Chapter 1
General introduction

Parts of this introduction were published before in:
GENERAL INTRODUCTION
This thesis consists of studies performed within the ‘Expert Center for Eczematous and Occupational Dermatoses’ at the department of Dermatology, University Medical Center Groningen, in the Netherlands. The overarching topic of this thesis is hand eczema. This general introduction gives a concise overview of hand eczema, leading up to the aims that this thesis is based on. These aims concern three areas relevant to hand eczema, which will be given special consideration in this introduction: impact, treatment, and outcome measures. More in depth introduction will be provided in the related chapters.

EPIDEMIOLOGY
Hand eczema is a common disease with a 1-year prevalence of at least 9.1% in the general population, including mild as well as severe cases. This was mostly measured in Scandinavian countries, showing an average 1-year prevalence of 6.4% in men and 10.5% in women in a systematic review from 2010. In the same review an incidence of 5.5 cases per 1000 person-years was found (9.6 in women, 4.0 in men). Self-reported hand eczema in women peaks at a young age, especially between 19 and 29 years, and decreases with age, while in men the incidence rate increases gradually with age. The higher prevalence in women is most likely explained by a difference in exposure, at home as well as occupationally, and not so much by a difference in susceptibility between the sexes. The pathogenesis of hand eczema is still largely unknown. According to a twin study, external factors explain up to 59% (confidence interval (CI) 47-72) of why an individual develops hand eczema. This means that around 40% of internal factors should explain why one individual is more prone to develop the disease than someone else.

There are several risk factors that are often associated with hand eczema: atopic dermatitis (AD) in childhood, persistent/severe AD, low age of onset of hand eczema, contact allergies, wet work, and occupation. Whether the use of tobacco is a risk factor for hand eczema is still subject of debate, but recent studies do seem to point in the direction of an association. Notable factors that were not associated with hand eczema in several studies are, for adolescents, asthma, rhinoconjunctivitis, specific IgE, and a parental history of allergy-related disease; and, for adults, body weight, alcohol consumption, lower educational level and stress. Conversely, other studies did find an association between incident as well as persistent hand eczema and generalized xerosis, food allergy, hay fever, asthma, lower educational level, stress (all self-reported) and obesity. Filaggrin gene (FLG) null-mutations seem not directly associated with incident hand eczema, although such mutations do strongly predict persistent hand eczema in individuals with AD. Clearly, much concerning the interplay between hand eczema and various possible risk factors still needs further elucidation.

DIAGNOSIS
To date, hand eczema is still a clinical diagnosis. The term eczema (in the literature often interchangeably used with the term dermatitis) is a general term used to describe an inflammation of skin in which, for hand eczema, a combination of erythema, scaling, fissures, erosions, infiltration, vesicles, hyperkeratosis, oedema and/or lichenification can be seen (see Figure 1). Hand eczema is called chronic when it lasts for more than three months or relapses twice or more in one year.
Figure 1 Examples of the clinical signs of hand eczema
No consensus has yet been reached on the classification of hand eczema. This is mostly because the disease is multifactorial, involving endogenous and exogenous factors. Known exogenous factors causing hand eczema are allergens and irritants, while the disease-inducing potential of these factors is largely based on a person’s susceptibility to them. Known predisposing endogenous characteristics are, however, still largely unknown. It must be emphasized that hand eczema in general cannot simply be depicted as ‘atopic dermatitis localized on the hands’. Although it is often associated with AD, there are numerous patients who present themselves with isolated hand eczema, while having no history of (or currently active) AD. Patients may have a contact allergy as underlying cause of the hand eczema, which is why every patient with hand eczema should be tested for allergies with patch tests (epicutaneous allergy testing). There are, however, many patients negative to patch testing. Such patients often have a contact dermatitis caused by irritant substances in the environment, which is the most common cause of hand eczema, but they may also have a type of endogenous hand eczema which cannot clearly be attributed to exogenous causes. In these patients we currently rely on morphological descriptions for classification until we learn more about the underlying triggers of disease.

One way of classifying the disease is from a clinical point of view. Menné et al. proposed a classification based on hand eczema morphology as seen in daily practice, with types of hand eczema that may be distinguishable, but can overlap and also change during the course of the disease:

- Chronic fissured hand eczema
- Recurrent vesicular hand eczema
- Hyperkeratotic palmar eczema
- Pulpitis
- Interdigital eczema
- Nummular hand eczema

Because a clear link between morphology and etiology is still not found and because knowledge about etiology is important for proper management of hand eczema, Menné et al. also put forward a separate etiological classification. This was later updated and resulted in a combined morphological/etiological classification (Table 1).

This table might give the impression that multiple items are mutually exclusive by definition, while in clinical practice they are often seen in conjunction. This again reflects the multifactorial nature of hand eczema. In daily practice more than one etiological diagnosis is often given. The combination of ICD and ACD is common, as is the combination of ICD and AHE.

It is clear that more knowledge is needed about what actually happens in the skin of hand eczema patients and whether a difference in function of (epi)dermal components could be linked to morphology. Until then, the definitions mentioned above can be used to classify hand eczema.
**Table 1** Subgroups of hand eczema and definitions by Agner et al.  

<table>
<thead>
<tr>
<th>Subgroup of hand eczema</th>
<th>Defined as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritant contact dermatitis (ICD)</td>
<td>A documented exposure of the hands to an irritant, which is quantitatively likely to cause contact dermatitis. No relevant contact allergy (no current exposure to allergens to which the patient has reacted positive in patch test). An example of a well-defined irritant exposure likely to cause contact dermatitis is wet-work: wet hands or wearing of gloves for 2 h, or more than 20 hand washes daily. Relevance of the irritant exposure may be defined as either suspected or certified.</td>
</tr>
<tr>
<td>Allergic contact dermatitis (ACD)</td>
<td>Positive patch test reaction to the topical exposure to an allergen or a cross-reacting allergen, and a relevant – either documented or suspected – current exposure to this allergen on the hands. Relevance may be defined as either suspected or certified.</td>
</tr>
<tr>
<td>Atopic hand eczema (AHE)</td>
<td>Hand eczema in a patient with a medical history of atopic eczema, previous or current, according to the UK criteria. No documented irritant exposure likely to cause ICD</td>
</tr>
<tr>
<td>Protein contact dermatitis / Contact urticaria (PCD/CU)</td>
<td>Hand eczema in patients exposed to proteins (food, latex and other biological material) with a positive prick test, or proven specific IgE, to suspected items. A considerable part of patients with PCD/CU will have atopic symptoms as well.</td>
</tr>
<tr>
<td>Vesicular endogenous hand eczema</td>
<td>Recurrent hand eczema with vesicular eruptions. No relevant contact allergy, and no documented irritant exposure likely to cause dermatitis, and no personal history of atopic dermatitis</td>
</tr>
<tr>
<td>Hyperkeratotic endogenous hand eczema</td>
<td>Chronic eczema with hyperkeratosis in the palms of the hands, or pulpitis, and no vesicles or pustules. No documented irritant exposure likely to cause ICD</td>
</tr>
<tr>
<td>Unclassified</td>
<td>Eczema which does not fit into any of the above-mentioned subgroups</td>
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**MEASURING HAND ECZEMA SEVERITY**

The management of hand eczema depends for a great deal on the severity of the disease. Severity can be estimated in part by determining the impact of the disease (see 'Impact'). However, the work-up of hand eczema should also always include an assessment of the morphological (clinical) severity to enable monitoring over time and quantification of treatment or prevention efforts in clinical studies as well as in daily practice. Various instruments to assess clinical hand eczema severity have been developed that incorporate different hallmark signs of eczema (e.g. erythema, scaling, edema, papules, vesicles) and often also the extent of the disease. Unfortunately, most of these instruments have not been validated properly.

Two instruments, which have been partly validated for use (only in Caucasian individuals), are currently often used:

- the ‘Photographic guide for the severity of hand eczema’ (‘Photoguide’), which functions as an image guided Physicians Global Assessment. The hand eczema severity is scored by the treating physician on a 5-point visual scale (clear, almost clear, moderate, severe, very severe) depicting 4 images representative for each of the severity grades. This instrument has also successfully been tested for use by patients to rate their own hand eczema severity.
- the Hand Eczema Severity Index (HECSI), which is a continuous scale from 0-360 points that takes morphological signs (erythema, infiltration/papulation, vesicles, fissures, squamae, edema), location and extent into account.

Both instruments have their drawbacks. For example, the Photoguide is not able to...
capture all subtypes in its images (like the severity of an isolated pulpitis), while HECSI has quite a large inter-observer variability, possibly owing to the lack of guidance on how the locations of the hand are defined and how to exactly score severity of the different signs. Also, responsiveness (sensitivity-to-change) and interpretability of the HECSI have not been studied.

The best instrument to assess severity of hand eczema has not yet been established and might not yet exist. In this thesis, the Photographic guide and HECSI are applied in various chapters and the HECSI is studied in more detail.

IMPACT

Hand eczema can have large impact on patients. The disease can severely affect patients financially, occupationally and psychosocially.

Regarding financial impact, several studies have been published that assess the cost-of-illness of hand eczema.33–38 In this thesis, these studies are systematically reviewed to obtain an estimation of how high the financial burden of hand eczema is, for patients as well as for society.

Occupationally, hand eczema can lead to sickness presenteeism and absenteeism from work.11,39,40 Many people with a chronic disease like hand eczema will often still attend work, while they should have stayed at home (presenteeism). These people will frequently be less productive and are prone to absenteeism in the long term. This holds true for many chronic conditions and is also relevant in eczema.41 For hand eczema, this has only been studied once, in a group of Dutch healthcare workers with generally mild disease.42 Frequent flares and more severe hand eczema are risk factors for a poor long-term prognosis. This might eventually lead to loss of job and problems getting a new job.40 This particularly applies to women, probably because they are more often employed in a wet-work occupation.3,43,44

When focusing on psychosocial consequences, it is known that depression and anxiety are correlated with hand eczema.45–47 In a large European multicenter study on the relation between depression/anxiety (measured using the Hospital Anxiety and Depression Scale) and 13 dermatological conditions, the strength of the correlation with hand eczema was in the top 3, along with psoriasis and ulcus cruris.48

Another way to measure the psychosocial impact of a disease is to look at quality of life impairment. This can be done using generic (non-specific) or skin-specific measurement instruments, but these may fail to grasp the real impact that a specific medical problem have on a patient. Because of this, disease-specific instruments are increasingly developed.49 Currently, the only disease-specific measurement instrument to assess quality of life in hand eczema is the Quality Of Life in Hand Eczema Questionnaire (QOLHEQ). The QOLHEQ consists of 30 questions, covering four subdomains: symptoms, emotions, functioning and treatment/prevention. The questionnaire was validated in a German and Japanese population.50,51 It can aid clinicians in determining an individual approach to optimize the care for a hand eczema patient, for example by supplying educational or psychological interventions in patients that score particularly high on specific subscales. Furthermore, it offers the opportunity to measure disease-specific quality of life as a Patient Reported Outcome (PRO) in clinical studies on hand eczema. The QOLHEQ has not been validated for use in a Dutch population. Also, it is not yet known how QOLHEQ scores should be compared across countries and how values should be interpreted.

TREATMENT

The European Society of Contact Dermatitis (ESCD) has initiated the writing of a guideline
on the diagnosis, prevention and treatment of hand eczema.\textsuperscript{23} Furthermore, a Cochrane review was performed on the available literature concerning the treatment of hand eczema.\textsuperscript{52} From these publications it becomes apparent that the cornerstone of treatment is topical therapy with emollients, corticosteroids and calcineurin inhibitors. The retinoid altretinoin is recommended as second line therapy, as several large trials have proven its effectiveness.\textsuperscript{53–59} This effectiveness was mainly seen in hyperkeratotic and chronic fissured hand eczema and less in the recurrent vesicular subtype. A large trial is currently being performed in the United Kingdom to compare psoralen ultraviolet A (PUVA) to altretinoin to add to the positioning of ultraviolet irradiation therapy in treatment strategies for hand eczema.\textsuperscript{60} The most used third line treatments are cyclosporine A, azathioprine, methotrexate and acitretin. For these drugs, studies in hand eczema patients are scarce. There is a need for well-designed randomized controlled trials (RCTs) and particularly for head-to-head trials, comparing the various systemic treatments. Also, the potential use of emerging treatments in the form of biopharmaceuticals (biologicals) for atopic dermatitis\textsuperscript{61,62} should be explored for hand eczema patients.

OUTCOME MEASURES

In quantitative science measurement plays a key role. It is vital to know what you are measuring and even more so that the instrument that you are using actually measures what you want it to measure. This is increasingly acknowledged and large initiatives have been started to improve measurement in medicine (also termed ‘clinimetrics’). The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative is an international group of experts aiming to “improve the quality of studies on measurement properties by developing methodology and practical tools for assessing measurement properties, and call for standardization of outcomes and outcome measurement instruments by developing core outcome sets (COS)”.\textsuperscript{63} This group provides guidance on how measurement properties of instruments should be assessed. We applied this to the field of existing outcome measurement instruments in hand eczema to assess whether meaningful measurements can be/are currently performed in hand eczema and to add a sense of how particular scores should be interpreted. Several chapters in this thesis use the COSMIN methodology.\textsuperscript{64}

AIMS AND OUTLINE OF THE THESIS

In this thesis we aim to study various elements of the impact and treatment of hand eczema (section I and II). Furthermore, a large part of this thesis concerns validity and interpretability of outcome measurement instruments used in studies with hand eczema patients (section III).

Section I of this thesis explores the impact of hand eczema on financial and occupational aspects of a patient’s life. Chapter 2 is a systematic review on cost-of-illness in hand eczema in which the available literature is summarized and analyzed. In chapter 3, the phenomenon ‘presenteeism’ (attending work while sick) is studied in hand eczema patients, providing a sense of how hand eczema affects patients in their work.

In Section II of this thesis we focus on how improvement can be gained regarding the systemic treatment for severe hand eczema. It comprises four chapters with studies on various drugs. In chapter 4, we describe a protocol for a clinical trial in which altretinoin is compared with cyclosporine-A for the treatment of severe recurrent vesicular hand eczema. Chapter 5 consists of a retrospective cross-sectional cohort study in which we report the effect of azathioprine on patients treated at our center since the beginning of the millennium. In chapters 6 and 7, the effect of the biological agent dupilumab, an interleukin 4 and 13 inhibitor, on hand eczema is described in a single observation and in a case series of 47 patients.
Finally, Section III contains several chapters in which two outcome measures used in hand eczema studies take center stage. Chapter 8 is a guideline explaining how validation of a quality of life measurement can be performed. The Quality Of Life in Hand Eczema Questionnaire (QOLHEQ) is taken as an example, paving the way for chapter 9-11 in which multiple stages of this validation process are described. In chapter 9, validation data of the Dutch version of the QOLHEQ is reported, demonstrating its validity in a Dutch population. The QOLHEQ is also internationally validated to assess comparability between several countries worldwide. Chapter 10 consists of a report on this cross-cultural validation study and in chapter 11 we describe how scores obtained with the QOLHEQ should be interpreted when comparing international values. Finally, in chapter 12, we turn to the Hand Eczema Severity Index (HECSI) and present a study on the interpretability of this severity measurement instrument for hand eczema patients, which can be used in daily practice as well as in clinical studies.
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SECTION I
IMPACT