GENERAL DISCUSSION
**General discussion**

This thesis focuses on the possible interventions for hand eczema. Based on the preceding chapters that deal with different aspects of treating hand eczema, it can be stated that the disease hand eczema is still poorly understood. Consensus on a concise, unambiguous definition is still lacking. The uncertainties about a clear disease definition may have led to unnecessary complicated intervention strategies. It may also have contributed to the relatively poor results of the trials published thusfar. We postulate that hand eczema is essentially different from other dermatoses and even different from other types of eczema or eczema on other areas of the body. In fact, it can be postulated that hand eczema encompasses a set of different diseases. These aspects are very relevant to the contents of this thesis and they will be addressed in the next paragraphs, together with some other important topics.

All trials described in this thesis mention the high prevalence of hand eczema. The exact prevalences however, are unknown. Studies estimate a point prevalence of 1 to 5% among adults in the general population, and a one-year prevalence of up to 10%. Practising dermatologists, wherever they work, will agree that this high prevalence is reflected in daily practice, making hand eczema one of the commonest reasons for consultation.

The high prevalence is in part a consequence of the chronic nature of hand eczema. Its chronicity is a sign of how difficult intervening can be and a sign of the complexity of the disease. Although chronicity is not a unique feature of hand eczema, there are several factors that do set it apart from other dermatoses, even other types or localisations of eczema. In hand eczema there is a multifactorial aetiology, where atopy, allergens and irritants all can play a role, alone or in combination. The main problem frustrating the intervention of hand eczema is the exposure to ubiquitous irritants and allergens. Complete avoidance of these factors is usually impossible. This is in part due to the fact that the relevance of major allergens (e.g. nickel) may remain elusive. Clinicians like to point out the parallels to foot eczema. Foot eczema is somewhat similar in the relative frequent encounter of irritants and allergens. However, these allergens are most commonly only related to footwear, such as leather and rubber, whereas in hand eczema there is a wider array of allergens. With regard to irritants, the major irritant in foot eczema is hyperhidrosis. Hand eczema patients may also suffer from hyperhidrosis, but encounter many other irritants.

Atopy can result in exacerbations, whereby the causal or triggering factor is often unclear. Very few trials described in the preceding chapters discuss this issue and very few trials clearly distinguish the cases of atopic eczema. It can be argued that many cases of hand eczema are in fact a subtype of atopic eczema,
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even in the absence of raised allergen-specific IgE in serum. Therefore, perhaps it should not be considered as hand eczema with atopy, but as atopic eczema located at the hands. Irritants, even minor irritant factors, play a role in the course of atopic eczema, making the distinction from ‘true’ irritant contact dermatitis difficult.

With regard to definition, should subtle skin changes, e.g. mild chapping, be considered as hand eczema or as a variation of otherwise healthy skin? Definition also pertains to the morphological subtypes of hand eczema, e.g. dyshidrotic hand eczema or hyperkeratotic hand eczema. In this thesis we have, where possible, tried to differentiate between subtypes. They are all considered variants of hand eczema, but are they? Surely they are eczematous dermatoses, but to what extent can hyperkeratotic hand eczema be compared to dyshidrotic hand eczema? The visible and histopathological differences between these two dermatoses are evident and it is not too unlikely that this has consequences for therapy. Topically applied corticosteroids on palmar hyperkeratotic eczema will have a different biological availability than the same treatment on digital dyshidrotic eczema.

An attractive possibility in studies of hand eczema is to set up self-controlled trials with left-right comparisons. It can be assumed that there will be no biological differences within one person and between the two hands. Many of the studies included in chapter 4 feature such a self-controlled left-right design. If an intervention proves to be more effective on one particular hand, the superior efficacy will be attributed solely to the drug. The left-right comparisons can enhance study efficacy and reduce bias. However, it is not unlikely that the patient’s dominant hand will be in contact with allergens and irritants more frequently than the non-dominant hand, thus introducing bias, favouring the intervention on the non-dominant hand, when the study design does not take this issue into account.

Left-right comparisons assume equivalence between the two hands, as discussed above, with independent behaviour. The skin however, from head to toe, is one organ. Although (bilateral) hand eczema is a localised infliction of the skin, hand eczema does have some aspects of a ‘systemic’ disease: it is not uncommon to see improvement in the untreated hand, when the contralateral hand is (successfully) treated. Apparently, the disease process on one hand is not independent from the contralateral hand. Therefore, the results of the trials based on a left-right comparison may be biased, probably towards a less favourable comparative advantage of the treatment that is evaluated.

In chapter 6 the physician-rated severity scores of the patient’s hand eczema were calculated by averaging the scores of both hands and rounding it off. Dexterity was not taken into account, although it may influence both the
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patient’s perception of his or her hand eczema (patient-rated severity score) and the burden of disease. As discussed above, in general the dominant hand is more severely affected. One might expect that an affected dominant hand would yield a higher impact on both parameters (lower patient-rated severity score and higher DLQI score).

An important consideration in intervention studies for hand eczema, is the problem of outcome parameters. Similar to the lack of consensus on disease definition, there is no universally accepted and validated outcome parameter for use in trials. In chapters 2, 3 and 4 various scoring methods are, more or less explicitly, presented. Besides the lack of validation, the relevance of these outcome parameters to patients is limited. This is illustrated in chapter 6 by the limited effect of improvement of visible skin changes on the patient’s satisfaction with treatment. In addition, the interpretation of the changes in scores derived by adding several physical parameters together is obscure even to clinicians. Simple, relevant and validated outcome parameters that can be understood by patients and clinicians are needed.

Burden of disease is a non-clinical outcome parameter. Measuring it in hand eczema can be equally difficult as assessing the clinical severity. Burden of disease, however, is a very important aspect of hand eczema to patients. The hands are important tools for communication and expression. It is therefore easy to understand that any impairment in form and function may result in major psychosocial problems, e.g. anxiety, low self-esteem and social phobia. It seems that other types or localisations of eczema do not have the same impact on the patients’ psychosocial well being, with the possible exception of facial skin changes. The itch that accompanies hand eczema is a major component of the burden of disease. It may interfere with sleep. A vicious cycle of symptoms and skin damage (the itch/scratch/itch cycle) can aggravate problems. We have found that reducing the visible skin changes of hand eczema may not be sufficient to satisfy the patient with the treatment (chapter 6). Therefore, other considerations than visible skin changes should be taken into account, such as burden of disease and the patient’s overall opinion.

Painful cracks and blisters can prevent or severely complicate manual work leading to significant disability, economic loss to both individuals and State, and distress to the affected patients. The economic impact may be direct or indirect. Direct costs include medical costs, social security and medical litigation; indirect costs may arise from absence from work and loss of productivity. Ideally an intervention would be cheap (with regard to medical costs) and lead to limited absence from work (directly related to the intervention). Phototherapy, one of the major treatment groups, may lead to
additional absence from work when performed in hospital. Our studies in chapter 5 and appendix 1 demonstrated that treatment with oral PUVA at home is equally effective as hospital administered bath PUVA. Also, it appeared to be cheaper and result in less time off work. A point of concern is whether hand eczema related absence of work warrants quick referral and treatment. Although this question does affect dermatological practice, it is also relevant for State institutions and healthcare insurance companies. It is recommended that future trials will include outcomes on the economic impact of this disease.

Summarising, the high prevalence of hand eczema contrasts with the lack of good quality trials of commonly prescribed treatments. In this chapter we discussed how quality can be compromised by the poor classification and definition of hand eczema, the possible introduction of bias due to the special trial-related properties of hand eczema and the problem of outcome parameters.