low TEWL values, boundary points for 'high', 'intermediate' and 'low' values were established by ranking each subject's average TEWL value according to the tertiles of the distribution of TEWL values in the total study population. Thus, transepidermal water loss on the hand was defined as 'low' when it was less than or equal to 7.7 g/m<sup>2</sup>.h; values between 7.7 and 10.1 g/m<sup>2</sup>.h were defined as 'intermediate' and those higher than 10.1 g/m<sup>2</sup>.h were defined as 'high'. Similarly, the boundary points for transepidermal water loss on the forearm were less than or equal to 5.5 ('low'), 5.5 to 6.8 ('intermediate') and above 6.8 g/m<sup>2</sup>.h ('high'). Preliminary analyses showed that the coefficient of variation of the duplicate measurements within individuals was 11.7 percent for TEWL on the forearm and 13.3 percent for TEWL on the hand.

### *Statistical analysis*

The incidence rate, expressed as the number of incident cases per 100 person-years of observation, was used as a measure for disease occurrence. Observation time was accumulated from the date of entry into the study to the date of exit from the study. The date of exit was defined as the date of the onset of first symptoms for cases or the date of lost-to-follow-up or end of the study for non-

cases. For comparison with results from other studies, the cumulative incidence of hand dermatitis was derived from the incidence rates using equation 1:<sup>24</sup>

$$\text{Cumulative incidence} = 1 - \exp[-\text{IR} \cdot \Delta t] \quad (1)$$

where CI = cumulative incidence over period  $\Delta t$ ;

IR = incidence rate per 100 person-years;

$\Delta t$  = period in years;

The relationship between variables of interest and the risk of hand dermatitis was assessed by means of Cox proportional hazard analyses.<sup>25</sup> This method makes use of the instantaneous incidence rate ("hazard rate") at each point in time that an individual developed hand dermatitis. The ratio of the hazard rates in subjects with and without the factor of interest (for example, atopic versus nonatopic constitution) is a measure of the relative risk of the factor of interest. The underlying assumption of the Cox proportional hazard regression is that the hazard ratio of the risk factor does not change over time ("proportional hazard assumption"). The term 'significant' is used throughout this paper to refer to statistical significance at the 5 percent level. The following steps were taken in the analysis.

1. The validity of the proportional hazard assumption was explored for all potential risk factors of interest. The assumption was valid for all such factors. Visual inspection of the baseline hazard rates in hairdressers and nurses indicated that these were not proportional over time, although the assumption of proportionality was not violated from the statistical point of view. Given the substantial differences in exposure conditions between hairdressers and nurses, separate analyses in both groups were initially performed. An overall relative risk of each factor in hairdressers and nurses combined was estimated by stratification on the type of training in this analysis, thus allowing for differences in the baseline hazard rate between the two groups.
2. The crude relative risk for each risk factor and its 95 percent confidence limits were estimated from the regression coefficients of a Cox regression model, modelling each risk factor separately. The presence of a linear relationship between transepidermal water loss and the risk of hand dermatitis

### *Individual susceptibility*

was investigated by modelling transepidermal water loss as a continuous variable. This gives an estimate of the relative risk of hand dermatitis per  $\text{g}/\text{m}^2\cdot\text{h}$  increase in transepidermal water loss. As an alternative, 'intermediate' and 'high' TEWL values were modelled as indicator variables to estimate the relative risk as compared with 'low' TEWL values.

3. Adjusted estimates of the relative risk were obtained by including more than one potential risk factor in the regression model. Variables were included in the model if they contributed significantly to it ( $p < 0.05$ ) or if they meaningfully altered the estimate of the relative risk for the variable of interest.

## **Results**

### *Completeness of the study*

Four hairdressers left school and were lost to follow-up after a minimum observation period of 22 weeks. Six apprentice nurses were lost during the first school year of observation for several reasons which were unlikely to be related to hand dermatitis (left school, lost interest in the study, lack of time, illness or accident). Thirteen apprentice nurses of the first group were lost in the second school year, mostly because they had a different schedule for practical work.

Patch test readings were obtained in 97 percent of the apprentice hairdressers and in 75 percent of the apprentice nurses. Prick tests were performed in 99 percent of the hairdressers and 78 percent of the nurses. The major reasons for refusal of dermatologic tests were fear or inconvenience. Prior dermatologic testing was not given as a reason for refusal by any of the subjects.

### *Characteristics of the study population*

Table 1 shows baseline characteristics of the 74 hairdressers and 111 nurses who contributed person-time to the study. The study population of apprentice hairdressers was four years younger on the average than apprentice nurses and contained a higher proportion of men. The proportion of self-reported (atopic) mucosal symptoms was higher in hairdressers than in nurses, whereas the proportion of sensitized subjects and the proportion of subjects with a dry skin were

smaller among hairdressers. A history of (atopic) mucosal symptoms was strongly related to the presence of one or more positive prick tests. Nevertheless, 10 percent (5/50) of the hairdressers and 10 percent (7/70) of the nurses without (atopic) mucosal symptoms showed a positive response to the prick tests, while 53 percent (8/15) of hairdressers and 50 percent (5/10) of the nurses with a positive history of mucosal symptoms showed a negative response to all prick tests. No significant relationship was observed between a history of childhood eczema and the results of prick tests or patch tests. Before the start of the study, 35 percent of the apprentice hairdressers had been occasionally involved in hairdresser's activities, mainly hair washing and drying. None of the nurses had been working as a nurse before the start of the study.

**Table 1** Baseline characteristics of the study population of apprentice hairdressers and nurses, Groningen, The Netherlands, 1990-1992.

Characteristic	Apprentice hairdressers		Apprentice nurses	
	n		n	
<b>Mean <math>\pm</math> SD*</b>				
Age (years)	74	17.9 $\pm$ 1.6	111	22.0 $\pm$ 2.5
TEWL <sup>+</sup> on the hand (g/m <sup>2</sup> .h)	74	8.5 $\pm$ 3.3	111	9.8 $\pm$ 3.2
TEWL <sup>+</sup> on the forearm (g/m <sup>2</sup> .h)	74	6.1 $\pm$ 1.9	111	6.5 $\pm$ 1.5
<b>Percentage</b>				
Men (%)	74	23.0	111	6.3
Childhood eczema (%)	74	8.1	111	6.3
(Atopic) mucosal symptoms (%)	74	23.0	111	11.7
Dry skin (%)	74	6.8	111	13.5
One or more positive prick tests (%)	70	17.1	87	13.8
One or more positive patch tests (%)	71	23.9	83	32.5
Positive patch test to nickel (%)	71	14.1	83	24.1

\* SD, standard deviation

<sup>+</sup> TEWL, transepidermal water loss (g/m<sup>2</sup>.h)

### *Individual susceptibility*

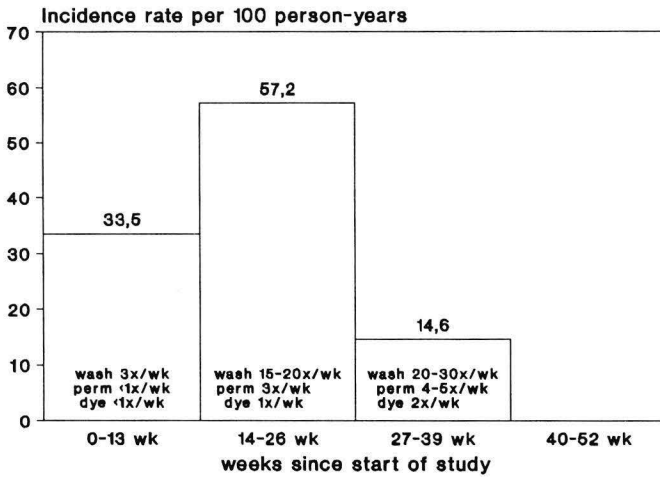
The mean transepidermal water loss of the hand in hairdressers was 1.3 g/m<sup>2</sup>.h less than that in nurses. No difference was observed between hairdressers and nurses in transepidermal water loss on the forearm. The measurement conditions were different on the six occasions that baseline measurements were performed. However, the differences in mean transepidermal water loss were not associated with differences in the measurement conditions.

### *Incidence of hand dermatitis*

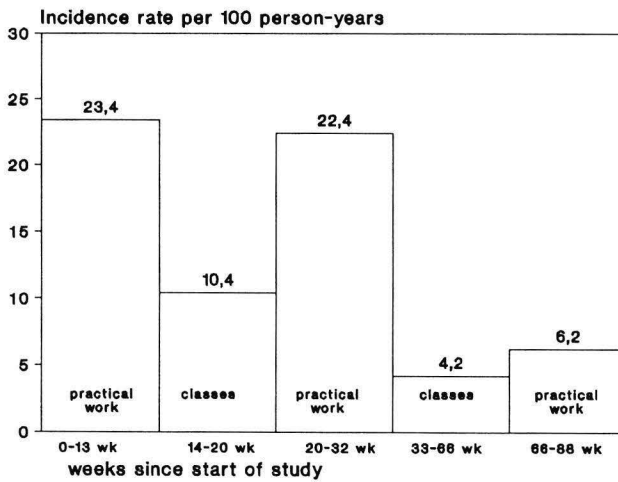
Seventeen hairdressers and 16 nurses developed hand dermatitis while they were under observation. In most cases, the symptoms were mild to moderate and occurred periodically. None of the apprentices discontinued their training due to hand dermatitis. However, one hairdresser who was diagnosed as having hand dermatitis during the study consulted the dermatology clinic within six months after she had been professionally employed. The average observation time was 36 weeks in hairdressers (2,691 person-weeks in total) and 52 weeks in nurses (5,747 person-weeks in total).

The type and intensity of exposure was fairly homogeneous within the study population of hairdressers. Figure 2 shows that the exposure frequency during hair washing, permanent waving and hair tinting, steadily increased during the practical training. The incidence rate was highest in the period of between three to six months after the start of the training and greatly declined afterwards. The average incidence rate in hairdressers was 32.8 cases per 100 person-years of observation. To enable comparison of the incidence rate per 100 person-years with results from other studies the cumulative incidence was calculated according to equation 1. Thus, the one-year cumulative incidence was 27.9 percent.

In apprentice nurses, the average incidence rate of hand dermatitis over the total study period was 14.5 cases per 100 person-years of observation (one-year cumulative incidence of 13.5 percent). The incidence rate was highest during the first two periods of practical training and was lower during periods of classes and during the last period of practical training (Figure 3). The difference in incidence rates between the periods was not significant. The average incidence rate in the first school year was 19.8 cases per 100 person-years of observation.



**Figure 2** Incidence rate of hand dermatitis in hairdressers in relation to time since start of the apprenticeship and exposure, Groningen, The Netherlands, 1990-1992



**Figure 3** Incidence rate of hand dermatitis in nurses in relation to time since first period of practical work, Groningen, The Netherlands, 1990-1992



In the second year, the average incidence rate was 5.2 cases per 100 person-years of observation. The type and intensity of exposure in apprentice nurses were more heterogeneous than in hairdressers. It depended mainly on the type of institution in which the period of practical work was spent. Hands were washed more frequently in general hospitals and nursing homes (varying from 10 to 40 times per shift on the average) than in institutions for psychiatric patients and for mentally defective patients (less than five times per shift on the average). Differences in frequency of washing and changing of patients were less marked between these two types of institutions; nevertheless, they showed some variation between individuals.

*Relation between baseline characteristics and the incidence rate of hand dermatitis*

The crude and adjusted relative risks of developing hand dermatitis for the risk factors of interest are shown in Table 2. Adjustment for mucosal atopy and skin type altered the point estimates of the relative risk to some extent. Other endogenous risk factors made no significant contributions to the model, nor did they meaningfully influence the magnitude of the point estimates of these relative risks. The relative risk of a dry versus normal skin was elevated in hairdressers and in nurses; however, the increased risk was significant at the 5 percent level only in hairdressers. The relative risk of (atopic) mucosal symptoms was elevated in both groups as well, but the increase was significant at the 5 percent level only in nurses. The relative risks of skin type and mucosal atopy differed in magnitude between hairdressers and nurses, but these differences were not significant at the 5 percent level. The overall estimates, adjusted for type of training, showed a significant 2.5-fold increased relative risk for a mucosal atopy and a significant 3.2-fold increase in the relative risk for a dry skin. No significant association was observed between age, gender, childhood eczema or presence of a positive skin test (prick or patch test) and the risk of hand dermatitis. It is noted that the relative risks of atopy (as determined by prick tests), and of contact sensitivity (as determined by patch tests), were increased by a factor of about 2 in hairdressers, although the increased risk was not significant at the 5 percent level.

**Table 2** Crude and adjusted relative risks of hand eczema in apprentice nurses and hairdressers, Groningen, The Netherlands, 1990-1992.

Variable	Hairdressers			Nurses			Total <sup>+</sup>		
	Crude RR <sup>+</sup>	Adjusted RR <sup>++</sup> §	95% CI <sup>+</sup>	Crude RR <sup>+</sup>	Adjusted RR <sup>++</sup> §	95% CI <sup>+</sup>	Crude RR <sup>+</sup>	Adjusted RR <sup>++</sup> §	95% CI <sup>+</sup>
<b>Gender</b>									
Men vs women	1.5	1.1	0.3-4.0	1.1	0.9	0.4-3.3	1.3	1.1	0.4-3.3
<b>Childhood dermatitis</b>									
Positive vs negative	0.6	0.4	0.1-6.8	1.0	1.2	0.1-9.0	0.8	0.7	0.2-3.2
<b>(Atopic) mucosal symptoms</b>									
Positive vs negative	1.6	2.2	0.7-6.7	3.1	3.4*	1.05-11.2	2.1	2.5*	1.1-5.7
<b>Skin type</b>									
Dry vs normal/oily	5.7*	7.3**	2.2-24.3	1.4	1.7	0.5-6.4	2.6*	3.2**	1.3-7.8
<b>Prick test<sup>  </sup></b>									
One or more positive vs all negative	1.6	2.2	0.7-7.2	0.6	0.6	0.1-4.9	1.2	1.4	0.5-3.9
<b>Patch test<sup>  </sup></b>									
One or more positive vs all negative	2.2	1.8 <sup>†</sup>	0.6-5.0	1.5	1.5 <sup>†</sup>	0.5-4.6	1.8	1.7 <sup>†</sup>	0.8-3.6
<b>Patch test to nickel<sup>  </sup></b>									
Positive vs negative	2.4	1.7 <sup>†</sup>	0.5-5.5	1.0	1.1 <sup>†</sup>	0.3-4.0	1.6	1.5 <sup>†</sup>	0.6-3.5

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**Table 2** continued

Variable	Hairdressers			Nurses			Total <sup>+</sup>		
	Crude	Adjusted	95% CI <sup>‡</sup>	Crude	Adjusted	95% CI <sup>‡</sup>	Crude	Adjusted	95% CI <sup>‡</sup>
	RR <sup>‡</sup>	RR <sup>‡§</sup>		RR <sup>‡</sup>	RR <sup>‡§</sup>		RR <sup>‡</sup>	RR <sup>‡§</sup>	
<b>TEWL<sup>-</sup> on the forearm</b>									
per g/m <sup>2</sup> h	1.16	1.19	0.94-1.52	1.07	1.07	0.8-1.44	1.12	1.12	0.93-1.35
intermediate vs low	1.3	2.4	0.6-9.6	0.5	0.5	0.1-1.9	0.8	0.9	0.4-2.4
high vs low	1.4	2.2	0.7-7.7	1.1	1.2	0.4-4.1	1.3	1.5	0.7-3.4
<b>TEWL<sup>-</sup> hand</b>									
per g/m <sup>2</sup> h	1.14	1.14	0.98-1.29	0.98	0.98	0.84-1.14	1.05	1.05	0.94-1.15
intermediate vs low	2.2	2.2	0.7-6.9	1.6	2.0	0.5-8.0	1.9	2.1	0.9-5.1
high vs low	1.4	1.6	0.5-5.4	1.5	1.6	0.4-6.4	1.5	1.5	0.6-3.6

\* 0.01 < p < 0.05

\*\* p <= 0.01

+ combined estimate of relative risk adjusted for type of training by stratification in the analysis

‡ relative risk (RR) with 95% confidence interval (CI)

§ relative risk adjusted for skin type and (atopic) mucosal symptoms

|| based on incomplete dataset because of missing values on the skin tests,

† relative risks are adjusted for skin type only, since (atopic) mucosal symptoms was highly correlated with prick test results

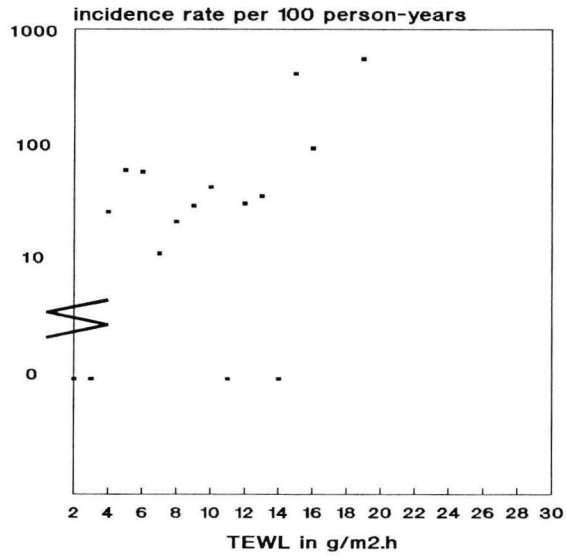
- TEWL, transepidermal water loss (g/m<sup>2</sup>.h)

Individual susceptibility

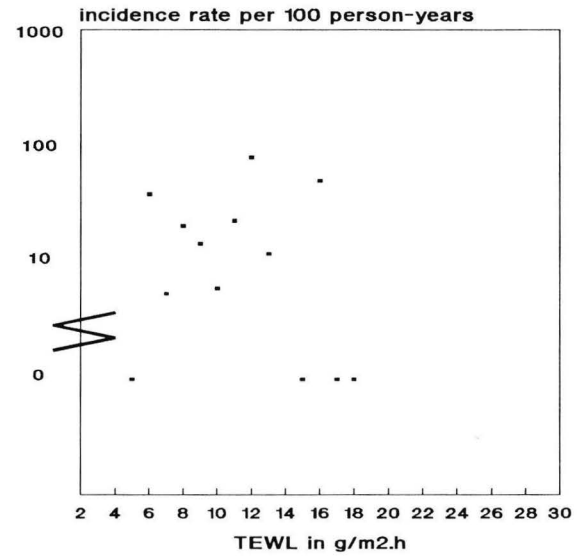
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The lack of a relationship with transepidermal water loss as a continuous variable indicates that there was no linear increase in risk of hand dermatitis with increasing transepidermal water loss on the hand or the forearm. Adjustment for temperature and humidity of ambient air did not alter the estimates of the relative risk. To visualize the relationship, figure 4 and 5 show the average incidence rate of hand dermatitis per gram increase in transepidermal water loss on the hand in hairdressers and nurses, respectively. It is noted that the average incidence rate in some categories of transepidermal water loss is based on small numbers of subjects.

Figure 4 (hairdressers) suggests that for transepidermal water loss below  $15 \text{ g/m}^2\cdot\text{h}$ ., there is no clear relationship with the incidence rate, whereas the incidence rate is elevated for transepidermal water loss above  $15 \text{ g/m}^2\cdot\text{h}$ . Figure 5 (nurses) provides no evidence for a relationship between transepidermal water loss on the hand and the incidence of hand dermatitis. The crude relative risks of 'intermediate' and 'high' transepidermal water loss on the hand and the forearm were not significantly elevated. After adjustment for mucosal atopy and skin type, the point estimates of the relative risk increased slightly to about two in hairdressers, but remained nonsignificant at the 5% level.



**Figure 4** Incidence rate of hand dermatitis in hairdressers in relation to TEWL on the hand, Groningen The Netherlands, 1990-1992



**Figure 5** Incidence rate of hand dermatitis in nurses in relation to TEWL on the hand, Groningen, The Netherlands, 1990-1992

*Individual susceptibility*

## Discussion

The incidence rate of hand dermatitis was higher in hairdressers than in nurses (32.8 versus 14.5 cases per 100 person-years). It is likely that differences in the type and intensity of exposure between hairdressers and nurses are responsible for the differences in incidence rates. A previous study among apprentice hairdressers<sup>16</sup> showed that about one third of them developed skin changes during the first year of their training. The one-year cumulative incidence of about 28 percent that was found among hairdressers in the present study is similar to that.

The cumulative incidence of hand dermatitis in nurses over the entire study period of 21 months was 21.8 percent. This can be compared with results from two previous studies. In a Swedish study, 41 percent of the newly employed nurses reported hand dermatitis over a period of 20 months on the average.<sup>2</sup> The cumulative incidence in a retrospective study among newly employed nurses who were free of hand dermatitis at the start of employment was 9.0 percent over a period of 18 months on the average.<sup>26</sup> The differences may result from differences in the exposure history of the study population. The present study involved apprentices who were not occupationally exposed before the start of the study. Both of the other studies involved newly employed nurses, most of whom had been previously exposed as a nurse. The Swedish study may have overestimated the incidence, since nurses who suffered from hand eczema at the start of employment due to previous exposure were included in the study. The reported 41 percent should therefore rather be interpreted as a "period prevalence". The retrospective study may have underestimated the incidence rate because nurses with previous hand dermatitis were excluded, which may imply that the study population consisted of less susceptible nurses.

The presence of a dry skin and a positive history of (atopic) mucosal symptoms were associated with the risk of hand dermatitis. Since these characteristics were recorded at the start of apprenticeship, the association cannot have been influenced by subsequent occupational exposure or hand dermatitis. The relationship between hand dermatitis and the presence of a dry skin was observed in a previous study among hairdressers and bricklayers.<sup>8</sup> An

### *Individual susceptibility*

experimental study demonstrated that individuals with dry skin reacted more strongly to exposure to irritants.<sup>9</sup> Other studies found that dry skin was a risk factor, particularly in combination with atopic dermatitis<sup>27</sup> or with atopic mucosal symptoms.<sup>28</sup> However, dry skin is known to be a diagnostic feature of atopic dermatitis.<sup>29</sup> In the present study, skin dryness was not associated with atopic dermatitis or atopic mucosal symptoms, suggesting that atopy cannot explain the association with a dry skin. Dry skin may also be an early manifestation of hand dermatitis resulting from previous involvement in wet work such as household chores, hairdressing or nursing activities. Although the populations in this study were selected because previous occupational exposure was unlikely, it appeared that 35 percent of the hairdressers had occasionally been involved in hairdressing activities occasionally before the start of the study. Inspection of the data showed that the presence of a dry skin was not associated with previous exposure or with a history of childhood eczema. This suggests that dry skin, at least in the present study, represents a risk factor for hand dermatitis per se, rather than an early manifestation of hand dermatitis.

The association between (atopic) mucosal symptoms and the risk of hand dermatitis was also observed in previous studies.<sup>5,30</sup> No association was observed in other studies.<sup>3,4</sup> However, the biologic mechanism that can explain how (atopic) mucosal symptoms are related to hand dermatitis is not fully understood. Also, the validity of self-reported atopic mucosal symptoms is unknown. About 50 percent of the subjects who reported (atopic) mucosal symptoms responded negatively to the prick tests. This suggests some overreporting of (atopic) mucosal symptoms, although local allergic reactions may occur in spite of negative skin tests. The absence of an association between hand dermatitis and a positive prick test indicates that the mechanism responsible for an elevated risk of hand dermatitis is closer related to the mucosal symptoms than to an atopic constitution, as determined by prick tests.

The lack of an association with childhood eczema in the present study is inconsistent with results from other studies suggesting that childhood eczema was the most important risk factor for hand dermatitis.<sup>3,4</sup> It is possible that our study lacked power to detect a potential association, because the study population contained only a small number of persons with childhood eczema.

Furthermore, four individuals with atopic dermatitis who presented with hand dermatitis at the start of the study were excluded from the analysis. They were examined at each follow-up measurement and hand dermatitis continued to exist throughout the study.

The risk of hand dermatitis in nickel sensitive apprentices was not significantly increased. However, this finding is inconclusive, because it not clear whether exposure to nickel or other sensitizing agents had occurred in the study population. The absence of a relation between the risk of hand dermatitis and age or gender is in agreement with results from other studies.<sup>13,31</sup>

Finally, the present study does not support the hypothesis that baseline transepidermal water loss is an indicator for the risk of hand dermatitis. The results suggested that hairdressers may have an increased risk of hand dermatitis at transepidermal water loss levels on the hand above 15 g/m<sup>2</sup>.h, but the increased risk was not statistically significant. No evidence of a relationship was observed in nurses. At present, no other epidemiologic studies are available to refute or confirm the lack of an association between transepidermal water loss and the risk of hand dermatitis. It has been suggested that transepidermal water loss merely reflects the barrier function of the skin for substances with physical chemical properties similar to those of water,<sup>32</sup> whereas occupational exposure of nurses and hairdressers may involve other types of chemicals as well. The lack of a clear relationship in this study would seem to confirm that suggestion. If a true relationship between transepidermal water loss and the risk of hand dermatitis exists, it is possible that it would not have been observed in this study. Firstly, it can be argued that the size of the current study (in terms of number of subjects and duration of follow-up) was too small to show a significant increase in the risk of hand dermatitis at increased levels of transepidermal water loss. Secondly, a (duplicate) measurement of transepidermal water loss on a single occasion may not accurately reflect the long-term average transepidermal water loss, which may have obscured a true relationship. A preliminary study indicated that the intra-individual variability of transepidermal water loss over a period of three weeks was 15.1 percent, suggesting that transepidermal water loss was relatively stable over that period.<sup>33</sup> Nevertheless, a period of three weeks is too short to evaluate seasonal fluctuations and it is likely that



### *Individual susceptibility*

these fluctuations are greater over longer periods of time (months, seasons, years). If great fluctuations in long-term transepidermal water loss occur, more than one measurement over a longer period of time should be made before the start of exposure to assess the long-term average transepidermal water loss. However, from a practical point of view, this would limit the value of transepidermal water loss as a predictor for the risk of hand dermatitis.

In summary, the incidence rate of hand dermatitis was increased in apprentices, especially in hairdressers with dry skin, which is biologically plausible. Apprentices with a history of (atopic) mucosal symptoms, particularly nurses, had an increased risk of hand dermatitis. A relationship has been observed in other studies, but a biologic mechanism that could explain this finding is not fully understood. The results of the study are inconclusive with respect to a potential association between an elevated level of transepidermal water loss and the risk of hand dermatitis. A larger study and a more precise assessment of the long-term average transepidermal water loss is needed to clarify a possible relationship.

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## 9. General discussion

### **Introduction**

Hand dermatitis is commonly observed in a variety of industries. Although it is not life threatening, the symptoms are perceived as troublesome in daily life. It is known to be a disease which tends to become chronic.<sup>1,2,3</sup> In severe cases, it may take months or even years for the skin to heal completely, particularly when exposure continues to exist. Epidemiologic research may shed more light on the etiology of hand dermatitis in combination with experimental and clinical investigations.

The investigations presented in this thesis deal with (1) the development and evaluation of a method for identifying cases of hand dermatitis in population-based studies, (2) the prevalence and incidence of hand dermatitis and (3) endogenous factors that may play a role in the causation of hand dermatitis.

### **Case ascertainment**

Morbidity or mortality statistics, which form the basis of many studies on chronic diseases, do not provide adequate information on the incidence or prevalence of hand dermatitis because hand dermatitis rarely leads to hospitalization or death.<sup>4-6</sup> Systematic methods for the ascertainment of cases of hand dermatitis that were used in other population-based studies, varied from intensive efforts by a medical examination of the complete study population<sup>7-9</sup> to the relatively easy-to-apply method of self-administered questionnaires.<sup>10-13</sup> No standardized methods for case ascertainment were available because the methods used in other studies were, with few exceptions, not clearly documented or made available through publication. Thus, the potential for quantitative comparison of prevalence figures is limited.

Case ascertainment in the studies presented in this thesis, was based upon a standardized self-administered questionnaire on symptoms of hand dermatitis and their frequency and duration. Criteria for the definition of hand dermatitis are described in chapter 4. Comparison of the questionnaire-based diagnosis with a diagnosis that was made by a dermatologist, showed that the questionnaire was highly sensitive in detecting potential cases of hand dermatitis. However, a large

proportion of the cases consisted of individuals with mild symptoms that were not considered to be clear cases of hand dermatitis according to the dermatologist. Only a small proportion of the cases, detected by the questionnaire, consisted of individuals with other skin disorders.

For etiologic studies, it is preferable to exclude mild cases of hand dermatitis and individuals with other skin disorders by examination of the hands because inclusion of those cases may dilute estimates of the relative risk. Although it will overestimate the prevalence of hand dermatitis, the questionnaire without subsequent dermatological evaluation appeared to be a relatively objective method in studies for identifying high-risk groups.

### **Prevalence of hand dermatitis in different occupational groups**

Estimates of the prevalence of hand dermatitis in the general population vary between 2 and 10%.<sup>7-13</sup> In most studies, the prevalence among women was twice as high as among men, which is assumed to reflect a higher exposure among women to wet work in daily life. The prevalence figures in different occupational groups are mostly higher than in the general population and may be as high as 30-40% in occupational groups with heavy exposure.<sup>8,13</sup> However, as was mentioned before, the prevalence figures could not be compared quantitatively because of differences in the method for case ascertainment.

To tackle this problem, the validated questionnaire (without subsequent medical examination) was applied in a series of cross-sectional surveys among different occupational groups and in a sample of the general population (chapter 5). The prevalence of hand dermatitis in the general population (5% among men and 10% among women) was in the same range as the prevalence that was observed in previous studies.<sup>7-13</sup> The prevalence of hand dermatitis among manual workers in a chemical company, an electricity company and public works was 2-3 times as high as in the general population, whereas the prevalence in non-exposed office workers was comparable to that in the general population. The manual workers experienced low or moderate exposure to irritants or allergens and the risk of hand dermatitis was not expected to be largely increased. This suggests that low or moderate exposure

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to irritants or allergens in combination with mechanical stress which occurs frequently in manual work, is sufficient to cause an increased risk of hand dermatitis.

The prevalence of hand dermatitis was highest in nurses, known to be heavily exposed to "wet work" (approximately 30%). The crude prevalence was equal in men and women, but the prevalence ratio in comparison with the general population was higher in men than in women, partly due to a higher background rate among women in the general population. The approximately equal prevalence in male and female nurses who experience similar exposure, supports the view that a higher prevalence of hand dermatitis among women in the general population rather reflects a heavier exposure in daily life than an increased susceptibility to hand dermatitis in women. Hairdressers, who are known to have a high risk as well and who were studied in the prospective study in this thesis, were not included in the prevalence study.

The prevalence figures as determined by the validated questionnaire involve episodes of symptoms during the period of one year. The prevalence includes individuals with long-lasting hand dermatitis as well as relatively recent cases and thus possesses all interpretational difficulties that are inherent to a period prevalence.<sup>14</sup> In particular, no inference can be made with respect to the relationship between exposure and hand dermatitis because the exposure that caused the symptoms may have changed over time, past exposure may be over- or underestimated by cases and preventive measures may have been taken after symptoms occurred. The point prevalence at one short time interval is less informative, given the recurrent character of symptoms.

Thus, prevalence figures may be useful to detect high risk occupations, when the limitations are kept in mind. However, incidence figures are preferred for investigations on risk factors for hand dermatitis.

### **Incidence of hand dermatitis in nurses and hairdressers**

Based on two consecutive cross-sectional studies, the incidence of hand dermatitis in the general population was estimated as 0.79 cases per 100 persons per year.<sup>9</sup> There are no other estimates of the incidence of hand dermatitis in the general population or in occupational groups.

Within the framework of this thesis, the incidence rate of hand dermatitis was estimated in newly employed nurses and office employees (chapter 6), and in apprentice nurses and apprentice hairdressers (chapter 8). The incidence rate among occupationally non-exposed office employees who were newly employed by a university hospital, was 1.2 cases per 100 person-years (chapter 6). This is in reasonable agreement with the previous estimate of 0.79 cases per 100 person-years in the general population.<sup>9</sup>

The incidence rate of hand dermatitis among nurses who were newly employed by a university hospital was 7.8 cases per 100 person-years. Compared with office workers, the incidence rate was approximately 6 times as high, which is presumably due to heavy occupational exposure in nurses. It was suggested that the incidence rate among apprentice nurses would be higher than among newly employed nurses because the majority of the newly employed nurses had been working as a nurse previously and only those who were free of hand dermatitis were eligible for the study. This group is likely to be less susceptible. The observation that the incidence rate in apprentice nurses was higher (14.5 cases per 100 person-years) supports this view.

The incidence rate among apprentice hairdressers (32.8 cases per 100 person-years) was more than twice as high as that among nurses. The type and intensity of exposure differed substantially between hairdressers and nurses. The results suggest that the occupational exposure in hairdressers is more harmful to the skin than that in nurses.

None of the apprentices who acquired hand dermatitis during the study, had called sick for these symptoms during the study. The duration of follow-up in the prospective study was too short to give a prognosis on the further development of hand dermatitis during their professional career.

## **Risk factors**

Occupational exposure to irritants or allergens plays an important role in the causation of hand dermatitis.<sup>15</sup> Environmental factors such as low humidity of ambient air, high temperatures, occlusion and sweating may contribute to the occurrence of hand dermatitis by damaging the surface of the skin and facilitating penetration of irritants

and allergens.<sup>16,17</sup> However, not all individuals are equally susceptible to the development of hand dermatitis even if they experience similar exposure. Atopic constitution is known to be a risk factor for hand dermatitis, in particular for irritant contact dermatitis.<sup>18-21</sup> Atopic dermatitis is more often observed to be a risk factor than mucosal atopy, but a biological mechanism is unknown for both characteristics. Dry skin is also known to be a risk factor but it is not clear whether this is a feature of atopic dermatitis, an early manifestation of hand eczema due to previous exposure, or a risk factor in itself.<sup>22,23</sup> Over the last decade, several authors<sup>24-26</sup> have suggested that baseline pre-exposure transepidermal water loss (TEWL) could serve as an indicator of individual susceptibility to the development of contact dermatitis. The biological mechanism underlying this hypothesis is that a diminished barrier function of the skin, reflected by an increased TEWL, allows harmful agents to pass through the stratum corneum more easily and cause damage in the underlying layers of the skin. If a causal relationship between hand dermatitis and atopic constitution or dry skin is mediated by an impaired barrier function, TEWL may be expected to be increased in atopics or individuals with dry skin.

Chapter 8 reports on a prospective study among apprentice hairdressers and nurses that was undertaken to investigate the relationship between hand dermatitis and atopic background, contact allergy, type of skin and TEWL. In this study, an increased risk of hand dermatitis was observed in apprentices with a dry skin on the hands and in apprentices with (atopic) mucosal symptoms. No significant association was found between hand dermatitis and contact sensitivity, childhood eczema or TEWL. The association between mucosal atopy and hand dermatitis is in correspondence with the expectation but the lack of an association with childhood dermatitis or atopic dermatitis is not. It is possible that the design of the prospective study was inadequate to investigate a relationship because those individuals who presented with hand dermatitis at the start of the study were (by definition) excluded from analyses on incidence of hand dermatitis. However, they continued to suffer from hand dermatitis during apprenticeship. In one retrospective study by Rystedt<sup>20</sup> which observed a strongly increased risk of hand dermatitis among atopics, the study population consisted of patients who had previously consulted a dermatology clinic for atopic dermatitis and used non-atopic patients as a reference group. In our prospective study, the number of apprentices who reported childhood eczema was



relatively small. Thus, the study by Rystedt<sup>20</sup> probably had more power to detect a relationship with atopic dermatitis than the present prospective study. It is noted that the validity of self-reported atopic constitution is unknown. Given the prospective study design, it is unlikely that (atopic) mucosal symptoms were overreported by apprentices who later developed hand dermatitis. This is strengthened by the lack of an association with childhood dermatitis. However, the size of a relative risk may have been underestimated due to imprecise assessment of atopic constitution.

Imprecise assessment of atopic constitution also implies that it can not be adequately adjusted for as a confounder. Thus, the observed association with dry skin may be confounded to some extent by atopic constitution although no association between dry skin and atopic constitution was observed in the data. Given the size of the relative risk of dry skin in hairdressers, it is unlikely that the increased risk of a dry skin is completely accounted for by the confounding effect of atopy. Also, there was no evidence that previous exposure before the start of apprenticeship, was responsible for the relationship with a dry skin. Differential overrecording of a dry skin in individuals who are going to develop hand dermatitis later in the study is unlikely. Thus, the results of the prospective study indicate that a dry skin is an independent risk factor for hand dermatitis.

The lack of an association with TEWL is inconclusive. A relationship may be absent if, as was suggested<sup>27</sup>, TEWL only reflects the barrier function for agents with physical-chemical properties of water. However, a true relationship may be obscured due to imprecise assessment of long-term average TEWL. The intra-individual variation in TEWL over a period of 3 weeks was approximately 15% (chapter 7). This is likely to be higher over a longer period of time. Performance of measurements on more than one occasion, to improve the precision of the long-term average TEWL, is needed to shed more light on a potential relationship.

### **Future prospective studies**

Some methodologic considerations which were taken into account in the prospective study and which may be relevant for the planning of future prospective studies are summarized below.

### *General discussion*

1. A prospective study is the only valid study design when the role of endogenous risk factors is to be studied. Some endogenous factors, in particular TEWL and contact sensitivity are not stable over time because they also act as intermediates in the causal pathway between exposure and clinically manifest hand dermatitis. Contact sensitivity for example, may be induced by occupational exposure and may subsequently cause hand dermatitis. Also, the barrier function of the skin may decrease as a result of exposure to irritants or allergens, which further facilitates the passage of these agents. Once this process has resulted into clinically manifest hand dermatitis, the barrier function is usually severely impaired. Therefore, it is necessary to assess these factors before exposure takes place.
2. A study among apprentices who are going to experience occupational exposure for the first time, is preferred to a newly employed study population because part of the latter population is likely to have been exposed previously. Excluding individuals with hand dermatitis before the start of the study would leave less susceptible individuals to be included in the study. Although this does not necessarily bias the results of the study, the study will be less efficient in identifying endogenous risk factors.
3. The type and intensity of exposure should be fairly homogeneous within the study population. Although exogenous and endogenous characteristics may be risk factors in itself, a combination of both may increase the risk disproportionately. Thus, occupational exposure may act as a confounder when the effect of endogenous risk factors is to be assessed. This can be controlled for in the study design by ensuring that exposure conditions are homogeneous within the study population and are unrelated to the endogenous characteristics under study. Apprentices are particularly suitable in that respect. However, this implies that a potential relationship with occupational exposure is more difficult to detect, unless the study population is very large and the effect of exposure is strong.
4. Case ascertainment should take place at regular short intervals of a few months. The shorter the intervals, the larger the probability to make an accurate diagnosis of hand dermatitis and to accurately determine the date of onset. As intervals get larger, the diagnosis of hand dermatitis will necessarily rely more on self-reported information by the responder.

5. Exclusion of individuals who present with hand dermatitis at the start of the study, implies that the role of atopic dermatitis is more difficult to assess because a large proportion of the atopics would be excluded from the study.

### *Desiderata*

The prospective study presented in this thesis, focussed on the role of endogenous risk factors. A similar study design is useful to study the effects of exogenous factors and, if the study population is sufficiently large, the interaction between endogenous and exogenous factors. If the contribution of specific agents is to be studied, accurate exposure information must be collected in each follow-up period and exposure should be treated as a time dependent variable in the analysis.

To obtain more precise estimates of the relative risk of atopic background, the method for assessing the presence of an atopic constitution should be improved and validated. A combination of a medical history taken by a physician and a clinical examination, such as attempted in the Erlangen Criteria of Atopic Skin Diathesis<sup>28</sup>, may give more reliable information than a self-administered questionnaire. More clinical and experimental research is needed to clarify the mechanism that is responsible for the association between an atopic constitution and the risk of hand dermatitis.

The results of the present study indicate that further research is needed to investigate the predictive value of transepidermal water loss for the development of hand dermatitis. In particular, the need for research on fluctuations in transepidermal water loss over longer periods of time is emphasized. If large fluctuations occur, it should be considered to perform baseline measurements of TEWL on more than one occasion over a longer period.

### **Conclusions**

The studies presented in this thesis deal with the description of the frequency and distribution of hand dermatitis in different occupational groups and with identification of endogenous risk factors for the development of hand dermatitis. The studies

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illustrate the contribution from application of epidemiological methods in the study of hand dermatitis.

Estimates of the prevalence of hand dermatitis, based on a standardized method for case ascertainment were in the same range as those from previous studies. The advantage of a standardized method was that prevalence figures in different study populations, measured at different points in time can be compared quantitatively. The prevalence of hand dermatitis in occupational groups, known to be at high risk for hand dermatitis, such as nurses, was strongly elevated. However, a moderately elevated prevalence was also observed in occupations with low to moderate exposure to irritants and allergens.

The standardized method for case ascertainment can also be used to estimate the incidence of hand dermatitis in occupational groups or subgroups of the general population. The present study demonstrated that almost 30% of the apprentice hairdressers and 20% of the apprentice nurses develop hand dermatitis in the first year of their practical training. The most important risk factors were skin dryness and a history of atopic mucosal symptoms.

Further studies are necessary to unveil why, under similar working conditions, some individuals develop hand dermatitis and others do not.

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## Summary

Hand eczema or hand dermatitis is a well-known problem in occupations with regular exposure to water and irritating agents ("wet work"). It is experienced frequently by nurses, hairdressers, housewives, food handlers and metal workers. Although hand dermatitis is a relatively infrequent cause of sick leave and medical care is sought by only a proportion of the cases, the symptoms are mostly perceived as troublesome in daily occupational and social life. Moreover, once these symptoms have given rise to a period of sick leave, this period tends to be relatively long.

The objectives of this thesis were (1) to assess the prevalence and incidence of hand dermatitis in different occupational groups, using a standardized method for case ascertainment and (2) to investigate the role of endogenous risk factors in the development of hand dermatitis.

Estimates of the prevalence of hand dermatitis in the general population vary between 2 and 10%. In most studies, the prevalence among women was twice as high as among men, which is assumed to reflect a higher exposure among women to wet work in household activities. The prevalence figures in different occupational groups are mostly higher than in the general population and may be as high as 30-40% in occupational groups with heavy exposure. However, no quantitative comparison of prevalence figures can be made due to substantial differences in the methods for case ascertainment. Within the framework of this thesis, a standardized questionnaire was developed and evaluated in a population of 109 nurses (Chapter 4). The questionnaire-based diagnosis of hand dermatitis was compared with a diagnosis made by a dermatologist. The results demonstrated that the questionnaire was highly sensitive in detecting cases of hand dermatitis, but the symptoms were mild in the majority of the cases. Less than 1% of the cases consisted of individuals with other skin disorders. The questionnaire may therefore be an efficient method for case ascertainment in relatively large study populations if subsequent examination of the hands is performed in individuals with a positive questionnaire-based diagnosis of hand dermatitis. Without subsequent dermatological evaluation, the questionnaire will provide a prevalence figure that includes a large proportion of mild cases. However, since the definition of hand dermatitis is based on objective criteria that are unknown to the responders, it can be used as a standardized method to compare prevalence figures between study populations.

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The prevalence of hand dermatitis in different occupational groups was estimated by administering the standardized questionnaire in a series of surveys among workers of a chemical company, a municipal electricity company, municipal public works, nurses and surgical assistants (Chapter 5). A survey in a sample of the general population was performed to obtain a reference estimate of the prevalence. The prevalence of hand dermatitis in the general population was 5.2% in men and 10.6% in women. The prevalence of hand dermatitis among the occupational groups ranged from 2.9% in office workers to approximately 30% in nurses. The results demonstrated that nurses (heavy exposure) as well as manual workers (low to moderate exposure to irritants in combination with mechanical stress) have an elevated prevalence of hand dermatitis in comparison with the general population, whereas the prevalence in office workers (without occupational exposure) is comparable to that of the general population.

Data on the incidence rate and induction time of hand dermatitis were not available from the literature. To assist the planning of a prospective study on risk factors for hand dermatitis, a retrospective cohort study was performed in nurses and office employees to obtain a rough estimate of the incidence rate and induction time of hand dermatitis in these occupational groups (Chapter 6). The study was performed among 371 nurses and 111 office employees who were newly employed by a university hospital between January 1, 1987 and December 31, 1988. The incidence rate was assessed retrospectively using the standardized questionnaire on hand dermatitis. It was estimated that the overall incidence rate was 7.8 cases/100 person-years in nurses and 1.2 cases/100 person-years in office employees. In nurses, 72% of the cases occurred within the first 3 months of follow-up. In the interpretation of these figures it should be taken into account that the majority of the nurses had been working as a nurse before start of employment by the University Hospital. To be eligible for the study these nurses had to be free of hand dermatitis at the start of the study and may thus represent a less susceptible group with a lower incidence rate. Therefore, it was concluded that it was preferred to perform a prospective study among apprentices who are less likely to have been occupationally exposed before entering the study.

Characteristics shown to be associated with hand eczema are atopic background (in particular atopic dermatitis), contact allergy (in particular nickel allergy) and



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skin dryness. Over the last decade, several authors have suggested that baseline pre-exposure transepidermal water loss (TEWL) could serve as an indicator of individual susceptibility to the development of hand dermatitis.

Before undertaking a prospective study to investigate this hypothesis, the intra- and inter-individual variability of TEWL was assessed under laboratory conditions (Chapter 7). The study was performed in 30 healthy individuals. The intra-individual coefficient of variation of TEWL measurements on 8 different sites on the forearm, was 13.5%. The intra-individual coefficient of variation of TEWL in 15 measurements over a period of 3 weeks was 15.1%. The intra-individual coefficients of variation were low compared to the inter-individual coefficients of variation. This suggested that transepidermal water loss can be studied as a personal characteristic in epidemiologic studies on hand dermatitis.

The role of atopic constitution, contact sensitization, skin dryness and TEWL in the development of hand dermatitis was investigated in a prospective study among 74 apprentice hairdressers and 111 apprentice nurses (Chapter 8). The average incidence rate was 32.8/100 person-years in hairdressers and 14.5 cases/100 person-years in nurses. The incidence rate of hand dermatitis was increased in apprentices, particularly in hairdressers, with a dry skin. Also, apprentices with a history of (atopic) mucosal symptoms, particularly nurses, had an increased risk of hand dermatitis. The results of the study are inconclusive with respect to a potential association between an elevated level of TEWL and the risk of hand dermatitis. A larger study and a more precise assessment of the long-term average TEWL is needed to clarify a possible relationship.

Chapter 9 discusses the main findings of the different chapters and gives some methodological considerations for future epidemiological studies on hand dermatitis.

## Samenvatting

Hand eczeem is een veelvoorkomend probleem in beroepen waarin regelmatig contact optreedt met water en irriterende stoffen ("nat werk"). Handeczeem komt bijvoorbeeld veel voor onder verpleegkundigen, kapsters, metaalbewerkers, voedingsbereiders en -verwerkers en huisvrouwen. Hoewel handeczeem slechts in een beperkt deel van de gevallen aanleiding geeft tot ziekteverzuim of doktersbezoek, wordt de aandoening in het dagelijks leven als zeer hinderlijk ervaren. Wanneer eenmaal ziekteverzuim is opgetreden blijkt dat de gemiddelde duur van het verzuim langer is dan gemiddeld.

De doelstellingen van dit proefschrift waren (1) het bepalen van de prevalentie en incidentie van handeczeem in verschillende beroepsgroepen, gebruik makend van een gestandaardiseerde methode voor het opsporen van personen met handeczeem en (2) het onderzoeken van de rol van endogene risicofactoren in de ontwikkeling van handeczeem.

Schattingen van de prevalentie van handeczeem in de algemene bevolking variëren van 2 tot 10%. In de meeste onderzoeken lag de prevalentie onder vrouwen ongeveer tweemaal zo hoog als die onder mannen. Dit is waarschijnlijk een gevolg van een hogere blootstelling van vrouwen aan "nat werk" tijdens het huishouden. De prevalentiecijfers in verschillende beroepsgroepen zijn meestal hoger dan in de algemene bevolking. In beroepsgroepen met intensieve blootstelling kan dit oplopen tot 30 à 40%. Vanwege aanzienlijke verschillen tussen onderzoeken, met name in de definitie van handeczeem en in de wijze waarop personen met handeczeem worden opgespoord, zijn de prevalentiecijfers van verschillende onderzoeken niet goed met elkaar te vergelijken. Daarom is een gestandaardiseerde vragenlijst ontwikkeld voor gebruik in epidemiologisch onderzoek. De vragenlijst werd geëvalueerd in een onderzoeksgroep van 109 verpleegkundigen (Hoofdstuk 4). De diagnose "handeczeem" gebaseerd op deze vragenlijst, werd vergeleken met de diagnose "handeczeem" zoals die werd gesteld door een dermatoloog. Uit het onderzoek bleek dat de vragenlijst een hoge sensitiviteit had voor het opsporen van personen met handeczeem, maar dat de meeste van deze personen slechts milde symptomen hadden. Minder dan 1% van de personen met een diagnose "handeczeem" gebaseerd op de vragenlijst, leed aan andere huid-aandoeningen dan handeczeem. De vragenlijst lijkt dan ook een efficiënte methode om personen met handeczeem op te sporen in omvangrijke onderzoekspopulaties, mits de personen met handeczeem vervolgens dermatologisch worden onderzocht

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zodat de personen met zeer geringe verschijnselen van handeczeem of personen met andere aandoeningen, kunnen worden uitgesloten. Wanneer geen aanvullend onderzoek van de handen plaatsvindt, zal de geschatte prevalentie van handeczeem aan de hoge kant zijn omdat een groot deel van de personen met handeczeem mogelijk slechts lichte symptomen heeft. De vragenlijst kan goed gebruikt worden als gestandaardiseerde methode voor het vergelijken van prevalentiecijfers tussen beroepsgroepen omdat de definitie van handeczeem in de vragenlijst gebaseerd is op objectieve criteria die niet bekend zijn bij de respondenten wanneer zij de vragenlijst invullen.

De gestandaardiseerde vragenlijst werd gebruikt in een aantal transversale onderzoeken naar de prevalentie van handeczeem bij werknemers van een chemische industrie, een gemeentelijk energiebedrijf, gemeentewerkers, verpleegkundigen en operatie-assistenten (Hoofdstuk 5). Ter vergelijking werd de vragenlijst toegepast in een onderzoek onder een steekproef van de algemene bevolking. De prevalentie van handeczeem onder de algemene bevolking was 5.2% bij mannen en 10.6% bij vrouwen. In de verschillende beroepsgroepen liep de prevalentie van handeczeem uiteen van 2.9% bij kantoorpersoneel tot 30% bij verpleegkundigen. Het bleek dat niet alleen verpleegkundigen, met hoge blootstelling aan water en irriterende stoffen, een verhoogde prevalentie van handeczeem hadden in vergelijking met de algemene bevolking, maar ook productiepersoneel met lage of matige blootstelling aan irriterende stoffen. Dit is mogelijk een gevolg van combinatie met mechanische belasting van de huid bij handmatig werk. De prevalentie van handeczeem bij kantoorpersoneel, zonder noemenswaardige beroepsmatige blootstelling, was vergelijkbaar met die van de algemene bevolking.

Gegevens over de incidentie rate en de inductietijd van handeczeem waren niet beschikbaar uit de literatuur. Om daarover alvast enige indruk te verkrijgen in verband met de planning van een prospectief onderzoek naar risicofactoren voor handeczeem, werd eerst een retrospectief cohortonderzoek uitgevoerd onder verpleegkundigen en kantoorpersoneel (Hoofdstuk 6). Dit onderzoek werd uitgevoerd onder 371 verpleegkundigen en 111 administratieve medewerkers die tussen 1 januari 1987 en 31 december 1988, in dienst gekomen waren bij een academisch ziekenhuis. De gestandaardiseerde vragenlijst werd gebruikt om de incidentie van handeczeem op retrospectieve wijze te bepalen. In verpleegkundigen was de incidentierate 7,8

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gevallen/100 persoonjaren en in kantoorpersoneel was deze 1,2 gevallen/100 persoonjaren. Bij verpleegkundigen trad 72% van de gevallen op binnen drie maanden na in dienst treden. Het is van belang voor de interpretatie van deze gegevens dat het merendeel van de verpleegkundigen al als verpleegkundige had gewerkt voordat zij in dienst kwamen van het ziekenhuis. Voor het bepalen van de incidentierate werden uiteraard alleen verpleegkundigen in aanmerking genomen die geen handeczeem hadden bij indiensttreding. Mogelijk waren diegenen die al eerder als verpleegkundige hadden gewerkt en desondanks geen eczeem hadden ontwikkeld, minder gevoelig voor het optreden van handeczeem. Er werd geconcludeerd dat een prospectieve studie daarom beter uitgevoerd zou kunnen worden onder personen die niet beroepsmatig blootgesteld zijn voor het begin van het onderzoek, zoals leerlingverpleegkundigen.

Een atopische constitutie, contact allergie en een droge huid worden beschouwd als risicofactoren voor handeczeem. In verschillende publikaties is de laatste jaren naar voren gebracht dat transepidermaal waterdampverlies (TEWL) voor het begin van de blootstelling, zou kunnen dienen als indicator van de individuele gevoeligheid van de huid voor het ontwikkelen van handeczeem.

De binnen-en tussenpersoonsvariatie in TEWL werd onderzocht onder laboratoriumomstandigheden (Hoofdstuk 7). Het onderzoek werd uitgevoerd onder 30 gezonde proefpersonen. De intra-individuele variatie-coëfficiënt op 8 verschillende plaatsen op de onderarm was 13,5%. De intra-individuele variatie-coëfficiënt van 15 metingen over een periode van 3 weken was 15,1%. De binnenpersoonsvariatie was klein in vergelijking met de tussenpersoonsvariatie, hetgeen suggereert dat transepidermaal waterdampverlies geschikt is om bestudeerd te worden als persoonskenmerk in epidemiologisch onderzoek op het gebied van handeczeem.

De rol van een atopische constitutie, contact allergie, droge huid en transepidermaal waterdampverlies in de ontwikkeling van handeczeem werd onderzocht in een prospectief onderzoek onder 74 leerling-kapsters en 111 verpleegkundigen in opleiding (HBOV) (Hoofdstuk 8). De gemiddelde incidentie rate in leerling-kapsters was 32,8 gevallen/100 persoonjaren en 14,5 gevallen/100 persoonjaren in verpleegkundigen. De incidentierate van handeczeem was verhoogd in leerlingen met een droge huid, in het bijzonder in leerlingkapsters. Ook leerlingen met (atopische) mucosale symptomen, zoals astma en hooikoorts, hadden een verhoogde incidentie rate. Dit

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gold met name voor verpleegkundigen in opleiding. De resultaten van het onderzoek geven geen duidelijkheid omtrent een mogelijk verband tussen de kans op handeczeem en een verhoogd waterdampverlies van de huid. Om meer inzicht te verwerven in dit verband is een groter onderzoek noodzakelijk waarin het gemiddelde transepidermale waterdampverlies over langere tijd nauwkeuriger bepaald kan worden. De belangrijkste resultaten van de verschillende onderzoeken in dit proefschrift worden besproken in hoofdstuk 9. Tevens worden daarin enkele methodologische aspecten belicht die van belang kunnen zijn voor toekomstig epidemiologisch onderzoek naar handeczeem.

## Appendix A

### Questions on hand dermatitis (translated from Dutch)

1. Have you had one of the following symptoms at your hands or fingers in the past 12 months:
  - a. red and swollen hands or fingers  yes  no
  - b. red hands or fingers and fissures  yes  no
  - c. vesicles on the hands or between the fingers  yes  no
  - d. scaling hands or fingers with fissures  yes  no
  - e. itching hands or fingers with fissures  yes  no
  
2. Did one or more of these symptoms last for more than 3 weeks?  
 yes  
 no  
 I don't know
  
3. Did one or more of these symptoms occur more than once?  
 yes  
 no

## Appendix B

		<b>Medical diagnosis</b>		total n
		hand dermatitis n	no hand dermatitis n	
<b>Questionnaire diagnosis</b>	hand dermatitis	a	b	a+b
	no hand dermatitis	c	d	c+d
	total	a+c	b+d	N

sensitivity:  $a/(a+c)$

specificity:  $d/(b+d)$

positive predictive value:  $a/(a+b)$

negative predictive value:  $d/(c+d)$

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## About the author

Henriëtte Smit was born on May 15<sup>th</sup>, 1954 in Hengelo. She attended secondary school at the Bataafse Kamp (Gymnasium  $\beta$ ) in Hengelo. In 1973/74 she spent a year in Neûchatel, Switzerland. She started to study at the Agricultural University in Wageningen in 1974, where she obtained her academic degree in environmental sciences in 1982.

From 1982 to 1991 she worked as an occupational epidemiologist at the TNO-Institute for Preventive Health Care (NIPG-TNO) in Leiden. The Central Organization TNO provided her with a grant to spend the academic year 1986/87 at the Harvard School of Public Health in Boston, where she obtained the degree of Master of Science in Epidemiology. After having returned to the NIPG-TNO, she continued to work on the research program "Epidemiology of occupational accidents and diseases". In 1989 she started the work that was described in this thesis.

Since 1991 she is working on the epidemiology of chronic diseases at the Department of Epidemiology of the National Institute of Public Health and Environmental Protection.