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Contact Dermatitis (A Gimenez-Arnau, Section Editor)

Scope and Efficacy of Preventive Measures in Contact Dermatitis

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Abstract

Purpose of review To describe the scope and review the efficacy of interventions to prevent contact dermatitis.
Recent findings Universal measures to prevent contact dermatitis start at the population level with legislation regulating exposure to skin irritants and sensitizers. Primary measures include health education on skin care and protection, use of moisturisers and proper use of protective gloves. The overall epidemiological evidence regarding the efficacy of such preventive measures varies from low to moderate. Secondary prevention comprises the application of specific diagnostic procedures and early intervention. Tertiary prevention measures focus on medical, psychosocial, and occupational rehabilitation of patients with a chronic form. Education on risk factors and skin protection is an essential element at all the levels of prevention.
Summary Evidence-based recommendations and international standards for prevention, diagnosis and management of contact dermatitis are available. The low evidence on the efficacy of several primary measures can be due to limitations in study designs and low comparability of the studies.
Stakeholders should address shortcomings of the current legislation. Randomised control trials studies including a homogenous assessment of the outcome measure, a longer follow-up and better adjustment for potential bias can enhance the current level of evidence for the efficacy of preventive measures.

Introduction

Contact dermatitis (CD) is one of the most common skin diseases associated to environmental exposures. The global burden is considerable, being among the ten leading skin and subcutaneous diseases with highest prevalence (third place) and incidence (fourth place) [1•]. According to the last estimates, contact allergy to at least one allergen of the European baseline series was diagnosed in more than one-quarter of the general European population, with a higher prevalence in women than in men. The most common allergen are fragrances, preservatives, and metals [2•]. CD is also the most frequent (up to 95%) work-related and occupational skin disease (OSD), where the related costs exceed five billion €/year in the EU by loss of productivity, sick-leave and job loss [3•]. Most of the current knowledge regarding the efficacy of primary interventions arise from occupational dermatology. In fact, these principles do not differ between occupational and non-occupational CD.

Consequently, preventive measures are mandatory to keep a healthy skin in safe environments. From a public health perspective [4], these can be classified into:

- Universal: includes proper legislation and health promotion strategies with impact on the full population.
- Selective: includes preventive strategies in specific risk groups such as education about risk factors and protective measures in risk occupations.
- Indicated: focuses on individuals with a manifest risk factor or abnormality through medical examination or laboratory testing. They are applied in a clinical setting and include diagnostic procedures and preventive advice at the individual level.

Evidence-based graded statements and recommendations for the prevention identification of occupational CD and urticaria have been defined by Nicholson et al. in 2010 [5••]. Moreover, STANDERM has recently established standards for effective prevention, diagnosis and treatment of work-related and occupational skin diseases [7••]. These standards classify preventive measures in:

- Primary prevention: aims to avoid the development of CD in healthy individuals. The STOP concept (*S*ubstitution, *T*echnical measures, *O*rganisational measures and *P*ersonal Protection) is useful in occupational settings after a risk management process, which identifies exposure to hazardous substances and preventive measures [8].
- Secondary prevention: aims to early diagnosis and treatment to avoid disease progression.
- Tertiary prevention: aims to medical, occupational, and psychosocial rehabilitation of individuals with CD.

This review gives an overview on the scope of measures to prevent CD from the population to the individual level. Current evidence on the efficacy of preventive measures as well as unmet needs is further discussed.

Universal measures and primary prevention

Legislation

Proper legislation aiming at the avoidance and limitation of skin exposure to irritants, sensitizers, and corrosive substances, as well as its implementation is the basis for universal prevention of CD [••]. Some examples of current regulations comprise:

Regulation on classification, labelling and packaging of substances and mixtures

Manufacturers, importers and downstream users should classify, label and package chemical substances as skin sensitizers (H317) following a harmonised classification. Thus, chemical mixtures can be classified according to the generic concentration limit of the sensitizer into moderate

sensitizers (1%), extreme sensitizers (0.1%) and extreme (0.001%). Packages should in addition contain information about content of a classified sensitiser above certain concentrations (1/10 of the concentration limit) to protect already sensitised individuals: "Contains (the name) may produce an allergic reaction" [9]. For Chromium, isocyanates, and epoxy, information should be included regardless of concentration [9, 10]. For immunological contact urticaria, some substances meeting the criteria for respiratory sensitizers should be considered as skin sensitizers. For substances producing signs of immunological contact urticaria only, classification will normally be based on human evidence, which will be similar to that for skin sensitisation [9, 10].

The National Institute for Occupational Safety and Health (NIOSH) includes a notation system for sensitizers (SK: SENS) to indicate that skin exposure to a chemical may cause or contribute to the onset of allergic CD (ACD) or other immune-mediated responses, such as asthma [11].

Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals

Registration, Evaluation, Authorisation and Restriction of chemicals (REACH) (EC 1907/2006) aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. The four processes of REACH are registration, evaluation, authorisation, and restriction of chemicals [12]. Some restrictions on skin sensitizers by REACH and the Cosmetics Regulation are contributing to reduce the incidence of allergic CD due to nickel, chromium, some preservatives, and biocides [13•].

Water soluble chromium (VI) in cement, the main cause of chromium allergy, was reduced in the Nordic countries already during the 1980s by adding iron sulphate to the cement [14]. The European Chromium Directive introduced in 2005, which prohibits selling or use of cement with more than 0.0002% of chromium, led to a reduction of contact allergy to chromium in the construction industry [13•]. Nevertheless, the use of chromium-tanned leather articles has led to an increasing of chromium allergy among women lately [14]. Future epidemiological studies will provide evidence of whether the EU regulation on the content of hexavalent chromium in leather adopted in November 2013 contributes to reduce chromium allergy among leather users [15].

Denmark was the first country to implement a restriction on nickel release from items in prolonged contact with the skin in 1990 [••]. The EU Nickel directive was adopted in 1994 and implemented from 2000. A systematic literature search by Ahlström et al. [17] showed a consistent pattern of decreasing prevalence of nickel allergy in some EU countries. For instance, a significantly lower prevalence of nickel following the implementation of the EU Nickel Directive was found in women aged 18–35 years (11.4% versus 19.8%), in female dermatitis patients aged ≤ 17 years (14.3% versus 29.2%) and in dermatitis patients aged 18–30 years (women: 20.2% versus 36.6%) (men: 4.9% versus 6.6%). Overall, the prevalence was higher in southern than in northern EU countries, and generally remained high, affecting 8–18% of the general population. The prevalence among young women still high [17].

Preservatives such as methylchloroisothiazolinone/methylisothiazolinone (CMIT/MIT, also known as MCI/MI, Kathon CG®), methyldibromo glutaronitrile (MDBGN), and several formaldehyde releasers are substances which have caused a rapid and alarming increase in contact allergy and dermatitis lately [18]. Liquid soaps, industrial hand cleansers, detergents, skin care products, paints, metal-working fluids, and their biocides, as well as fountain solution additives in printing work are the most common sources of exposure to MIT or MCIT/MIT. Legislation, restriction and classification of preservatives as skin sensitizers contributed to reduce the occurrence of sensitisation in some European countries [18], but clinically relevant MI contact allergy remains prevalent across European countries according to a prospective study by Schewnsen et al. (2017) [19]. Julander and a group of experts from the Nordic countries summarise important dates concerning legislation, classification and restriction of sensitising preservatives in Europe [8••]. Restrictions introduced in February 2017, completely prohibited the use of MI in leave-on cosmetics [12], and the acceptable MI concentration in rinse-off cosmetics on the European market was lowered to 0.0015% from the end of April 2018 [19].

Whilst data from Australia shows the highest prevalence of MI allergy reported in the literature, recent data shows a decreasing trend [20]. Although the epidemic of MIT allergy is decreasing in some parts of the globe, is not yet gone [21], and still of great concern in North America [22] and South America [23]. Future epidemiological evidence will show whether current measures are sufficient to prevent sensitisation and allergic CD in already sensitised patients. Regulation and restriction is still lacking in some parts of the world [22, 23].

The reduction of contact allergy to dimethylfumarate, a fungicide in clothing, furniture and footgear from Asian articles, is another good example of the effectiveness of legislation to decline sensitisation [24–26].

Nowadays legislation is needed to reduce contact allergy to acrylates, which is increasing in both consumers and those who are occupationally exposed mainly nail technicians and beauticians [27, 28].

Detergents and cosmetics regulations

According to the Detergent regulation, all preservatives should be identified on labels regardless of concentration [29]. Cosmetic products are a frequent cause of fragrance contact allergy, for example, deodorants and after-shaves products among men and perfumes, and deodorants among women. The Cosmetics regulations banes or severely restricts the use of some hair dyes, preservatives, fragrances and nickel. In addition, the names of all ingredients, except fragrance substances should be labelled, regardless of concentration [30].

Latex allergy

An important reduction of contact urticaria attributed to latex is reported in several countries after the successful implementation of legislation to reduce occupational exposure to latex [31, 32].

Measures to reduce skin exposure to irritants

The National Institute for Occupational Safety and Health (NIOSH) includes a notation system to indicate that a chemical is a skin irritant (SK: IRR) and that a chemical is corrosive (SK: CORR) [11].

The German Federal Institute for Occupational Safety and Health (BAuA) created, based on experimental and epidemiological data, a definition of wet work.[1] Technical and organisational measures are also suggested to prevent hand dermatitis by reducing wet work [33]. The European standards for prevention of WRSD and OSD also encourages adopting such preventive measures [7••].

Unmet needs of legislation

Unfortunately, the current legislation has several shortcomings [8••] that should be addressed urgently to not only decrease the occurrence of CD, but also protect patients with the disease:

- The concentration limits for classification in the CLP Regulation are generally too high for universal prevention of induction and elicitation. Moreover, already sensitised individuals may react to very low concentrations.
- REACH restricts very few skin sensitizers.
- Information on skin sensitizers at Safety Data Sheets are often incomplete and misleading due to high concentrations limits for classifications, which may in addition lead to a late or deficient diagnosis of allergic CD [34].
- Time from risk assessment to decision on risk management is often too long.
- Seventy-four known fragrance sensitizers are not required to be stated on the label.
- Hair dye manufacturers still recommend a self-allergy-test, which is not standardised and may contribute to active sensitisation [35].
- EU regulations such as REACH and the Cosmetics Regulation should also be applied for occupational exposures. New knowledge on minimum elicitation dose (ED10) for some skin exposures will contribute to the development of limits for occupational exposures [8••].
- Regulation on limits of rubber accelerators and mandatory labelling in medical gloves. Medical gloves should also contain detailed information on sensitizers.
- Measures to reduce skin exposure to irritants and corrosives be included in current legislations.

Selected and indicated preventive measures

The measures below apply for all levels for primary, secondary, and tertiary prevention in both risk groups and patients with the disease (indicated).

Education programs

Education on skin care and protection is crucial in all levels of prevention [7••]. Little knowledge about risk factors, skin care and protection has been reported among exposed workers at risk of developing CD [8]. Educational programs should include how to choose and use gloves, advice on how to apply moisturisers, and how to recognise early symptoms of CD.

[1] Wet work: activities where workers have to immerse their hand in liquids, wear waterproof (occlusive) gloves for two or more hours per shift, or wash their hands more than 20 times per shift.

When assessing the effect of skin protection education vs no or minimal intervention in trials for primary prevention of irritative CD, the pooled risk reduction was not large enough to be clinically important [36••]. Such a low quality level of evidence for an association between efficacy of education and primary prevention of skin irritation could be a result of study limitations such as different methods to assess hand dermatitis, poor adjusting for potential bias, and short follow-up [36••].

Protective gloves

Whilst the use of protective gloves is recommended to reduce direct skin exposure to irritants, allergens, and urticariogens when substitution, technical and organisational measures are not sufficient [5••, 7••], none randomised control trial, has assessed the effectiveness of protective gloves [36••]. This does not mean that protective gloves should not be a part of a strategy to prevent CD, but it is against ethical standards to prohibit control group participants from using protective gloves. Protective gloves are not mean either to replace other preventive measures previously presented.

Recommendation on use of protective gloves should be based on a risk assessment by occupational and safety health personnel [8]. For instance, the choice of proper gloves depends on the risk of skin exposure, the toxic, irritant or allergenic properties of the substances, the type and duration of work activities. The data safety material sheet of products usually contains recommendations on glove type. The producer, occupational hygienists or safety engineers can also give advice on glove choice in case of doubt [7••]. For example, for health workers, veterinarians, food handlers, catering, cleaners, and hairdressers "accelerators-free" gloves may be effective for primary and secondary prevention [37].

Latex allergy due to glove use is almost historical nowadays [31, 32]; however, contact allergy to rubber additives is an increasing problem [38•], specifically among healthcare workers [39]. New technologies have developed low-protein rubber gloves, vulcanisation accelerator-free and gloves with antimicrobial agents or moisturisers [38•]. Crepy reviews current allergens in gloves and recommends glove alternatives and websites with useful information on gloves composition [38•]. Health workers with hand dermatitis due to contact allergy to rubber accelerators had a clinical improvement after switching single-use gloves with accelerators to accelerator-free medical gloves [40].

Extensive and prolonged use of protective gloves may lead to skin barrier disruption and development of irritant CD [41•]. Jacobsen et al. found moderate evidence of an association between glove use and risk of irritant CD due to occupational exposure [42••]. Therefore, in a clinical setting is important to register the number of hours using protective gloves in both occupational and non-occupational activities, the type of gloves, and the presence of skin problems while using gloves. To prevent the negatives effect of glove occlusion on the skin barrier is important to use them when necessary, but for as short time as possible. Gloves should be intact, clean and dry inside, gloves with long cuffs avoid water and

chemicals coming inside the glove [8]. Moreover, inner gloves made of cotton or bamboo viscose fibre are useful as they absorb moisture and sweat due to prolonged glove use [37].

Occupational groups at risk of developing CD may lack knowledge on how to handle and choose gloves properly. Continuous education and training on glove use can contribute to improve glove use [43].

The suitability and effectiveness of gloves, the use of cotton liners, as well as barriers and facilitators to proper glove use should be addressed by future experimental and qualitative studies [36••]. Material safety data sheets for gloves should also include more detailed and complete information about glove composition and suitability [44].

Moisturisers

The skin is a dynamic organ needing to be protected and restored from the effect of physical, chemical and mechanical environmental factors. Lachapelle et al. [45•] reviews the best practices for the ideal moisturiser in the management of CD [1•]. Proper use of moisturisers is not only necessary for symptom relief in patients with CD, but also for primary prevention as it improves the structural integrity and restoration of the skin barrier.

The ideal moisturiser should be safe (without fragrances, preservatives and colours) and effective to restore the skin barrier. Ceramides are important components of moisturisers that in the right proportion will contribute to restore a damaged skin barrier [45•].

According to the evidence-based statements developed by Nicholson et al. [5••], there is moderate evidence of an association between regular application of moisturisers and primary prevention of occupational CD [46, 47].

An expert panel has newly suggested three moments for moisturiser application to prevent irritant CD in the workplace: before work; during work after hand washing and after work [48•]. The effectiveness of this proposal has not yet been assessed in a real occupational scenario.

A Cochrane systematic review by Bauer et al. [36••] has recently concluded that moisturisers used alone or in combination with "barrier creams" may result in a clinically important protective effect, either in the long- or short-term, for the primary prevention of occupational irritant hand dermatitis. Barrier creams alone may have slight protective effect, but without clinical relevance. The authors highlight that all these comparisons were inaccurate, with a low quality of evidence. The low effect estimates shown in this Cochrane review can be due to heterogeneity of study designs, differences in the assessment of the final outcome, and short follow-up.

Secondary prevention

Early diagnosis and management

Early diagnosis and intervention avoid disease progression and chronicity [7••]. For instance, a population-based study found that diagnosis and treatment within 6 months after onset was associated to a better prognosis

in patients with hand dermatitis [49]. Hald et al. found an association between medical attention delay and prognosis of hand dermatitis, indicating that medical advice should be sought immediately [49]. This is also relevant for occupational dermatitis where a longer exposure to the causative effect leads often to a poorer prognosis [50]. The diagnosis should be based on medical history, examination and supplementary testing. Assessment of occupational exposure has to be performed in case of suspicion of work-related or occupational CD [7••]. Physical examination should include the entire skin and not only the sites presented by the patient.

Epicutaneous patch testing

The gold standard for diagnosing allergic CD is epicutaneous patch testing, complemented with prick testing in case of immediate symptoms [7••]. It is essential if CD persists longer than 3 months or relapses. The guideline for diagnostic patch testing developed by the European Society of CD summarises all aspects of patch testing for the diagnosis of contact allergy in patients suspected of suffering, or having been suffering, from allergic CD or other delayed-type hypersensitivity skin and mucosal conditions [51••].This guideline recommends considering patch testing in patients with [51••]:

- Suspected CD, acute or chronic, including dermatitis related to occupational exposures,
- Other types of (chronic) dermatitis (eczema) not improving with treatment.
- Skin and mucous membrane eruptions (including delayed-type drug eruptions) in which delayed-type hypersensitivity is suspected.

Assessment of clinical relevance

The assessment of the clinical relevance is the second step in the presence of a positive patch test reaction. A positive reaction can be of current and/or past relevance, unknown relevance, or attributable to cross-reaction [52]. Information on the medical history such as occupational exposures, leisure-time exposures, material safety data sheets, clinical examination, spots tests, and chemical analysis facilitate such assessment. Different suggestions for assessment of clinical relevance are available [52–54]. Uter et al. has developed a new concept system to document clinical relevance which enables more precise analysis of causation and relevance of CD, as well as whether CD is occupational or not [55]. Further development and digitalisation of this tool can help to shorten and standardise relevance assessment in clinical practice.

When diagnosing WRSD/OSD, workplace exposure assessment is crucial for making a diagnosis of WRSD and OSD [7••]. The standards for diagnosis of WRSD and OSD are summarised by Alfonso et al. in an evidence-based expert consensus [7••]. Mandatory full labelling of product ingredients on MDSD will contribute to establish

the occupational relevance of CD [7••]. The Mathias' criteria, a validated tool with seven criteria, can also be used to assess occupational causation or aggravation [56•].

Differential diagnosis

To document skin exposure to irritants and rule out allergic CD with epicutaneous patch testing is crucial for diagnosing irritant CD. A standardised, comprehensive and user-friendly form to document irritant exposures has been tested by Uter et al. in a pilot study including 193 patients with occupational hand dermatitis. The tool is feasible and useful as a "check-list" in both clinical practice and epidemiological studies [57].

Atopic dermatitis or chronic hand dermatitis can often be complicated with immediate reactions. Standardised skin prick test or prick-by-prick test should be performed to confirm contact urticaria or protein CD, respectively [7••].

It has to be highlighted that an overlap of an allergic and irritant component is frequent in patients with CD [58••]. For instance, irritative CD is a classical component of atopic dermatitis, especially in those patients with filaggrin mutations. Other skin diseases such as pompholyx, nummular eczema, fingertip dermatitis, hyperkeratotic eczema can also be complicated by allergic CD.

Holistic approach to manage CD

Irritants and allergen avoidance, topical corticosteroid to reduce inflammation, education on skin care, and daily care of the skin barrier with moisturisers contribute to the management of CD [7••]. For instance, a systematic review found moderate evidence of an association between cessation and decrease of exposure with improved prognosis in patients with occupational irritant CD [42••]. The evidence for improvement regardless of change in exposure is limited [42••].

The medical treatment is reviewed by an evidence- and consensus-based guideline developed by the European Society of Contact Dermatitis (ESCD) [58••]. Topical corticosteroids are recommended as first-line treatment; continuous long-term treatment beyond 6 weeks only if necessary and under careful medical supervision. The therapeutic index by Luger et al. is useful when assessing efficacy and safety of topical corticosteroids [59]. Alitretinoin is recommended as a second-line treatment (relative to topical corticosteroids) for patients with severe chronic hand dermatitis [58••]. The ESCD guideline highlights the necessity of more randomised control trials to assess the efficacy of other systemic treatments.

According to a recent Cochrane review, the regular use of moisturisers in secondary prevention is safe, prevents flares, prolongs time to flare and reduce the amount of topical corticosteroids needed [60••]. Moreover, the topical treatment with corticosteroids is more effective when used in combination with moisturisers. The authors found high certainty evidence for physician-assessed disease severity for glycerol-containing creams versus control and all moisturisers versus control. Future randomised controlled trials are encouraged

to include more participants, and follow the Consolidated Standards of Reporting Trials (CONSORT) [60••].

Education is an essential part of this holistic approach for not only avoidance of irritants and allergen, but also to improve treatment adherence [61, 62].

Tertiary prevention

Worldwide, dermatitis is the second skin disease with largest years lived with disability (YLDs)[2] and disability-adjusted life-years (DALYs)[3] [1•]. In Europe, CD is among the skin conditions with largest impact on patient well-being measured as health-related quality of life [63].

Therefore, tertiary preventive measures offering medical, psychosocial and occupational rehabilitation to patients suffering from CD are of great importance [7••]. For example, tertiary individual programs with psychological interventions in Germany contribute to improved mental health in patients with severe occupational hand dermatitis [64].

For work-related and occupational CD, return to work measures and compensation will contribute to enhance quality of life and social integration of patients suffering of chronic CD [7••]. For example, in Germany, intensive interdisciplinary measures of tertiary individual prevention, comprising 2–3-weeks in-patient treatment plus intensive health-pedagogic counselling, and consecutive 3-week out-patient treatment by the local dermatologists lead to successful medical and social rehabilitation of patients suffering of CD [65•].

The legal frame for compensation of an occupational disease varies across borders, but the adoption of common standards for the recognition of work-related and occupational CD can contribute to a more homogenous recognition and compensation practice [66].

Knowledge dissemination from research to stakeholders is necessary for the design and implementation of preventive measures. A successful knowledge dissemination strategy requires building linkages among stakeholders to gain support in the design and implementation of health promotion and preventive measures [67].

Interdisciplinary teams composed of dermatologists, occupational physicians, allergists, safety engineers, and health educators are necessary for effective measures in all levels of prevention [8].

Conclusion

Most of the current knowledge on the scope and efficacy of measures to prevent CD arise from occupational dermatology. Evidence-graded recommendations and international standards for primary, secondary, and tertiary prevention are available. Regulation and restriction through legislation seem to be the most effective measure to reduce allergic CD to common allergens.

[2] YLDs: refer to the number of years that a subject lives with some disease, and it is closely related to the severity of the disability that the disease causes to the affected individual.

[3] DALYs: a summary measurement of the overall burden of disease refers to health loss from both fatal and nonfatal disease burden. One DALY represents 1 year of healthy life lost

Surprisingly, the overall epidemiological evidence supporting the efficacy of primary preventive measures such as education, use of moisturisers and glove use is low. Nevertheless, this should not be interpreted, as a total lack of efficacy of such preventive measures. In fact, many preventive measures may have a positive effect at the individual level, which becomes less evident when pooling data from epidemiological studies with heterogeneous study designs, populations, outcome measures, and length of follow-up. Available data from systematic reviews support that protection creams and moisturisers may be effective to some extent. Further studies focusing on primary interventions should include longer observation periods, standardisation of the outcome measure, and better adjustment and reporting of potential bias. Stakeholders should urgently address shortcomings of current legislation and facilitate its full implementation to reduce exposure to allergens and irritants leading to CD at the population level.

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Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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