Contact Allergy to Hexavalent Chromium. Clinical and Experimental Studies Focusing on Cement

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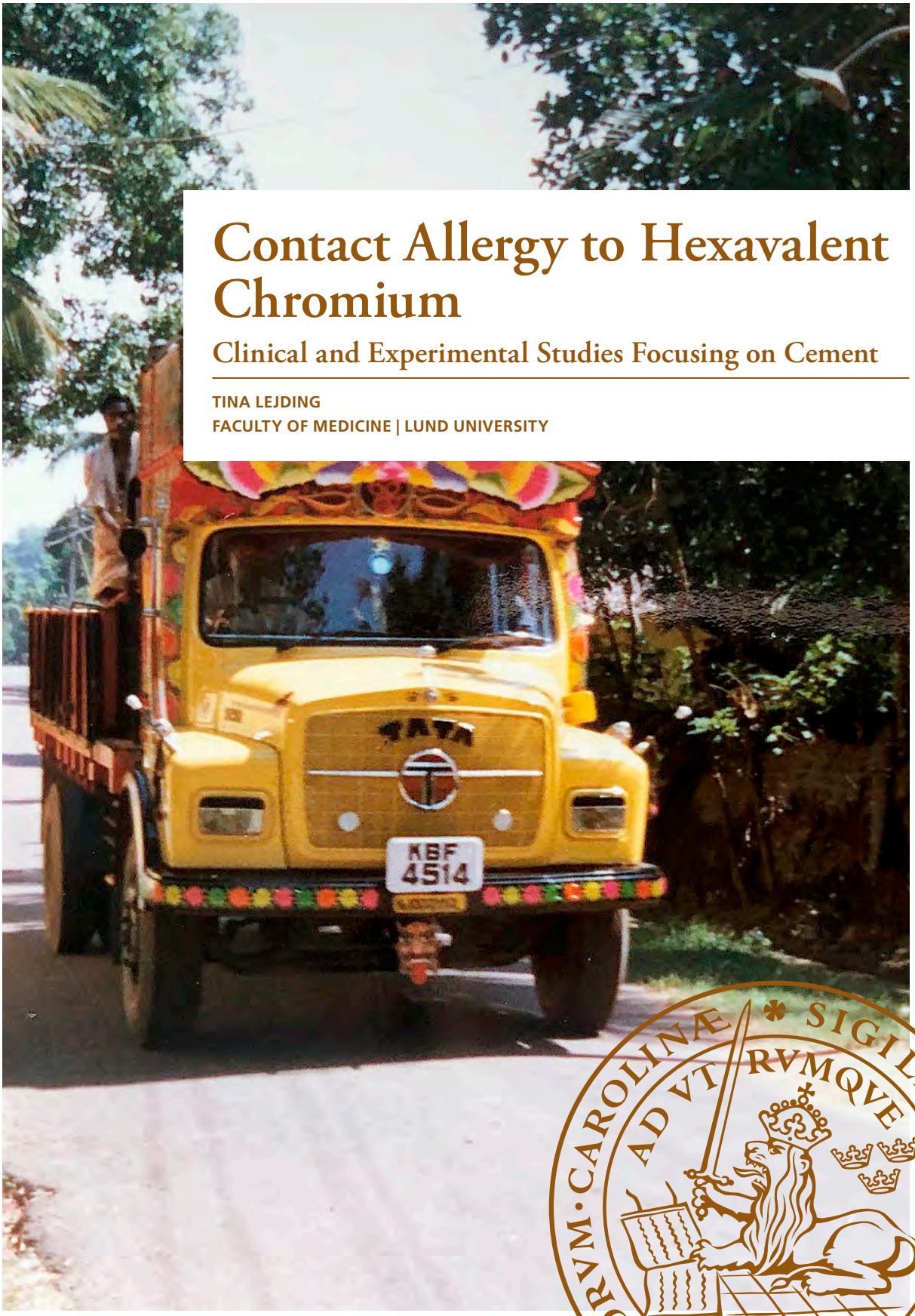
2021

Document Version:
Publisher's PDF, also known as Version of record



Contact Allergy to Hexavalent Chromium

Clinical and Experimental Studies Focusing on Cement

TINA LEJDING
FACULTY OF MEDICINE | LUND UNIVERSITY

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Tina Lejding

LUND UNIVERSITY

DOCTORAL DISSERTATION

By due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Doktoranden, Jan Waldenströms gata 1, Skåne University Hospital, Malmö on Friday 15th October 2021 at 9 a.m.

Faculty opponent
Associate Professor Bjørg Eli Hollund, Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway

Organization	Document name
LUND UNIVERSITY Department of Occupational and Environmental Dermatology Skåne University Hospital Malmö, Sweden	**DOCTORAL DISSERTATION** **Date of issue: October 15, 2021** Sponsoring organization
Author(s) Tina Lejding	

Title and subtitle Contact Allergy to Hexavalent Chromium
Clinical and Experimental Studies Focusing on Cement

Abstract

Chromium is a metallic element, ubiquitous in the environment, with several valences and oxidation states. In nature, chromium is most commonly encountered in its trivalent state, but oxidation of trivalent chromium to hexavalent chromium can take place through human activities. Hexavalent chromium is a potent sensitizer, and can be found in many everyday items. Allergic contact dermatitis to hexavalent chromium tends to be severe and longstanding. One of the most common routes of exposure to hexavalent chromium is through handling cement and cement-containing building materials. Occupational contact dermatitis caused by hexavalent chromium in cement has had, and still may have, a very serious impact on construction workers since dermatitis may be handicapping, resulting in the inability to continue working with the hands. Attempts to find solutions to this problem resulted in a method of reducing the amount of hexavalent chromium in cement to the less sensitizing trivalent chromium by adding iron(II) sulfate to the cement. This considerably lowers the risk of sensitization and handicapping allergic contact dermatitis. The addition of iron(II) sulfate to cement has no negative effects on the quality of the cement, and does hardly increase the cost. In the Scandinavian countries, iron(II) sulfate has been added to cement since the 1980s, and the same measure has been in force in the EU since 2005. This has had an immense impact, and allergic contact dermatitis caused by hexavalent chromium in cement is now rare in countries where the regulation is implemented. However, allergic contact dermatitis to hexavalent chromium in cement continues to be a serious problem globally.

The general aim of the research presented in this thesis was to help people who are allergic to hexavalent chromium, foremost construction workers affected by allergic contact dermatitis due to chromium in cement, and, if possible, to prevent elicitation, or at least reduce their clinical symptoms. This work focuses on the persisting occupational risks in the construction industry and means of alleviating them.
The findings of this work show that there may be alternative measures to prevent elicitation or reduce the clinical symptoms of allergic contact dermatitis in hexavalent-chromium-allergic individuals. Barrier creams containing reducing compounds were found to inhibit the elicitation of allergic reactions in hexavalent-chromium-allergic individuals in a patch test situation. However, the main finding of this work was that the addition of iron(II) sulfate to cement is the best measure to prevent sensitization and thus contact allergy among construction workers.
The cement industry is under pressure to reduce its negative impact on the environment, and now is a suitable time to take responsibility for workers through the addition of iron(II) sulfate, or another reducing substance, to cement in order to ensure that working with cement is safe.

Key words hexavalent chromium, chromate, allergic contact dermatitis, cement, occupational allergic contact dermatitis, prevention, social sustainability

Classification system and/or index terms (if any)

Supplementary bibliographical information	**Language** English
ISSN 1652-8220 - Lund University, Faculty of Medicine, Doctoral Dissertation Series 2021:97	**ISBN** 978-91-8021-104-8

Recipient's notes	**Number of pages** 104	Price
	Security classification	

Signature  Date 2021-08-27

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Malmö 2021

Cover photo/front page: Truck with daily wage earners, Kerala South West India.
Photos where nothing else is mentioned by Tina Lejding

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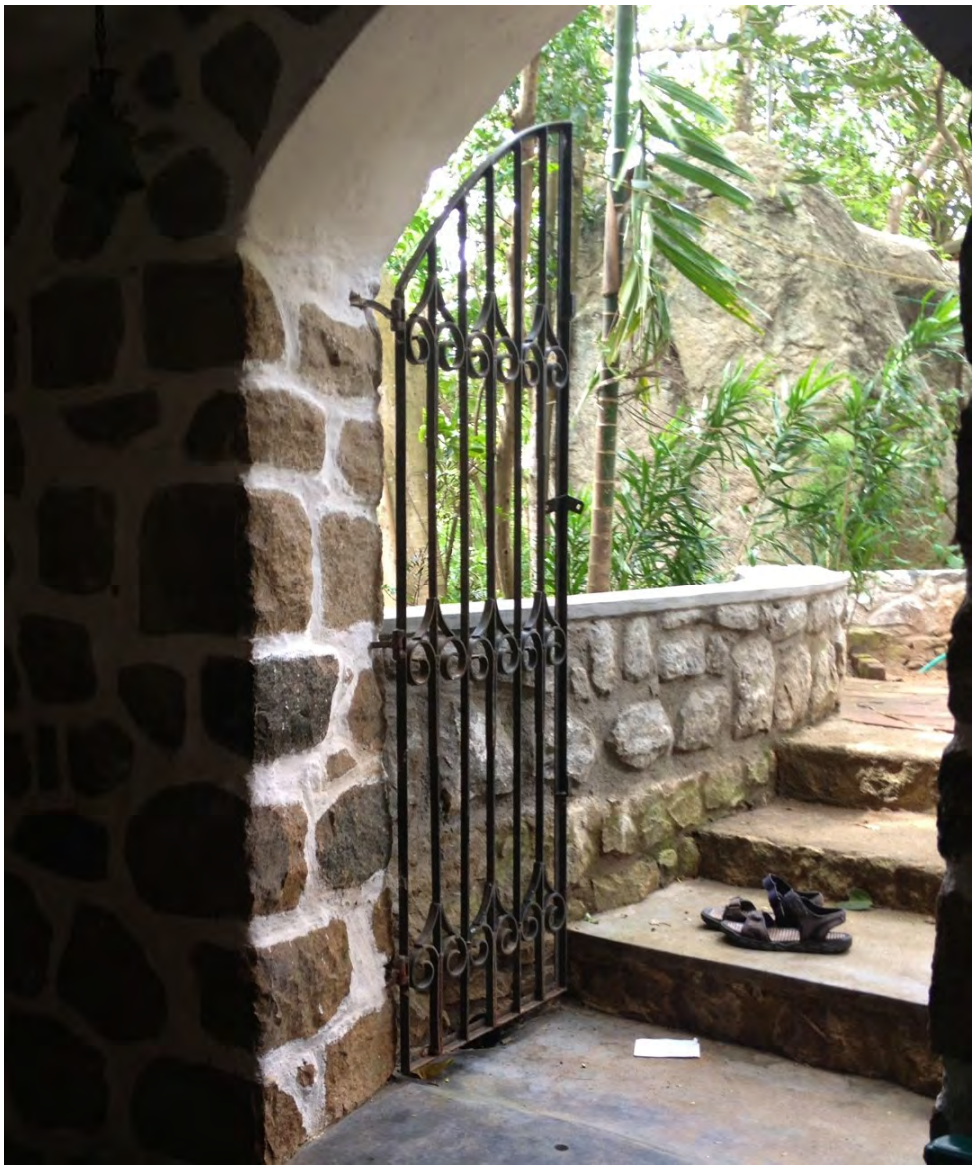
ISBN 978-91-8021-104-8
ISSN 1652-8220
Printed in Sweden by Media-Tryck, Lund University
Lund 2021

Till polaren Olle som såg till att hålla
rätt på bokstäverna åt mig



“En timme ovanför plågorna.

Det var lätt!

Alla log bakom uppfällda kragar.”

From “C-Dur”, “Den halvfärdiga himlen”, Tomas Tranströmer, 1962.

Table of Contents

Thesis at a glance

Paper	Objective	Method	Main findings
I	To provide an overview of the frequency of contact allergy to hexavalent chromium and patient characteristics in dermatitis patients in southern Sweden, 2005-2014.	Analysis of data from DALUK, a local database, and patient medical records.	Chromium is still a frequent allergen: 3.6% of the dermatitis population tested positively. In the retrospective analysis, no association was found with construction work.
II	To find a suitable reducing chemical for further investigations in a possible barrier cream.	Selected chemicals were investigated with regard to their ability to reduce hexavalent chromium.	Several chemicals showed the ability to reduce hexavalent chromium, making them candidates for use in a barrier cream. Due to their different properties, iron(II) sulfate and glutathione were chosen for further studies.
III	To investigate clinically the reducing effect (i.e. the change in reactivity) of barrier creams in a patch test situation in individuals allergic to hexavalent chromium.	18 volunteers allergic to hexavalent chromium were treated with barrier creams of different formulas followed by patch testing with a dilution series of potassium dichromate, the chromium salt used to diagnose hexavalent chromium allergy.	All the in-house-prepared barrier creams reduced the reactivity to potassium dichromate, compared to untreated areas, in a patch test situation. Also petrolatum, one of the vehicles as such, proved to have protective properties.
IV	The protective properties of a commercial barrier cream was evaluated in a patch test situation.	As in Study III.	In the present test situation, the commercially available barrier cream did not perform as expected, i.e. it did not reduce the reactivity.
V	To investigate the amount of hexavalent chromium in cement from countries within and outside the EU.	Dermatologists from different countries within and outside the EU were asked to participate in a study by collecting cement used in their respective country. The cement samples were analysed concerning the content of hexavalent chromium using the diphenyl carbazide spot test.	18/40 cement samples (4 from within the EU) had hexavalent chromium levels above the limit stated in the EU directive 2005, i.e. >2 ppm. Significantly more cement samples from outside the EU contained >2 ppm hexavalent chromium, hence implying a risk of sensitization *(p*=0.027).

List of publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are to be found at the end of the thesis.

I. **A retrospective investigation of hexavalent chromium allergy in southern Sweden**
Lejding Tina, Mowitz Martin, Isaksson Marléne, Bruze Magnus, Pontén Ann, Svedman Cecilia, Zimerson Erik, Engfeldt Malin
Contact Dermatitis 2018 78:386-392

II. **Can reducing cosmetic substances help prevent chromate contact allergy?**
Lejding Tina, Engfeldt Malin, Bruze Magnus, Isaksson Marléne, Persson Lena, Svedman Cecilia, Zimerson Erik, Mowitz Martin
Contact Dermatitis 2020 82:39-44

III. **Skin application of glutathione and iron sulfate can inhibit elicitation of allergic contact dermatitis from hexavalent chromium**
Lejding Tina, Engfeldt Malin, Bruze Magnus, Isaksson Marléne, Svedman Cecilia, Zimerson Erik, Verma Kaushal, Mowitz Martin
Contact Dermatitis 2020 82:45-53

IV. **Can the Reactivity to Chromate Be Changed in Patch Testing Using a Barrier Cream?**
Lejding Tina, Bruze Magnus, Engfeldt Malin, Isaksson Marléne, Svedman Cecilia, Zimerson Erik, Mowitz Martin
Dermatitis 2020 31:373-377

V. **Analysis of hexavalent chromium in cement samples from countries within and outside the EU. A study from the International Contact Dermatitis Research Group (ICDRG).**
Lejding Tina, Persson Lena, Andersen Klaus Ejner, Bruze Magnus, Derevyanko Ludmyla, Elsner Peter, Goh Chee Leok, Gonçalo Margarida, Goossens An, Gülgün Mehmet Ali, Isaksson Marléne, Ljubojevic Hadzavdic Suzana, Matsunaga Kayoko, Mowitz Martin, Nixon Rosemary, Puangpet Pailin, Pratt Melanie, Shuttelaar Marie-Louise A, Sukakul Thanisorn, Verma Kaushal, Zimerson Erik, Özkaya Esen, Svedman Cecilia. In manuscript.

Abbreviations

AAS	Atomic absorption spectroscopy
ACD	Allergic contact dermatitis
aq.	Aqua
CAS	Chemical Abstracts Service
HCA	Hexavalent chromium-allergic
ICDRG	International Contact Dermatitis Research Group
MEC	Minimal eliciting concentration
OR	Odds ratio
ROAT	Repeated open application test
TEWL	Transepidermal water loss
v	Volume
w	Weight

1 Background

In a way, this thesis had its origin in 1990, when I first came to Kerala in the south west of India. That was when India entered my heart. I never thought it would be so. I never thought that a country of which I had heard so much misery, could be so enchanting. During the following decades I have spent years in India, letting my heart lead me there whenever possible for education and work, and also just for leisure. My naïve feelings have matured, but my love for the country remains, although it is obvious that there are many inequalities in Indian society.

In 2014, several years after my first meeting with India, I was introduced to the field of Occupational and Environmental Dermatology, and I was similarly made conscious of my unawareness. I was surprised by the great sphere of Occupational and Environmental Dermatology. Until then, I lacked the perception to identify what I afterwards interpreted as one of the main ambitions in the discipline. Occupational and Environmental Dermatology is about solidarity, focusing on those who are marginalized due to social inequalities. Studies in Occupational and Environmental Dermatology provide knowledge that makes it possible for the voices of people affected by skin disease due to their work, or other forms of exposure, to be heard.

It is well known that allergic contact dermatitis caused by hexavalent chromium often is very severe, difficult to treat, and long-standing, with the risk of invalidity of those affected. The overall aim of the work presented in this thesis was to try to help people allergic to chromium, foremost cement workers affected by hexavalent chromium in cement. The best solution would be to prevent allergy to hexavalent chromium in cement, but this is not yet possible. Therefore, the objective was to find a means of preventing the manifestation of chromium allergy, i.e. the painful skin inflammation resulting from exposure to cement containing hexavalent chromium.

The work described in this thesis has enabled me to combine my love for India, the fight for social equality, and the reduction of occupational diseases.

My motivation, and hope, throughout this work was that the findings could be used by cement workers in the near future. However, due to the COVID-19 pandemic, it has not been possible to carry out clinical research, particularly in India. It was thus necessary to change the plans for this research project, although I still have the ambition to complete the original clinical research.

Figure 1. Construction worker, Kerala, south west India.

1.1 Introduction

This PhD project started as a collaboration between colleagues in New Delhi, India, and Malmö, Sweden. A workshop was held in Malmö in April 2013. This workshop and the initial planning was led by Professor Magnus Bruze at the Department of Occupational and Environmental Dermatology in Malmö, and the participants were interested Swedish and Indian colleagues. Several collaborative projects were discussed, among them, one on chromium. The main idea was to develop a barrier cream to protect against allergic contact dermatitis (ACD) resulting from exposure to hexavalent chromium in cement. The problem of ACD resulting from chromium in cement in India is probably underestimated (1, 2).

Figure 2. Construction worker team, Kerala, south west India.

1.2 Occupational and environmental dermatology

According to the textbook *Yrkes och miljödermatologi*: "Occupational and environmental dermatology can be said to include environmental chemistry, dermatology and social medicine, i.e. causes of disease, skin disease, and social consequences" [translated from the Swedish] (3).

The most common skin disease diagnosed In Occupational and Environmental Dermatology is eczema, also known as dermatitis, mainly of the hands. Dermatitis is an inflammatory skin disease that may have many causes. Dermatitis can be endogenous, i.e. the individual is genetically predisposed, as is the case in atopic dermatitis, or exogenous, i.e. caused by external factors. Examples of exogenous factors are a cold dry climate, frequent hand washing, the use of dehydrating products, irritants, occlusion of the skin by gloves, and so on. Exogenous factors can also include substances to which an individual develops a contact allergy (see below). Occupational and Environmental Dermatology also includes investigations of skin conditions other than dermatitis of the hands, as skin diseases caused or aggravated by exogenous factors can also engage other parts of the body. Occupational skin disease can also manifest itself as skin cancer, certain kinds of acne, photodermatoses, i.e. skin disease related to exposure to ultraviolet radiation, urticarial skin disease, different kinds of chemical burns and ulcers, etc.

Occupational diseases were recognised several hundred years ago. The first textbook on occupational disease, "De Morbis Artificum", was published by the Italian physician Ramazzini in 1700. Two hundred years later, in 1915, Prosser White, a British dermatologist, became a pioneer in occupational dermatology with his book, "The Occupational Affections of the Skin". In 1939, the Committee on Occupational Dermatology of the American Medical Association defined the term occupational dermatosis: "An occupational dermatosis is a pathological condition in the skin for which occupational exposure can be proven to be a main or a contributory reason" (3).

There are two interest groups in Sweden focusing on contact allergy and Occupational and Environmental Dermatology. One is The Swedish Contact Dermatitis Research Group (*Svenska kontaktdermatitgruppen*), which was formed in the 1970s, and the other the Swedish Society of Occupational and Environmental Dermatology (*Svenska Sällskapet för Arbets- och Miljödermatologi*), founded in 2004. These two groups focus on the clinical aspects of Occupational and Environmental Dermatology, but are also performing scientific investigations aimed at improving clinical diagnosis, i.e. patch testing, and prevention. There are a few centres in Sweden working specifically within Occupational and Environmental Dermatology, one of which is the Department of Occupational and Environmental Dermatology at the Skåne University Hospital in Malmö, at which the studies described in this thesis were performed.

The Department was founded 1960 by Sigfrid Fregert, who was then working as a dermatologist in Lund. The need for a specialized unit was identified by Fregert, who worked hard to build up the Department. The work started in close cooperation with the Department of Occupational Medicine in Lund, where Fregert performed his initial laboratory work in Occupational Dermatology. In 1972, Fregert was able to employ the first occupational hygienist in Dermatology ever in Sweden, a chemist specially trained in occupational chemistry, Birgitta Gruvberger. The first focus area when Gruvberger started her work at the Department was the overwhelming problem associated with contact allergy to hexavalent chromium in cement, leading to cement dermatitis in many construction workers (oral communication Birgitta Gruvberger, 2021). Translational research finally led to today's legislation restricting the amount of hexavalent chromium in dry cement to 2 ppm (0.0002% or 2 mg/kg). During the following decades, the Department continued to grow as others were employed, including biomedical analysts, chemists, physicians, social workers, nurses and assistant nurses. The Department moved from Lund to Malmö in 1995 (4).

In most countries, basic investigations of occupational and environmental contact allergies are performed at general dermatology clinics. Units for occupational patients, sometimes coupled to an occupational and environmental medicine department, are common, but they sometimes work independently. Examples of countries were care is given via an occupational dermatology clinic are Finland, the Netherlands, Germany and Sweden.

Research in the field of Occupational and Environmental Dermatology almost always starts with the patient. The translational approach has led to many different research fields and new challenges as workers become exposed to new possible irritants and allergens.

In occupational dermatology, there is a unique opportunity to identify risks and change routines in order to reduce the exposure to allergens and irritants, or to introduce means of protection. This is usually done in collaboration between workers and their employer. The aim of each investigation is to benefit not only the worker, but also the workplace and the society as a whole. The knowledge gained can be used to influence legislative organs leading to the implementation of regulations protecting a whole group of workers. An example of such a group is cement workers in Sweden.

Figure 3. Construction worker digging for stones to build with, Kerala, south west India.

1.3 The skin and allergic reactions

Allergic reactions may be local or systemic, and different organs may be affected. The subject of this thesis is reactions that are usually localized in the skin, and where the skin is the main organ affected. The most important concepts of ACD are explained in figure 4 below.

Allergy: An immune response to something the body experiences as foreign. Individual factors contribute to the sensitization leading to an allergy. Whether this leads to clinical manifestations of the allergy depends on how the individual is exposed to the allergen, and the dose. Allergic reactions are divided into four major types based on their pathophysiological background, immunological mechanism and clinical manifestation. Type I (antibody-mediated, antibodies against external allergens such as pollen), Type II (antibody-mediated, antibodies against cell-bound antigens), Type III (antibody-mediated, antibodies form immune complexes) and Type IV (cell-mediated) (3). The first three types of allergies will not be further discussed in this thesis. **Allergen:** A substance able to sensitize, and thus cause an allergic response (3), often used synonymously with hapten. **Atopic dermatitis:** Dermatitis that can be found as one of the manifestations in atopic individuals. The pathogenesis of atopic dermatitis is linked to both immune and barrier abnormalities (5). **Atopy:** An umbrella term including allergic asthma, allergic rhinoconjunctivitis (Type I allergy) and dermatitis. The condition is hereditary. An atopic individual can have manifestations of one, two or all three of the components with varying severity. An atopic individual may also have subclinical atopy, i.e. dry skin that has not yet, or will not ever, proceed to dermatitis (3, 6).	**Contact allergy:** Synonymous with contact sensitivity (7) and refers to Type IV allergy which often manifests as ACD affecting the skin. **Contact dermatitis:** Dermatitis caused by contact with a substance or trauma to the skin. Contact dermatitis may be *allergic*, i.e. due to allergy to a substance, or *irritative*. Irritative contact dermatitis can be caused by irritating substances (which in many cases are not allergenic, although some substances have the potential to cause both irritative and allergenic reactions), and by traumiteration, for example, repeated hand washing. Despite the different immunological mechanisms underlying ACD and irritant dermatitis, it appears that these conditions have at least partially overlapping pathophysiology (8) and immunology. **Eczema:** Used synonymous with dermatitis. **Hapten:** Sensitizing chemical, directly protein-reactive (9, 10). Often used synonymously with allergen by contact allergologists. **T-cell:** Also called T- lymphocyte and is a kind of white blood cell. There are different subsets of T-cells with specific tasks active in the adaptive immune system (11, 12).

Figure 4. Basic concepts in allergic contact dermatitis, ACD.

1.3.1 The skin

The skin is the largest single organ in humans. In an adult, the skin weighs about 2 kg (excluding the subcutis) and has an area of ~2 m^2. The main function of the skin is to provide protection and to regulate temperature. The skin is a very important part of the immune system, providing protection from threats in the surrounding environment and changes that can occur within the body itself, for example, the development of cancer. The skin is divided into three main compartments: the epidermis, the dermis and the subcutis. Each of these compartments in turn consists of functional layers communicating with each other as illustrated in Figure 5 (13-15).

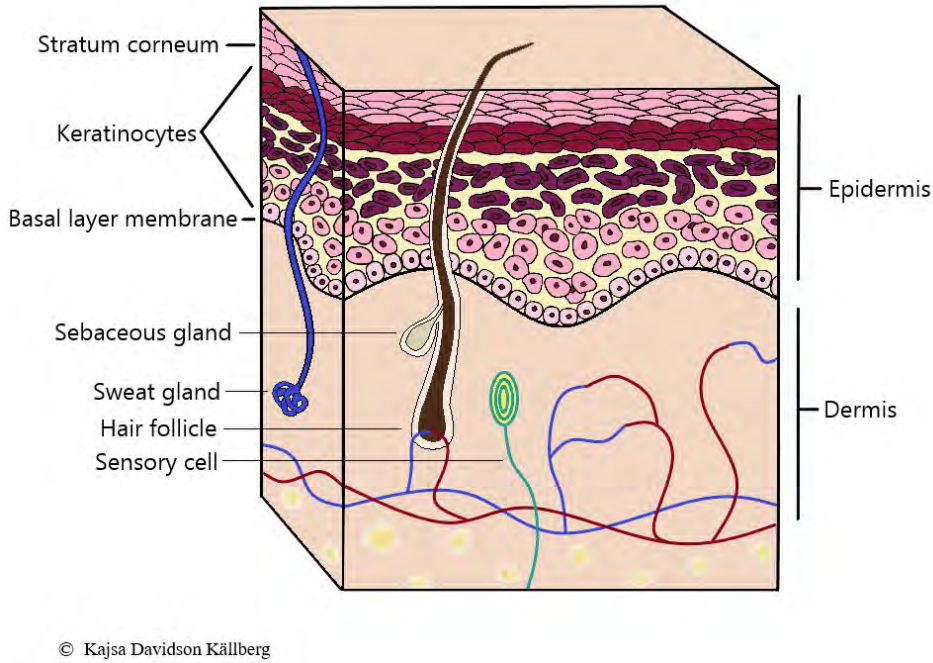


Figure 5. The structure of the skin showing the various kinds of cells and appendages.

The epidermis is the part of skin that we can see and touch. It is between 0.05 and 0.1 mm thick in most areas, except on the hands and feet, where it is thicker. The epidermis consists mainly of two types of skin cells, keratinocytes and melanocytes. Melanocytes are pigment cells producing pigment to protect the skin from the harmful effects of UV radiation. Keratinocytes are by far the most common cells, and they are responsible for the regeneration of the epidermis. Keratinocytes develop just above the dermis, in the basal cell layer, and wander upwards to the outermost layer, the stratum corneum, during maturation and regeneration of the epidermis. When they reach the stratum corneum the keratinocytes have lost their cell nucleus and are dead. These cells, called corneocytes, as well as the rest of the epidermis, are embedded in lipids and other kinds of moisturising substances which together provide the barrier function of the skin. The primary function of the epidermis is to produce the stratum corneum, constituting the semi-permeable barrier that is the prerequisite for terrestrial life. The loss of water from the skin is regulated by the epidermis and its ability to do so depends on the nature of the stratum corneum (14, 16, 17). The barrier function of the stratum corneum is necessary for sustained health. An intact barrier also offers protection from bacteria, microorganisms, and other foreign substances that could possibly harm the body.

The dermis, situated just below the epidermis, is thicker, up to about 5 mm. The dermis provides stability to the skin, helps regulate the body temperature, provides nutrition and oxygen to the epidermis (which has no blood vessels) and directs signals from sensory cells in the skin to the brain. The dermis consists of the proteins collagen and elastin produced by cells called fibroblasts. Adnexal structures, such as sebum-, and sweat-producing glands and hair follicles are located in the dermis.

The subcutis is the deepest layer of the skin. It provides protection against cold and mechanical stress, and is made up of adipocytes, cells that contain fat. The vascular structures in the subcutis are coarser than those in in the dermis. Nerves and lymph vessels are also located in the subcutis.

The skin also has different kinds of sensory cells and circulating immune cells.

The viable structures of the skin can be reached from the outside as the stratum corneum can be penetrated by substances that can then give rise to reactions in the skin. This is sometimes exploited in the treatment of skin diseases, or systemic symptoms such as pain and internal diseases. The size of a molecule, i.e. its molecular weight, determines its ability to penetrate the skin. Healthy skin allows the penetration of mainly molecules with molecular weights up to about 500 Da (18). However, other factors such as lipophilicity, hydrophilicity, etc. are also important, and therefore larger molecules may also be able to penetrate healthy skin. Damaged skin allows the penetration of larger molecules.

Transepidermal water loss (TEWL) is often used as a measure of the degree of permeability of skin. Measurements of the TEWL provide information on how well the protective properties of a specific area of skin are maintained. The same kinds of factors that are believed to influence the TEWL also influence the properties of the skin (19-22). These factors include age, season, and location on the body. The function of the skin is strongly connected to its properties (15) and a healthy skin provides better protection. TEWL can be used to assess the efficiency of protective measures such as barrier creams (23). External factors affect the skin and its barrier function. This can be exemplified by the association between the barrier function, dermatitis of the hands and the time with wet hands, and washing the hands with soap and water with subsequent towel drying (24, 25).

1.3.2 Contact allergy and allergic contact dermatitis

Contact allergy is a Type IV reaction, also called hypersensitivity. Contact allergy is caused by exposure and sensitization of the individual to a substance that can cause an allergy, an allergen (also called a hapten). Contact allergy is not a disease per se; it is an immune status. If the exposure to the allergen, or a cross-reacting substance, is not sufficient, no disease will manifest. Contact allergy can be caused by a large number of substances. Today, about 5000 substances have been identified as possible allergens (26, 27). However, most contact allergies are caused by the 50

allergens we are most often exposed to. Contact allergy is common, and is believed to affect about a fifth of the general population in Europe (28-31). The prevalence is twice as high in women as in men. Metal allergy is the most frequent contact allergy among both dermatitis patients and the general population (32). It has been estimated that about 15-20% of the Western population is allergic to at least one metal (33). The most common contact allergens in the European population are the metals nickel, cobalt and chromium, but fragrances, preservatives and para-phenylenediamine, a marker for permanent hair dyes, are also common allergens (34).

The clinical manifestation of ACD in the skin involves inflammation of the skin caused by repeated or prolonged exposure to a sufficient dose of the substance to which the individual is sensitized. Thus, ACD requires a specific acquired immunity, leading to the development of immune cells, which mediate skin inflammation. Inflammation is usually restricted to the exposed area of the skin, i.e., where the allergen comes into contact with and penetrates the skin. However, systemic contact dermatitis may arise when an individual who is allergic to a certain substance exhibits dermatitis when the substance in question is ingested or inhaled (34-36). Exposure to hexavalent chromium is usually via the skin, however, oral provocation studies have shown the possibility of systemic disease. Fregert challenged chromium-allergic patients with an oral dose of potassium dichromate (the chromium salt used to detect allergy to hexavalent chromium in investigations of contact allergy), and found that they all reacted by dermatitis of the hands, and one exhibited generalized dermatitis (37).

ACD develops through two phases: sensitization, i.e., the development of an allergy to a certain substance due to continuous or repeated exposure, and elicitation, the response of the skin to re-exposure to the substance, resulting in clinical manifestation. Some authors also include a third phase: resolution or the recovery phase, describing the return to clinically normal skin (38).

The immunological mechanisms behind ACD are complex, and are still not fully understood. Immunity, i.e., the ability to resist damaging substances or organisms, is classified as either innate or acquired, and involves the whole body, including its physical barriers, comprised of the skin and the mucous membranes in the gastrointestinal and respiratory systems (11). Immunology as a discipline is relatively young, and evolved in the last quarter of the 19th century. The four types of hypersensitivity, including Type IV hypersensitivity, were categorized in the 1960s. It is difficult to study the mechanisms in immunology. Several methods have developed, including murine studies, however, the use of animals in such studies is controversial (39, 40).

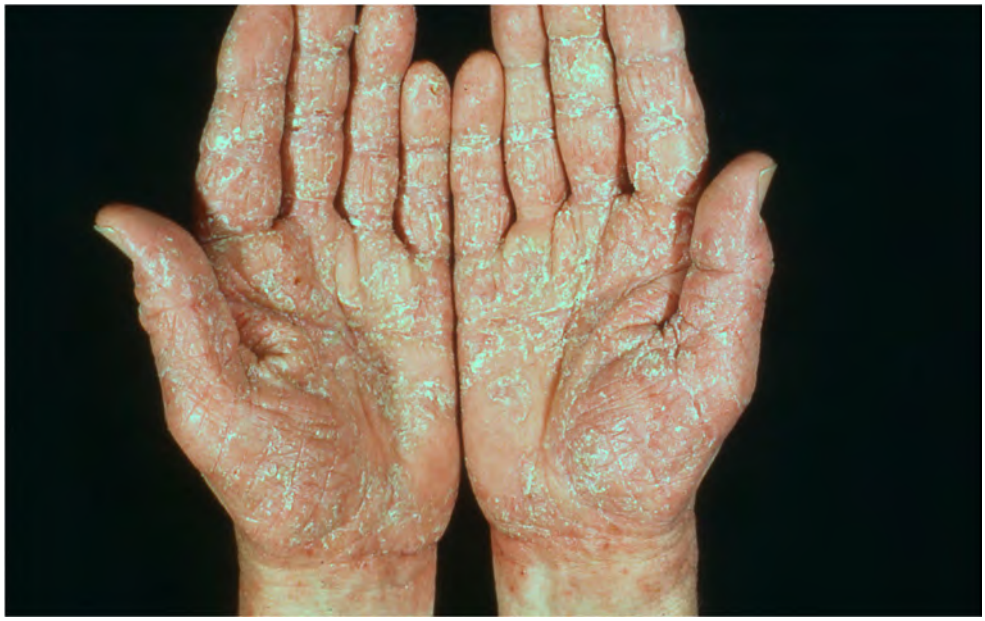


Figure 6. Occupational allergic contact dermatitis. (From the picture archive of the Department of Occupational and Environmental Dermatology, photographer unknown)

Sensitization

The first step in the development of ACD is the induction phase, also called the afferent phase or the sensitization phase. This phase includes the introduction of an allergen into the immune system. The allergen must first penetrate the skin, foremost the stratum corneum of epidermis.

Most contact allergens are so-called haptens, small molecules which, after penetrating the skin, to bind to proteins, modifying them into immunogenic proteins, forming a complete allergen (8). Some haptens must undergo additional transformation to form an allergen. This transformation can take place through metabolism inside the body, and such haptens are called pro-haptens. The transformation can also take place through chemical reactions such as oxidation, or by UV radiation outside the body; such haptens are called pre-haptens. Hapten–protein complexes are formed via strong covalent binding of the hapten to specific amino acids of proteins in the individual being sensitized (9, 10, 12).

Skin inflammation is induced via innate immunity directly upon exposure of the skin to contact allergens as a result of the production of molecules causing inflammation, mainly interleukins. The inflammatory response caused by these molecules leads to the activation of antigen-presenting cells (34). There are different kinds of antigen-presenting cells, all of which are white blood cells, called dendritic-

cell-type leukocytes. When located in the epidermis they are usually called Langerhans cells, and when located in the dermis, dermal dendritic cells (31).

The inflammation leading to activation of the antigen-presenting cells also causes them to migrate from the skin. The antigen-presenting cells capture the antigens in the skin and transport them via the lymphatic vessels to the draining dermal lymph node, where the antigen is presented to T-cells, priming and activating them (41). The priming of naïve T-cells leads to clones of diverse kinds of allergen-specific effector T-cells that have different tasks in the immune response. Some of them have the potential to become long-lived memory T-cells (33, 34, 42, 43). Memory T-cells can spread to peripheral tissue where they can participate in a subsequent immune response and in surveillance (12). The individual has now become sensitized.

Sensitization is almost without exception asymptomatic (33), but in some cases it presents as primary acute ACD. The sensitization phase can take place after days, weeks, months, or even years, of exposure to an allergen. When it occurs, it commonly lasts for 8-15 days in humans, but may be shorter or longer. Subsequent exposure to the remembered allergen will cause elicitation (12).

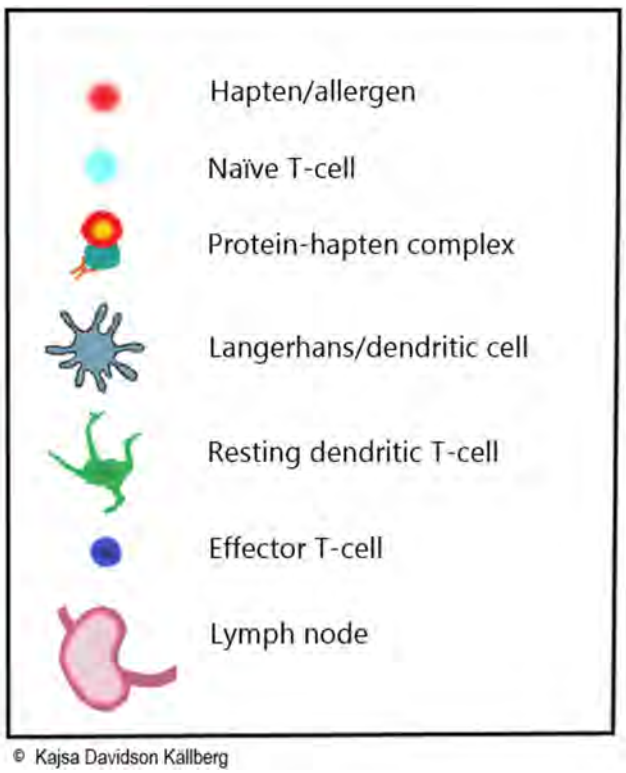


Figure 7. Key to Figures 8-10.

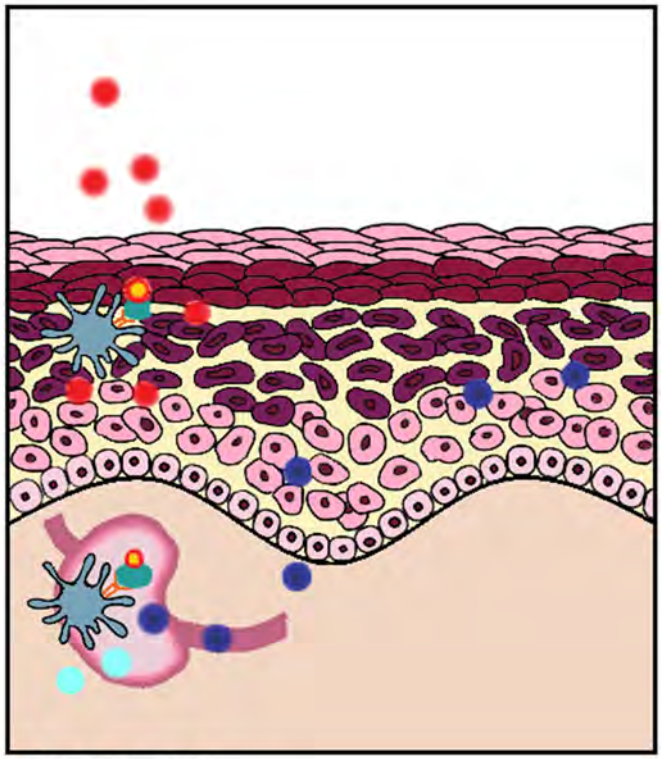


Figure 8. Illustration of the sensitization phase. The key to the symbols is given in Figure 7.

Elicitation

The second step in the immunological process of ACD is called the efferent phase, the challenge phase or the elicitation phase. The elicitation phase is triggered upon re-exposure to a sufficient dose of the same or a cross-reacting allergen, resulting in specific T-cell activation with clinical symptoms (7). Upon contact, the allergen-specific T-cells that have developed are activated and trigger the inflammatory process responsible for the manifestation of skin inflammation (12, 33, 34).

The memory response is much faster than the primary response to allergens. Infiltration of allergen-specific effector and memory T-cells causes a local inflammatory response within 24-72 h after re-exposure.

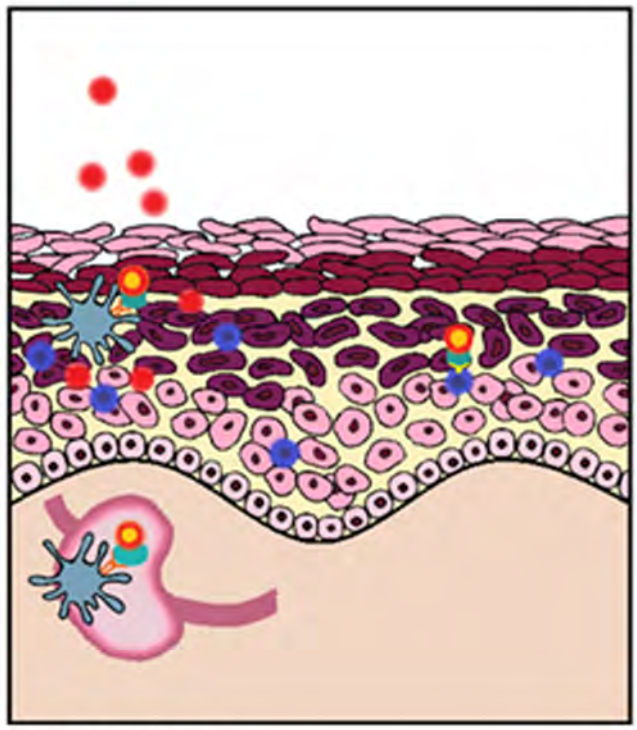


Figure 9. Illustration of the elicitation phase. The key to the symbols is given in Figure 7.

Resolution and site-specific memory

Resolution is regarded as a passive process, resulting in a return to homeostasis. As described above, some T-cells are found at the site of previous allergen contact. T-cells can be detected in clinically normal skin after the initiation of ACD (38), and the status of the skin is thus altered compared with before sensitization took place.

The local retention of T-cells is thought to explain local skin memory as observed in re-test and flare-up reactions of previously allergen-exposed skin. In these cases, accelerated inflammatory reactions are seen at previously exposed sites after epicutaneous, oral or inhaled contact with an allergen to which sensitization has occurred (35). In the case of oral intake or inhalation, the reaction is caused by allergens in the circulation. Circulating allergens can trigger persisting T-cells, resulting in a flare-up reaction (38) where the response is greater than at previously unexposed sites. Exposure to contact allergens hence leads to a strong site-specific and weaker global memory response to the allergen (44). From a clinical point of view, it can be noted that sites of previous ACD resulting from an allergen have higher test reactivity upon re-testing with the same allergen (45, 46).

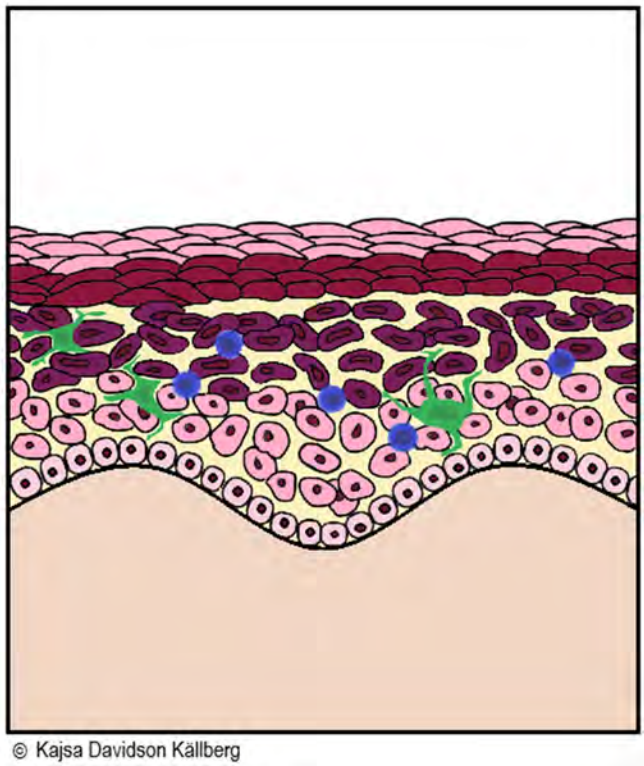


Figure 10. Illustration of the resolution phase. The key to the symbols is given in Figure 7.

1.4 Diagnosis of contact allergy

Patch testing is the gold standard for the diagnosis of contact allergy, as described below. Research performed to find alternative methods of diagnosing contact allergy that could be useful during certain circumstances are also presented.

1.4.1 Patch testing

As the environment and exposure are constantly changing, there is a need for standardization with regard to patch test substances, the testing technique and patch test result reading (7, 47-52).

During patch testing, substances are usually applied on the upper part of the back of the individual. The test substances are placed in test chambers held on the skin by adhesive tape as illustrated in Figure 13. The material of the test chambers can vary, but they are often made of aluminium or plastic. A given amount of the test

substance, defined by the chamber area, mixed in a vehicle, usually petrolatum or water, is loaded into the test chamber, or on a filter paper put in the test chamber, using a micropipette for aqueous solutions (53) and a syringe for petrolatum mixes. The test chambers remain in place for 48 h before being removed and discarded. Patch test readings are recommended on Day 3 or 4, and Day 7.

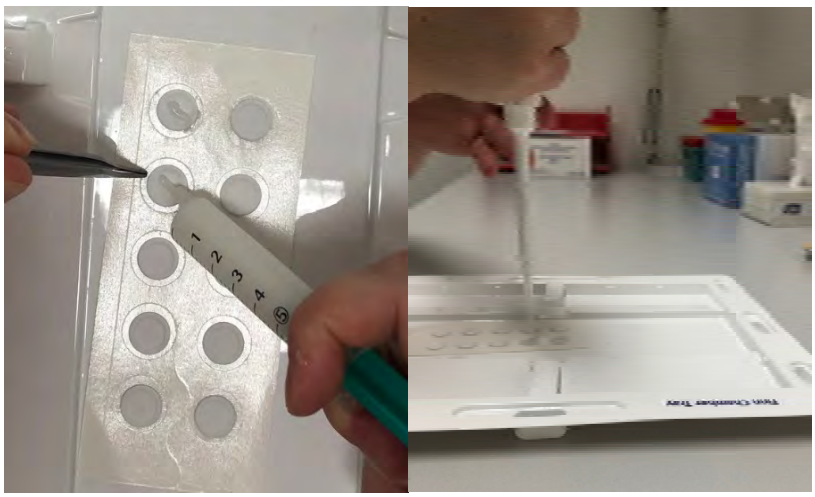


Figure 11 and 12. Loading a patch test substance mixed in petrolatum using a syringe, and liquid patch test substance using a micropipette, into test chambers.

Patch test readings has been performed by this routine at our Department since the mid-1990s (4). It is important to perform readings of the patch test reactions on two different occasions, the latter on Day 7, since there is variation in how allergens penetrate the skin, depending on whether they are initially pro-haptens or pre-haptens, and in how they elicit ACD (54). Most patch test substances give rise to a stronger reaction on the first test reading, and the reaction has often started to fade at the second patch test reading, while others, for example, corticosteroids may not appear until the second test reading (4). Up to 15% of contact allergies in a baseline series may be missed if a second test reading on Day 7 is not performed (55).

The International Contact Dermatitis Research Group (ICDRG) has developed a classification system for the scoring of patch test reactions (47). "+" denotes a weak positive reaction, seen as faint erythema and infiltration covering the whole test area; "++" denotes a strong positive reaction and is defined as erythema covering the whole test area which also contains infiltration, papules and one or few vesicles. "+++"denotes an extreme positive reaction, showing more vesicles and sometimes also coalescing vesicles forming a bulla. Doubtful reactions are denoted "? +" and irritative reactions, "IR". This classification system is accepted internationally, and used to present results in studies in the area of contact allergy worldwide. However, there are some local variations and modifications of the ICDRG classification

system (46). Despite the standardization of the reading and interpretation of patch tests, they may be user dependent. However, it has been shown that the variability between experienced patch-test readers is low (56).

Patch testing can be performed with an individual's own material if necessary. In such cases, the substance must be evaluated to ensure that it does not cause harm, i.e., it must not be toxic, an irritant or cause sensitization of the individual. For example, to perform patch testing without causing irritation the pH must be between 4 and 9, and substances that are more alkaline or acidic must be buffered (57). In the work presented in this thesis, patch testing with cement was planned. This required the preparation of an extract of the cement, so as not to harm the skin mechanically, and buffering due to the alkalinity of cement (58). When interpreting the results one should bear in mind that the method of exposure is different from normal exposure, which may affect the clinical response.

The marker for allergy to hexavalent chromium at patch testing is the chromium salt potassium dichromate ($Cr_2K_2O_7$). Patch testing with 0.5% potassium dichromate in petrolatum was introduced in 1931 (59) and it is still used in the same way in the Swedish and European baseline series.

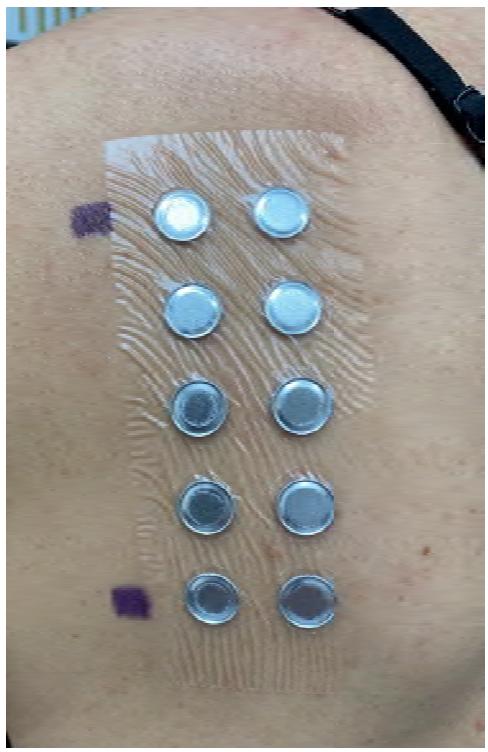


Figure 13. Patch test unit with 10 chambers mounted on the upper back. (Photo: Kajsa Davidson Källberg)

1.4.2 Other tests

Other tests may be useful in the investigation of ACD when patch testing does not provide sufficient information, when additional diagnoses are suspected, when assessing the relevance of a positive reaction or to rule out a diagnosis. Some additional tests related to the subject of this thesis are described briefly below.

A *repeated open application test* (ROAT) can be performed clinically, for example, when a hygiene product contains an allergen that an individual has reacted to, but the patch test of the hygiene product "as is" was negative. The test is designed to mimic a real-life exposure of the substance (60, 61). The ROAT is often applied on the ventral forearm, and the area of skin tested is about 3 cm^2. The substance is applied to the test area as often as it would have been in real life, e.g. twice daily. The test continues until a skin reaction appears or, if no reaction is seen, usually for a maximum of 28 days. The method is described in standardized guidelines (7), and patients can easily be instructed in how to perform it at home (62). A positive ROAT result can indicate a contact allergy, but cannot prove it, since the reaction seen in the skin may also be irritative. To interpret a positive reaction as a contact allergy, controls must be tested in the same way, and show negative results. The method is also used in scientific studies to assess the efficiency of barrier creams, for example.

Intra-cutaneous tests have been used in the clinic historically, and may still today be used in cases of doubtful patch test reactions (63). Intra-cutaneous tests can also be used in research studies. In these tests, the substance is dissolved in saline and injected, usually, into the volar forearm. An injection that raises a wheal of about 4 mm in diameter, equivalent to about 0.1 mL fluid is used. A red, raised dermal infiltration of ≥4 mm diameter after 72 h is considered a positive result (63, 64).

The lymphocyte transformation test is an *in vitro* method rarely used in the clinic. The test relies on radioactive labelling to detect proliferating lymphocytes. It can be used to identify metal sensitization, but has the disadvantage that it involves the handling of radioactive material (65). The method has been revised a number of times, and is suggested for certain kinds of investigations, for example in suspected drug allergies (66, 67), but also in the investigation of ACD (68).

As a further development of this test, *the lymphocyte proliferation test* has been described. The method is suggested to offer an alternative for diagnosing vulnerable patient groups and patients who live far from a patch test clinic, so that they do not need to expose themselves to unnecessary risks or travel far to a patch test clinic to undergo the investigation. This test could potentially be a complement to the patch test (69, 70).

1.5 Chromium

Chromium, from the Greek “chroma” meaning colour, is a metallic element with number 24 in the periodic system and an atomic weight of 52.0. It was named by the French chemist Vauquelin, who identified it in 1797 (71). Chromium is found in different valence states (39, 72-74), and these occur in many kinds of compounds (75). When in the metallic form chromium has zero valence, and is not a sensitizer (76). Chromium is almost always encountered in the trivalent (Cr(III)) or hexavalent (Cr(VI)) form, since the other valences are unstable and prone to react with other chemicals.

Many terms are used to describe chromium. Chromate is a frequently used term, and is often used synonymously with chromium, however, the term chromate describes the salts of hexavalent chromium. The main parameters of importance for the sensitizing and eliciting capacity of chromium in a product is its valence, state, solubility, concentration, pH, exposure time, presence of reducing material, and biological factors such as the skin barrier (39, 59, 73, 77). Only trivalent and hexavalent compounds of chromium are sufficiently stable to act as sensitizers (76, 78, 79). It is important to distinguish between hexavalent chromium, which is the form of chromium that is most harmful to humans, and trivalent chromium.

The skin is virtually impermeable to some trivalent chromium compounds and marginally permeable to others. This is explained partly by the affinity of trivalent chromium for epithelial and dermal tissues, forming stable complexes that slow the rate of diffusion (80). Trivalent chromium has a strong binding capacity to proteins once inside the body (81) and can act as a sensitizer with the capacity to elicit ACD, foremost when released from leather (62, 73, 82). The eliciting capacity of trivalent chromium is much lower than that of hexavalent chromium, i.e. higher concentrations of trivalent chromium are needed to elicit the same reaction (83-85). Trivalent chromium is also less toxic and irritating than hexavalent chromium (86).

Hexavalent chromium is the most powerfully sensitizing form of chromium. This is explained by its solubility and capacity to penetrate into the skin. Hexavalent chromium has higher membrane permeability than trivalent chromium (87) and is negatively charged at neutral and alkaline pH (39, 78, 86) leading to greater skin penetration (highest at alkaline pH) (39). The threshold for sensitization by hexavalent chromium is reported to be approximately 10 ppm (86). Hexavalent chromium can be harmful to humans not only as a contact sensitizer, as described below.

1.5.1 Chromium in the environment

Chromium is ubiquitous in nature (37, 85, 88). It is the fourth most common material in the Earth's crust (76) and the 17th most common in the mantle (89). Chromium occurs naturally in its trivalent state in soil, plants and animal tissues (73, 90).

Chromium also enters the environment artificially through human activities such as timber treatment, leather-, textile- and steel manufacturing, and industrial applications such as electroplating. Chromium can pollute drinking water as a result of ground water contamination by mining (91, 92). Environmental effects, such as genotoxicity and hyper-accumulation of chromium in plants, have also been described (89).

1.5.2 Sources of exposure to humans

The focus of this thesis is occupational exposure to hexavalent chromium, i.e. cement in concrete, mortar and other kinds of building materials. However, hexavalent chromium is omnipresent, and others sources of exposure should be considered.

Hexavalent chromium is found in a wide variety of metal items such as metallic ear rings and in the metal industry. It is also found in domestic devices and household products such as pots, hand laundry and detergents and bleaches, matches and in mobile phones. More industrial sources of hexavalent chromium are anti- rust paints, sealant hardeners used in the aircraft industry, in galvanized sheets, foundry sands, wood preservatives in processing of sulfate pulp, and fuel ash. Hexavalent chromium is also present in dental implants and prostheses. Less common but described sources of hexavalent chromium is toys, textiles, stamps, magnetic tapes, tattoo inks, and cosmetics. Finally hexavalent chromium can be found in food such as mushrooms, potatoes and chocolate (at levels of μg/g) and drinking water (59, 76, 92-113).

Trivalent chromium is very common in leather tanning (114) and is found in consumer products such as shoes (115-117), as well as in occupational products such as protective leather gloves (118). Chromium-tanned leather is currently believed to be the most common cause of allergic chromium dermatitis, for example, in Denmark (119, 120).

Figure 14. Tea shop in Kerala, south west India, where chromium is present in the stainless steel equipment.

1.5.3 Human effects

It is generally accepted that chromium is an essential element for humans but the daily requirement of chromium in human nutrition has not yet been defined. During the latter part of the 20th century, it was suggested that chromium was necessary for adequate glucose uptake, and that it was involved in blood lipid levels (121-123). There was also a discussion as to whether chromium supplementation in athletes resulted in anabolism (124). However, it was concluded in an extensive review in 2014 that theories concerning the role of chromium in metabolism could not be proven (125).

In addition to the possible positive effects of chromium in humans, several negative effects are well known and have been described. In addition to ACD, skin exposure can also induce chrome ulcers (126) or “chrome holes” as they have also been called

(127), irritative dermatitis (37, 76, 128) and photosensitivity (88, 129). Chromium can also cause ulcers of the mucous membranes (88), corrosive reactions on the nasal septum (76), and neurotoxicity (130). Systemic effects affecting the kidneys, liver, airways (e.g. bronchitis) (88) and the cardiovascular system have also been reviewed (131).

The carcinogenic effect of hexavalent chromium in humans has been known for a long time, and there is considerable documentation of the elevated risk of cancer in respiratory organs among workers exposed to chromates (88, 131-134). Hexavalent chromium in drinking water has also been associated with an increased risk of cancer in the gastrointestinal tract (91, 92). Regarding allergic reactions to chromium, ACD is by far the most studied, and well-known manifestation. It rarely causes allergic asthma or rhinitis, but has been suspected of doing so (39). Rhinorrhoea in a chromium-sensitive individual working with chromic acid etching has been described (135). Metal allergy has also been associated with device failure following the insertion of hip and knee prostheses, and other implants (136).

Chromium allergy can also cause systemic allergic dermatitis which, in contrast to ACD, involves other parts of the body than the exposure site. Oral provocation has been reported to result in a flare of dermatitis in challenged chromium-allergic individuals (37, 76, 137). It has been reported that small quantities of potassium dichromate taken orally, as a “homeopathic drug containing dichromate”, resulted in severe exacerbation of dermatitis in a chromium-allergic bricklayer (76).

1.5.4 Historic aspects of chromium immunology

Knowledge concerning the precise immunological effects of chromium is growing continuously, and the complex mechanisms behind them have been discussed and described for many years (138).

Originally, it was assumed that hexavalent chromium compounds were the sensitizing agent since no reactions had been seen to trivalent chromium in individuals allergic to hexavalent chromium (139). It was, however, soon found that hexavalent chromium did not bind to proteins. This led to the theory that trivalent chromium is the hapten since it binds strongly to skin proteins by covalent bonds (140, 141). It was also reported that trivalent chromium had a minimal sensitizing capacity if it had to penetrate the skin and that it is hexavalent chromium that enters the epidermis (141, 142).

Fregert and Rorsman described the capacity of chromium to sensitize in the mid-1960s when they demonstrated hexavalent chromium to be the most potent valence state, but that trivalent chromium could also elicit reactions in individuals allergic to hexavalent chromium (143). This has later been described by numerous authors (83, 142, 144). It was found that hexavalent chromium was almost completely taken

up by blood cells after intravenous injection, whereas trivalent chromium was bound to plasma proteins, leading to the conclusion that only a small part of trivalent chromium manages to penetrate into the cells (81). At the beginning of the 1980s, Fregert concluded that hexavalent chromium penetrates the cell membranes in the body and is thereafter reduced to trivalent chromium, which binds to the proteins forming the conjugate acting as the actual allergen (73). This theory is now generally accepted (39, 76, 79, 145, 146).

Different factors determine the degree of penetration of each metal species into the skin (80). Chromium has similarities with other metals regarding immunology, but also its own unique mechanisms. The initiation of contact allergy to metals requires both an antigen stimulus leading to an adaptive immune response, and a pro-inflammatory danger signal. Chromium is able to generate both at the same time, explaining its potency as an allergen (33, 39). The mechanism by which hexavalent chromium induces immune activation differs from that of other metal allergens, since it apparently generates its own pro-inflammatory signal in intact skin. It has also been speculated that hexavalent chromium triggers a stronger inflammatory response due to activation via mitochondrial reactive oxygen species production (39, 130, 146, 147).

1.5.5 Prevention

The term prevention can be used in a variety of situations. In health care the terms primary and secondary prevention are used with slight variations in their definitions. The term tertiary prevention is also sometimes used in health care. Since the meaning of the term “tertiary” implies treatment or rehabilitation, it is not recommended for use in health care since these actions might be difficult to interpret as “prevention”. Primary prevention attempts to prevent a disease. Secondary prevention attempts to detect a disease early and prevent further negative consequences of the disease (148). The required action differs depending on which disease is to be prevented. Preventive actions can be viewed from an individual and from a general point of view.

In the context of contact allergy, prevention is foremost concerned with avoidance or reduction of exposure in order to reduce the risk of sensitization.

Secondary prevention involves diagnosing ACD as early as possible to prevent, or at least reduce further exposure, and thus additional negative effects. Importantly, in this case, secondary prevention includes all actions to reduce the elicitation of ACD in already sensitized individuals.

If it is possible to avoid or sufficiently reduce the allergen to which an individual is contact allergic, the allergy will not manifest as a disease. This implies a unique opportunity to remain healthy after the development of a contact allergy. Consequently, completely avoiding exposure, or reducing the dose sufficiently is

the only way to heal ACD. The measures necessary to avoid further exposure differ depending on which allergen causes the allergy. In occupational ACD it might be very difficult for individual workers to protect themselves and thus prevent harmful exposure.

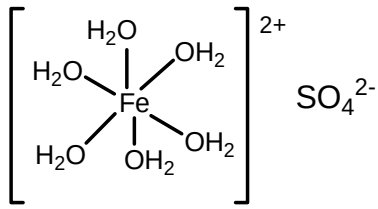
Iron(II) sulfate heptahydrate ($FeSO_4$) CAS: 7782-63-0 MW: 278 © Erik ZImerson	Formula: $FeSO_4 \times 7H_20$ In solution: 

Figure 15. Iron(II) sulfate is added to cement to prevent ACD by reducing hexavalent chromium to trivalent chromium.

Figure 16. Cement workers in Kerala, south west India, handling wet cement.

Different kinds of protective measures can be used to prevent an allergen from coming into contact with the skin if total avoidance cannot be guaranteed. In the building industry, protective working clothes, gloves and different kinds of barrier creams have been tried to prevent chromium allergy in construction workers (80, 127, 149-152). The most efficient preventive action by far is the addition of iron(II) sulfate to reduce the hexavalent chromium in cement (88, 149, 153-156).

1.5.6 Regulations

The content of hexavalent chromium in cement has been regulated in Sweden since 1989. The regulation states that the content of hexavalent chromium in dry cement may not exceed 2 ppm (2 mg/kg or 2 µg/g, or 0.0002%). The same regulation has been in force in the EU since 2005 (153, 157). In 2015 the EU also regulated the release of hexavalent chromium from leather, which may not exceed 3 ppm (59, 158).

Figure 17. Cement workers in Kerala, south west India.

1.6 Cement

Cement is derived from the Latin “cementum” meaning “crushed stone”, and is the binding component in construction materials such as concrete and mortar, and as such is one of the world’s most used materials. We are surrounded by houses, bridges, tunnels and other constructions in which cement is essential. Concrete and mortar consist of cement, water and ballast, i.e., sand, gravel and stones. The exact composition of concrete and mortar depends on the purpose for which the product is to be used (159).

Figure 18. A brick wall where the bricks are held in place by mortar. (Photo: Pixabay)

Figure 19. A concrete wall. (Photo: Pixabay)

The main component of cement is limestone (calcium carbonate) which when burnt becomes lime (sometimes called quicklime, or calcium oxide). When mixed with water, the lime produces slaked lime (calcium hydroxide). The method of cement manufacture as we know it today was patented in1824. However, lime burning as a method to produce a binder for use in construction dates back to ancient times. The remnants of a lime-burning hearth in Israel are believed to date from about 10 000 B.C. Mortar based on burned lime was used in the Mediterranean area from about 1000 B.C. The art of making mortar was known by the ancient Greeks, as well as the Romans (160). Cement that could harden under water was used in the Roman Empire. This kind of water-resistant cement was made by mixing slaked lime with “pozzolana”, a sort of volcanic ash from Mount Vesuvius. Cement that not only hardens by reacting with water, but also forms a water-resistant product, is called hydraulic cement.

Figure 20. Cement bricks and concrete walls, Kerala, south west India.

Most of the foundations of the buildings in the Roman Forum were constructed with a kind of hydraulic concrete, and many famous buildings still standing, such as the Coliseum and the Basilica of Constantine, are examples of buildings in which this material was used. The skill and knowledge of the Romans was lost, and it took until the 18th century for hydraulic cement to be re-discovered. This is said to be the result of hard work and repeated failure during the building of the Eddystone Lighthouse off the coast of Cornwall, England. The British engineer John Smeaton conducted experiments with mortar in both fresh and salt water, and in 1756 found that cement made from limestone containing clay hardened under water. The Eddystone Lighthouse, rebuilt in this way in 1759, stood for 126 years before it had to be replaced (161). In 1824, Joseph Aspdin, a British bricklayer from Leeds, patented the production of a kind of hydraulic cement he called "Portland cement" (159, 162). It was called this because of its colour, which resembled the stone that was quarried on the Isle of Portland off the British coast. The first large-scale use of Portland cement was in a tunnel under the river Thames in 1828. Portland cement is still the most used cement today (161, 163).

Figure 21. Lighthouse and wall built with bricks and stones, respectively, and mortar, Kerala, south west India.

1.6.1 Cement production

Cement was originally produced in static kilns. Kiln is the name of the industrial oven where the raw materials are processed to form what is called cement clinker. The traditional static kiln was egg shaped, with a conical extension at the top to increase the draught, thus enabling the high temperature needed in the process to be attained. Aspdin's original Portland cement oven was vertical and static. It still exists as a monument in Norfleet, England (73). Around 1885, continuous kilns were developed. These kilns, called shaft kilns due to their design, had a lumen in which the cement clinker was processed. The use of shaft kilns continued, resulting in the development of the rotary kiln in the late 19th century (161, 162).

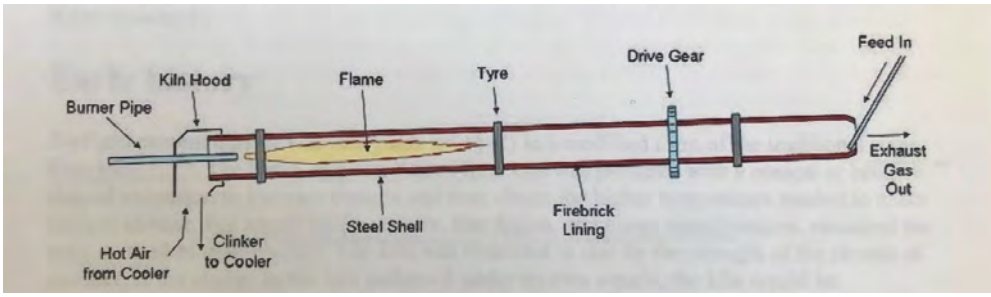


Figure 22. Schematic of a rotary kiln. (From Fregert Undated)

Figure 23. Rotary kiln at the Cementa plant in Degerhamn, Öland, Sweden. (From the picture archive of the Department of Occupational and Environmental Dermatology, photographer unknown)

The rotary kiln consists of a large cylinder made of steel plate. Its lumen is lined with firebricks. The tube slopes slightly, and rotates slowly around its own axis. The mixture of raw material is fed into the upper end of the kiln. The slope and rotation of the kiln cause the material to move downwards to the lower part, i.e. the exit of the kiln. A burner is situated at the lower end of the kiln. As the raw material moves through the flame it reaches a peak temperature of about 1450°C. It is during this heating in the kiln that the cement clinker is produced. The clinker leaves the kiln at the lower end and is fed into a cooler. After the clinker has cooled, it is ground and mixed with sand and gypsum to form the grey powder recognised as cement (161, 164-166). Rotary kilns run 24 h a day and are usually stopped for only a few days once or twice a year for necessary maintenance.

Figures 24 and 25. Birgitta Gruvberger and Sigfrid Fregert standing inside Cementa's rotary kiln in Limhamn, Sweden in the 1970s. (Photo: courtesy of Birgitta Gruvberger, photographer unknown)

1.6.2 Cement and hexavalent chromium

The content of hexavalent chromium in cement is determined mainly by the presence of chromium in the raw material, for example, in the clay (167, 168), and partly by the kiln lining and by chromium steel abrasion during the grinding process. The chromium content in cement thus varies with geographical region (159). Chromium exists as trivalent chromium in the raw materials, and is the source of water-soluble hexavalent chromium in the final cement. It is not until the cement is mixed with water that this chemical reaction takes place, releasing water-soluble

hexavalent chromium, which is responsible for ACD. Trivalent chromium is oxidized to hexavalent chromium when heated in the kilns. According to Fregert, almost no chromium was probably oxidized in the vertical ovens used historically (169). He thus suggested that chromium sensitization due to cement appeared at the turn of the 19th century (73).

Figure 26. Metal balls used to grind cement clinker to cement powder. (From the picture archive of the Department of Occupational and Environmental Dermatology, photographer unknown)

1.6.3 Cement and dermatitis

Dermatitis caused by cement can be of toxic or allergic nature, or a combination of both (170). Cement is alkaline with a pH of about 11, hence irritating to the skin. Irritant dermatitis resulting from the alkalinity of cement may in some cases precede the development of ACD to hexavalent chromium in cement (161). The patch test threshold for the reactivity of chromium allergy is about 10 times higher in normal skin than in skin with an induced irritation (138). Additionally, hexavalent chromium shows its highest skin penetration at alkaline pH (39), resulting in potentially synergistic hazardous effects.

ACD caused by hexavalent chromium is more severe, often with more extensive involvement, than irritant cement dermatitis, and it tends to be chronic (88, 123, 154, 171-173). It is common for ACD caused by hexavalent chromium to persist in allergic individuals also after they stop working (37, 88, 141, 142, 171, 174-181). Only minute amounts of chromium are considered necessary to elicit dermatitis in allergic individuals. Contamination by cement dust or chromate salts in solution, for example, in diesel engine coolants, can constitute a constant source of allergen (181). There are many sources of chromium in our surroundings, not only in occupational settings, which is believed to be one of the reasons for long-standing dermatitis in hexavalent-chromium-allergic (HCA) individuals since it is very difficult to avoid exposure (37, 168). This emphasizes the need to employ the exceptionally effective primary preventive measure of reducing the amount of hexavalent chromium in cement (153) worldwide to ensure equal prevention and work environments for construction workers.

The first known outbreaks of cement dermatitis appeared when the Paris metro system was built between 1900 and 1905, and the London underground in 1925 (73). Industrial development, with increasing demands of expanded infrastructure and new buildings led to changes in both the production of cement and exposure. Although a benefit of larger amounts of cement that could be produced in rotary kilns, the negative consequence was the increased formation of hexavalent chromium. Exposure to hexavalent chromium in cement increased as a result of large-scale building projects, and many workers were affected by ACD. In Sweden, cases of dermatitis due to cement have been known since 1943 (167). Some historical investigations showed a positive reaction to potassium dichromate (the chromium salt used to detect allergy to hexavalent chromium) at patch testing in more than 80% of individuals with cement dermatitis. Chromium compounds were also used in other industries, but appeared to be most hazardous in the cement industry (182, 183).

It took until 1950 before water-soluble chromate, i.e. hexavalent chromium, was found in cement (149, 170, 184, 185) and identified as the cause of ACD. Between 1960 and 1970, the incidence of cement dermatitis increased in many European countries. In Sweden, among other countries, it was the most common form of dermatitis leading to invalidity among construction workers at this time (154, 155, 186).

1.6.4 Reduction of hexavalent chromium in cement

During the 1970s, co-operation was established between Fregert and Gruvberger at the Department of Occupational Dermatology, then located in Lund, and the principal cement producer in Sweden, Cementa. The result of this collaboration was a suggestion by Fregert and Gruvberger together with an engineer, Sandahl, at Cementa, for a method of reducing hexavalent chromium in cement by adding

iron(II) sulfate in 1979 (167). Earlier patch test studies by Buckhardt had shown that the majority of HCA patients did not react to a solution of 40% cement in water to which 0.3% iron(II) sulfate had been added (59). Possible negative consequences of this method on the quality of cement were also investigated. It was found that iron(II) sulfate could be added without having any negative effects on the cement (167).

The reduction of hexavalent chromium in cement has taken place in Scandinavia since the 1980s; Denmark being the first country to introduce the method in 1981 (149, 155). In 1983, six years before Swedish legislation was introduced in 1989, cement producers in Sweden voluntarily decided to add iron(II) sulfate to cement to reduce the amount of hexavalent chromium.

Within a decade, this preventive measure resulted in a real decrease in the number of cement workers affected by ACD. The prevalence of allergy to hexavalent chromium and dermatitis among workers in daily contact with wet cement declined significantly 6 years after the content of hexavalent chromium in Danish cement was reduced, and this was found to be significantly more influential in preventing cement dermatitis than traditional methods such as the wearing of gloves (88, 149, 155).

Unfortunately, follow-up revealed that workers already sensitized to hexavalent chromium and affected by ACD did not heal (154). This was attributed to the fact that exposure to a lower dose is sufficient to elicit ACD in already sensitized individuals. Furthermore, chronic ACD is due to the omnipresence of chromium in the environment.

Although it makes a considerable difference, the reduction of hexavalent chromium in cement does not eliminate all the problems associated with ACD. The chemical relation between trivalent and hexavalent chromium is dynamic. Oxidation and reduction can occur as a result of environmental factors and added chemicals. Hence, after reducing hexavalent chromium to trivalent chromium by the addition of iron(II) sulfate, it may return back to the hexavalent state through oxidation. This takes place, for example, during the storage of cement, and ACD can thus also be caused by cement to which iron(II) sulfate has been added (187-189).

The chromium in bagged and bulk cement remains in a reduced state as trivalent chromium for about 8 weeks (159). The storage conditions govern oxidative reactions. If bagged cement is stored in open sacks or exposed to moisture, the chromium will not be reduced when the cement is subsequently mixed with water (187). This was known to the originators of the iron(II) sulfate reducing method, and Fregert carefully noted spontaneous oxidation in stored cement (73). One suggestion to solve this problem is to provide iron(II) sulfate together with the cement, so that it can be added at the building site (159).

The risk of spontaneous oxidation does not undermine the importance of reducing hexavalent chromium in cement. The overall risk of workers becoming sensitized is lower when all kinds of cement are reduced. Since the threshold for hexavalent chromium sensitization has been assessed to be approximately 10 ppm, reducing the amount of hexavalent chromium in cement to 2 ppm involves the need for only a 5-fold reduction (37, 86). This was recognized by Fregert, who stated that: "a person already sensitized may not be helped by the addition of iron sulfate" and that: "iron sulfate is added to prevent sensitization to chromium" (161). There is no doubt that the addition of iron(II) sulfate to cement has had an immense impact (83, 184, 190), and it has been described as the most successful preventive measure taken in the history of occupational contact dermatitis (88, 149, 153-155).

The improved situation for workers in Europe is known internationally, and the need for change has been pointed out by authors in countries such as Israel, Australia, Turkey and India (171, 174, 191, 192). The cost of adding iron(II) sulfate to reduce hexavalent chromium to the proposed level of 2 ppm is estimated to be equivalent to about 1% of the total value of the cement (76, 149, 159, 168, 175, 193).

The World Health Organization has classified cement dermatitis among construction workers as the most important occupational skin condition in developing countries (194). This is due largely to the lack of regulatory measures, protection and work-place regulations governing how cement should be stored and used. Sensitization and ACD are still common in many countries, and constitute a major concern for construction workers and their families.

1.6.5 Cement and the environment

The negative environmental effects of cement have been the subject of discussion for several decades (195, 196). The production and use of cement lead to the emission of carbon dioxide. It has been suggested that the construction industry gives rise to 8 times more carbon dioxide emissions than aviation (before the pandemic) per year. Between 5% and 8% of the global emission of carbon dioxide arises from cement production (163, 196-198). Carbon dioxide is emitted both when quarrying the raw material, and in the kilns where the cement clinker is produced. The high temperature in the kiln during the production of cement cause the release of carbon dioxide bound in the raw material to the air. Furthermore, the fuel used to heat the kilns is largely of fossil origin, also leading to carbon dioxide emission (163, 165, 166, 196-201). About 20% of all industrial emissions of carbon dioxide in Sweden originates from the production of cement. Various initiatives are being considered, for example, the production of concrete that contains only half the normal amount of cement, using the slag that has already emitted its carbon dioxide instead of limestone, or using limestone that has not been burnt, as part of the raw material (however, only a limited amount of limestone can be replaced), and adding fly ash to the ground cement clinker (personal communication, Åsa Nilsson,

Cementa, 2021). The Swedish electricity-producing company, Vattenfall, and the country's main cement producer, Cementa, have initiated a pilot project at the cement plant at Slite, on the island of Gotland. The main aims of the project are to produce cement using renewable energy, and to capture and store the carbon dioxide emitted underground (199). To meet the future needs of both social and environmental sustainability, a holistic view is necessary that includes the workers and engages academics, the business community, policy makers and institutions (196, 202).

Figure 27. Concrete is used in buildings and car parks, Havana, Cuba.

2 Aims

The overall aim of the work presented in this thesis was to help people who are allergic to hexavalent chromium, foremost construction workers affected by ACD due to chromium in cement and, if possible, to prevent elicitation or at least reduce their clinical symptoms. The construction industry is a large employer in many countries, and a strong driver of national economies. The economic interests are huge, and in an increasingly global society, infrastructure such as bridges, airports, hospitals and leisure complexes are being built worldwide. The fact that the construction industry is also a risk industry, both environmentally as well as for the workers, must be addressed. The problem of ACD in workers has mainly been solved in Europe through the addition of iron(II) sulfate to cement and the use of protective clothing. However, this occupational problem has still not been addressed in many countries, despite the fact that the cost of this measure is low, and the effects on the performance of the cement are negligible. In this work, I have focused on the persisting occupational risks in the construction industry, and means of alleviating these problems.

Figure 28. Construction worker, Kerala, south west India.

2.1 Study I

The aims of Study I were to retrospectively investigate the frequency of contact allergy to hexavalent chromium and co-existing allergy to cobalt and nickel in dermatitis patients attending the Department of Occupational and Environmental Dermatology in Malmö during the 10-year period between 2005 and 2014. Furthermore, the presence of atopic dermatitis, the localization of their dermatitis and exposure to cement in those allergic to hexavalent chromium was investigated and compared with those from an age-matched control group of dermatitis patients attending the clinic without allergy to hexavalent chromium.

2.2 Study II

The aim of Study II was to investigate the capacity of selected chemicals to reduce hexavalent chromium *in vitro* in order to find a chemical suitable for further investigation in a barrier cream.

2.3 Studies III and IV

The aim of Study III was to investigate the ability of glutathione and iron(II) sulfate in barrier cream formulas to reduce reactivity or inhibit elicitation in HCA volunteers when exposed to hexavalent chromium and cement extract at patch testing. The method of evaluation was then applied to a commercial barrier cream in Study IV.

2.4 Study V

The aim of Study V was to investigate the content of hexavalent chromium in cement samples from countries within and outside the EU.

To achieve the overall aim of this work, the studies presented below were initially planned.

ROAT using a barrier cream to protect against hexavalent chromium

The aim of this study was to evaluate the barrier cream in Study III in a situation similar to real-life exposure. The study was approved by the Ethics Review Board in Lund. The study was planned to take place in 2020 and volunteers with known chromium allergy were to be invited to participate in the study. However, the study had to be cancelled due to the COVID-19 pandemic as it would have meant that patients would have had to come to the hospital, at least, to initiate and conclude the ROAT.

Field study in India

Provided that the ROAT study of the barrier cream gave positive results, i.e. a protective effect when individuals with chromium allergy were exposed to hexavalent chromium, the aim was to carry out a field study in India. The study would have been carried on construction workers exposed to chromium and with chromium allergy to investigate the possibility of using the protective barrier cream in real life. Once again, this study had to be postponed due to the COVID-19 pandemic, which has now had a considerable impact in India. It was hoped that it would be possible to carry out a small pilot study to investigate compliance and whether the logistics of such a study was actually possible in India, but this has also had to be postponed.

Figure 29. Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi, India.

At the present time, we do not know how this pandemic will develop, but the workers in India, and elsewhere, affected by dermatitis due to contact allergy to hexavalent chromium in cement, still exist, and hopefully the ROAT study and the field study can be performed at a later date.

3 Methods

3.1 Study I

Data were collected retrospectively from consecutively patch-tested dermatitis patients at the Department of Occupational and Environmental Dermatology in Malmö. All contact allergies are registered in a database together with information on the patient, such as age, sex, atopy, occupation, and localization of dermatitis at the time of patch testing (203). For each individual allergic to hexavalent chromium, an age- and sex-correlated control, i.e. an individual not allergic to hexavalent chromium, was retrieved from the database. To verify the data extracted from the database, and to complete missing information in some cases, patients' records were consulted. The study was approved by the Regional Ethics Review Board, Lund, Sweden (Approval No. 2015/491).

3.1.1 Test preparations

Potassium dichromate (0.5% in petrolatum), nickel sulfate hexahydrate (5.0% in petrolatum), and cobalt chloride hexahydrate (0.5% in petrolatum) (Chemotechnique Diagnostics, Vellinge, Sweden) had been used throughout the study period. The patch test dose used was 20 mg for the petrolatum preparations (48).

3.1.2 Patch testing

Patch testing was performed with 8-mm-diameter Finn Chambers® (Epitest, Tuusula, Finland; or Smartpractice, Phoenix, AZ, USA) mounted on Scanpor® adhesive tape (Norgesplaster, Oslo, Norway). The chambers were left in place for 48 h, and patch test readings performed on Day 3 or Day 4 and on Day 7, according to ICDRG criteria (47). The strongest reaction on either Day 3 or Day 4, or on Day 7 was used in the evaluation.

3.1.3 Statistics

Fisher's exact 2-sided test was used to compare the results from those allergic to hexavalent chromium to the controls with respect to the frequency of atopic

dermatitis, hand dermatitis, foot dermatitis, leg dermatitis and face dermatitis. Fisher's exact test was also used to compare the frequencies of hexavalent chromium allergy in men and women, in patients <40 years old and those ≥40 years, and to compare the co-reactivity with nickel and cobalt. For Fisher's exact test, differences were considered to be significant when $p < 0.05$. The multivariate logistic regression analyses were performed using STATA (STATA SE 14.2, StataCorp, Texas, USA). The analysis was based on a starting model that included the following variables: sex, age, atopy and localization of dermatitis. The variables nickel allergy, cobalt allergy, and simultaneous nickel and cobalt allergy were added to this model separately, in order to examine the effect of each allergy separately before a final model was estimated. In the regression analysis odds ratios were considered significant when $p < 0.1$.

3.2 Study II

3.2.1 Reducing substances

CosIng, which is a database containing information on cosmetic ingredients (204), was used to select substances functioning as reducing agents in cosmetic products. The following approved reducing chemicals were found suitable for this study: glutathione, dihydroxyacetone, iron(II) sulfate heptahydrate, cysteine and acetylcysteine.

3.2.2 Preparation of test solutions

A 10.0% w/v stock solution of each reducing chemical: glutathione (ICN Biomedicals, Aurora, Ohio) pH 3; dihydroxyacetone (Merck, Darmstadt, Germany) pH 5,5; iron(II) sulfate heptahydrate (Sigma-Aldrich Chemie, Steinheim, Germany) pH 6,5; and cysteine (ICN Biomedicals) pH 5, was prepared in MilliQ water. (MilliQ water, Millipore, Molsheim, France). A dilution series of each chemical with concentrations of 5.0%, 1.0%, 0.010% and 0.0010%, was prepared from each 10.0% stock solution. The solution with the highest concentration of acetylcysteine (Sigma-Aldrich, St Louis, MO, USA) at pH 2 that could be achieved was 5.0%, and the dilution series was prepared from this. The acetylcysteine solutions were used only for analysis on Day 0. Three sets of each test solution, with 5.0 mL in each test-tube, were prepared. To each test solution, 100 µL of 1000 ppm CrO_4^{2-} (corresponding to 448 ppm hexavalent chromium) stock solution of hexavalent chromium (K_2CrO_4, Merck, Darmstadt, Germany) was added on Day 0. One set was used immediately for spot tests on Day 0, the second set on Day 2, and the third set on Day 7, in order to investigate the effect of storage on the hexavalent chromium

content. As hexavalent chromium may be adsorbed on the walls of glass vessels, spot tests were performed on solutions prepared in both glass vessels and plastic vessels in order to compare the results. No difference was observed and therefore glass vessels were used for all solutions.

Figure 30. Preparation of laboratory analyses.

3.2.3 Spot test procedure

The colorimetric diphenyl carbazide spot test (72, 205) was used to assess the concentrations of hexavalent chromium in the tested samples. The following reagents were used: (i) sym-diphenylcarbazide (Acros Organics, Geel, Belgium) 1.0% (w/v) in 99.5% ethanol (Kemetyl, Haninge, Sweden); and (ii) sulphuric acid 18 M (Merck, Darmstadt, Germany) diluted with water to 1.0 M. Reference solutions with known hexavalent chromium content (expressed as CrO_4^{2-}) were prepared as follows. A 100 ppm CrO_4^{2-} solution was prepared from a 1000 ppm stock solution of K_2CrO_4, (Merck, Darmstadt, Germany) The 100 ppm CrO_4^{2-} solution was further diluted in water to 5 ppm (5 µg/mL), 2 ppm, 1 ppm and 0.5 ppm. The study was designed to identify the most effective reducing chemicals; therefore calibration was not performed above 5 ppm. To these solutions, three

drops (~60 µL) of 1.0 M H_2SO_4 and three drops (~30 µL) of 1.0% diphenyl carbazide were added. A fresh set of hexavalent chromium reference solutions was prepared for each new analysis, i.e., on Day 2 and Day 7.

3.2.4 Spot tests of test solutions

On Day 0, three drops of 1.0 M H_2SO_4 and three drops of 1.0% diphenyl carbazide were added to the first of the three sets of test-tubes containing the test solutions. The colour that developed in the test solution was compared to the colours of the set of reference solutions to assess the approximate concentration of hexavalent chromium (expressed as CrO_4^{2-}). The analysis of the test solutions was performed three times with solutions prepared on Day 0. The procedure was repeated on Day 2 and Day 7 with the second and third of the three sets of tubes. The solutions were kept sealed at room temperature and were not exposed to direct sun light.

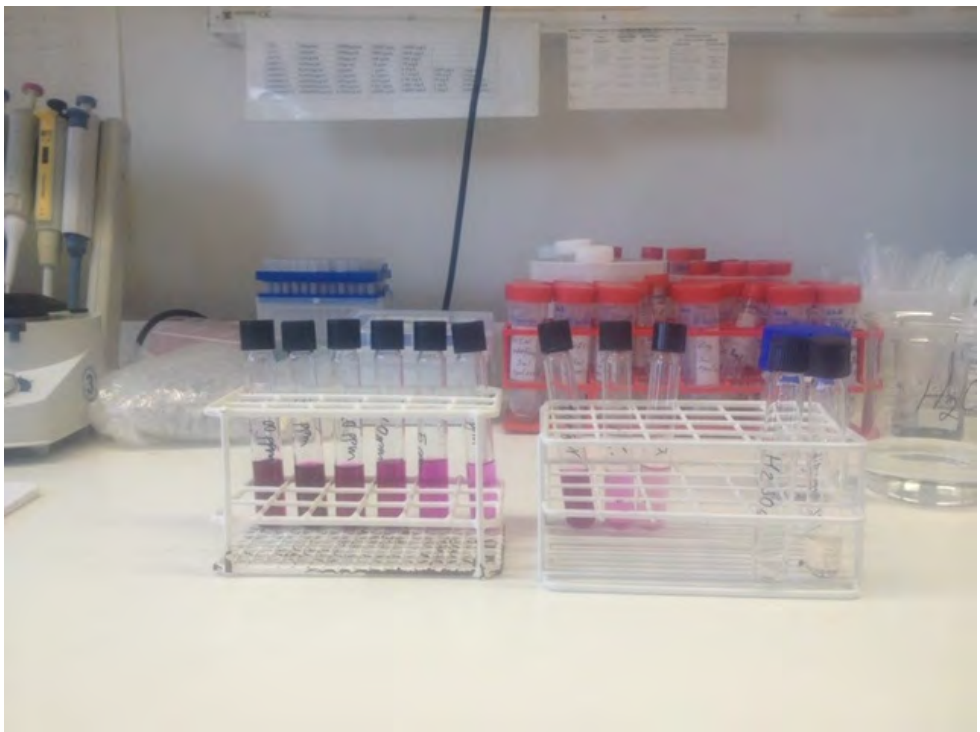


Figure 31. Spot tests of test solutions.

3.2.5 Preparation and spot tests of cement extract

The cement used in the preparation of cement extract originated from Sweden and has a low content of hexavalent chromium. Amounts of 10 g of this cement were placed in 23 separate beakers. To each beaker, 200 µL of 1000 ppm chromate, CrO_4^{2-}, was added to achieve a hexavalent chromium concentration corresponding to 20 ppm or 20 µg/g cement in the samples. Immediately thereafter, 10.0 mL of each solution of reducing chemicals described above was added to each beaker. The resulting mixtures were placed in an ultrasonic bath for 5 minutes. Thereafter, the samples were filtered with Munktell filters papers (Munktell Filter AB, Grycksbo, Sweden) and transferred to test-tubes. The extracts, which had a pH of about 11, were made to simulate a typical cement milieu. The diphenyl carbazide spot test was performed, and any change in colour noted. All analyses were performed once, immediately on Day 0.

Figure 32. Ultrasonic baths.

3.3 Studies III and IV

The study sample consisted of 18 dermatitis patients (ten women and eight men, age range 31-81 years, mean age 57 years), previously tested at our department with the baseline series, showing strong or extreme allergic reactions (++, +++) to potassium dichromate ($Cr_2K_2O_7$) 0.5% in petrolatum. (Chemotechnique Diagnostics, Vellinge,

Sweden). The individuals enrolled in the study signed an informed consent form, and the study was approved by the Regional Ethics Review Board, in Lund, Sweden (Approval no. 2016/814). The study was performed as a standard patch test using a dilution series. Prior to patch testing the skin was treated with barrier creams of different formulas, with and without glutathione or iron(II) sulfate dispersed in two different vehicles, i.e., petrolatum and Essex cream. This was done before application of the test chambers loaded with the respective test solutions. On Day 2, after removing the test chambers, the skin was treated with the same formulas again. The individuals were also patch tested with trivalent chromium on an untreated area. This was done as the reactivity to trivalent chromium may be important as hexavalent chromium is reduced to trivalent chromium by glutathione and iron(II) sulfate (the reducing additives) in the formulas.

3.3.1 Formulation of the barrier creams

The aim was to test the reducing substances in barrier creams to investigate their protective effects. Two different vehicles were used to obtain one lipid-based matrix petrolatum (Vaselin; vitt APL, Stockholm, Sweden) and an oil-in-water emulsion Essex cream (Schering-Plough, Heist-op-den-Berg, Belgium). Based on the results of Study II, glutathione (ICN Biomedicals, Aurora, Ohio) and iron(II) sulfate heptahydrate (Sigma-Aldrich Chemie, Steinheim, Germany) were selected as reducing additives. Each of the two substances was mixed at a concentration of 10.0% (w/w) in both petrolatum and Essex cream, resulting in four formulas. Petrolatum and Essex cream without any reducing additives were used as vehicle controls. A commercial barrier cream with an oil-in-water formula protecting against metals was also tested on a separate test area on each volunteers back.

3.3.2 Patch test preparations

A dilution series of potassium dichromate ($Cr_2K_2O_7$; Janssen Chimica, Geel, Belgium) in water was prepared for evaluation of the various barrier creams. The dilution series consisted of nine preparations. A stock solution containing potassium dichromate 0.67% (w/v) aq. was further diluted by a factor of $\sqrt{10}$ to 0.000067%. A preparation of chromium (III) chloride hexahydrate ($CrCl_3 \cdot 6H_2O$; Fluka, Sigma-Aldrich Chemie) 1.21% (w/v) in aq. was prepared at an equimolar concentration to hexavalent chromium (i.e. $Cr_2K_2O_7$ 0.67% aq.). In addition, a cement extract was prepared from approximately 200 g of a cement sample obtained from India, to which no reducing agent had been added. Approximately 25 g of cement was placed in eight separate plastic test-tubes (50 mL; Sarstedt, Nümdrecht, Germany) to which 25.0 mL MilliQ water was added. The test-tubes were placed on a rocker for 10 minutes and then centrifuged for 10 minutes at 2500 rpm. The water phases were collected and filtered, resulting in a total volume of 95 mL. This was then reduced

to a volume of 3.0 mL by evaporation. The pH was adjusted to 8.5 with 1.0 M HCl and 0.1 M NaOH.

The total chromium content of the cement extract was determined to be 84 ppm using atomic absorption spectrometry (AAS), and the hexavalent chromium content was determined to be approximately 50 ppm using AAS and the diphenyl carbazide spot test. The AAS device used at our laboratory is a graphite furnace spectrometer (AAnalyst 800, PerkinElmer, Waltham, MA, USA).

Figure 33. The AAnalyst 800 at our laboratory.

3.3.3 Application of formulas and patch testing

On Day 0, the back of each volunteer was divided into eight areas, of which were treated with the four barrier creams described above, the vehicles petrolatum and Essex cream, and the commercially available formula; one area was left untreated. Templates were made from laboratory paper (Disposable lab mat absorbent liner; Bel-Art products, Pequannock, NJ, USA) and used to standardize the test area when applying the formulas. The inner area of the template was 3.5×10 cm, corresponding approximately to the dimensions of a Finn chamber patch unit with 10 test chambers with diameters of 8 mm, (SmartPractice, Phoenix, Arizona), as used in our standard

patch testing. The amount of the formulas applied to each area was 350 mg, corresponding to 10 mg/cm^2. Relatively large amounts of the creams were used as the concentration and amounts of chromium were relatively high compared to a real-life situation. The order in which the formulas were applied to the test areas was the same for all volunteers but rotated one step in each volunteer to create a blinded test-reading situation. The volunteers were patch-tested with the dilution series of potassium dichromate and cement extract on each area. A preparation of chromium (III) chloride hexahydrate ($CrCl_3 \cdot 6H_2O$) was applied separately to an untreated area of the back. Patch testing was performed using 8 mm diameter Finn chambers mounted on Scanpor tape (Norgesplaster, Vennesla, Norway) with 48 hours occlusion. The dose of the liquid preparations used for patch testing was 15 µL, and the solutions were applied to the filter paper using a micropipette (53). The test chambers were removed at the Department on Day 2, and discarded before reapplication of the barrier creams, using smaller amounts (70 mg; 2.0 mg/cm^2). The patch tests were read by experienced dermatologists on Day 3 or 4 and Day 7, according to ICDRG and ESCD (European Society of Contact Dermatitis) criteria (7, 47) but with some minor modifications (46). The readers were blinded and did not know which formula had been applied to each area. However, the readers knew that the highest concentration in the dilution series was placed apically.

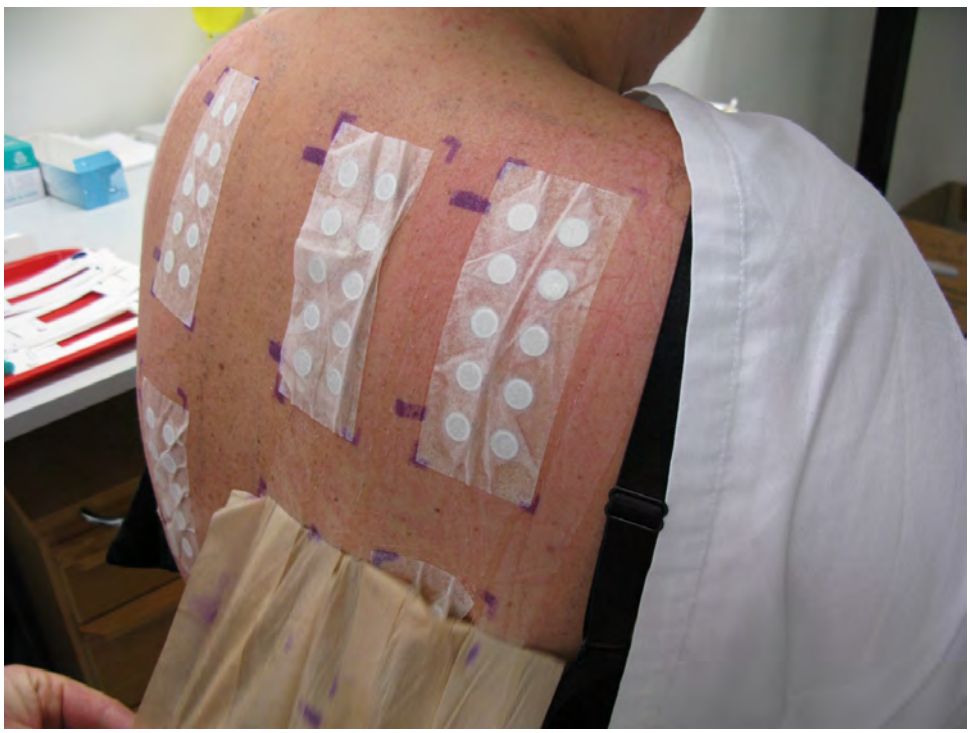


Figure 34. Removing the test chambers from the back of one of the volunteers in Study III. (Photo: Martin Mowitz)

3.3.4 Statistics

The exact McNemar two-sided test was used to compare the number of volunteers showing positive reactions on the untreated area with each of the treated areas and to compare the different cream formulas. Fisher's exact two-sided test was used for the statistical calculations concerning trivalent chromium and cement extraction. To enable statistical analysis, the following scores were assigned to the reactions: negative = 0; (+) = 0.5; + = 1; +(+) =1.5; ++ =2; ++(+) =2.5; +++ =3. The patch test results were considered in respect to both the lowest concentration eliciting at least one + reaction, i.e., the minimal eliciting concentration (MEC), and the summarized test score i.e., all skin reactions summarized (46). For statistical calculations, MEC was defined as the lowest positive reaction on either Day 3 or 4, or Day 7. The positive patch test reactions were not always continuous. When the number of negative and/or doubtful reactions was followed by at least the same number of positive reactions, the lowest positive reaction was considered the MEC. In all other cases, the concentration above that eliciting the first negative or doubtful reaction was recorded as the MEC (46).

3.4 Study V

3.4.1 Collection of cement samples

Cement samples were collected from countries within and outside the EU, in collaboration with ICDRG members and through contact with dermatologists in countries around the world where there was a presumed risk of exposure to chromium. An invitation to participate in the study was sent together with a study protocol to 22 clinicians in 22 countries. Sixteen dermatology clinics agreed to participate, and a total of 40 cement samples were collected for analysis: 17 from within the EU and 23 from outside the EU.

3.4.2 Preparation of the cement samples prior to the spot test

4.5-5.4 g of each cement sample was weighed and added to a beaker containing 10.0 mL water. The mixture was placed in an ultrasonic bath for 3 minutes. Each cement-water mixture was then filtered through a filter paper (Schleicher&Schnell, Dassel, Germany) and the liquid collected in vials. Some of the cement-water mixtures required extra filtering with a syringe filter.

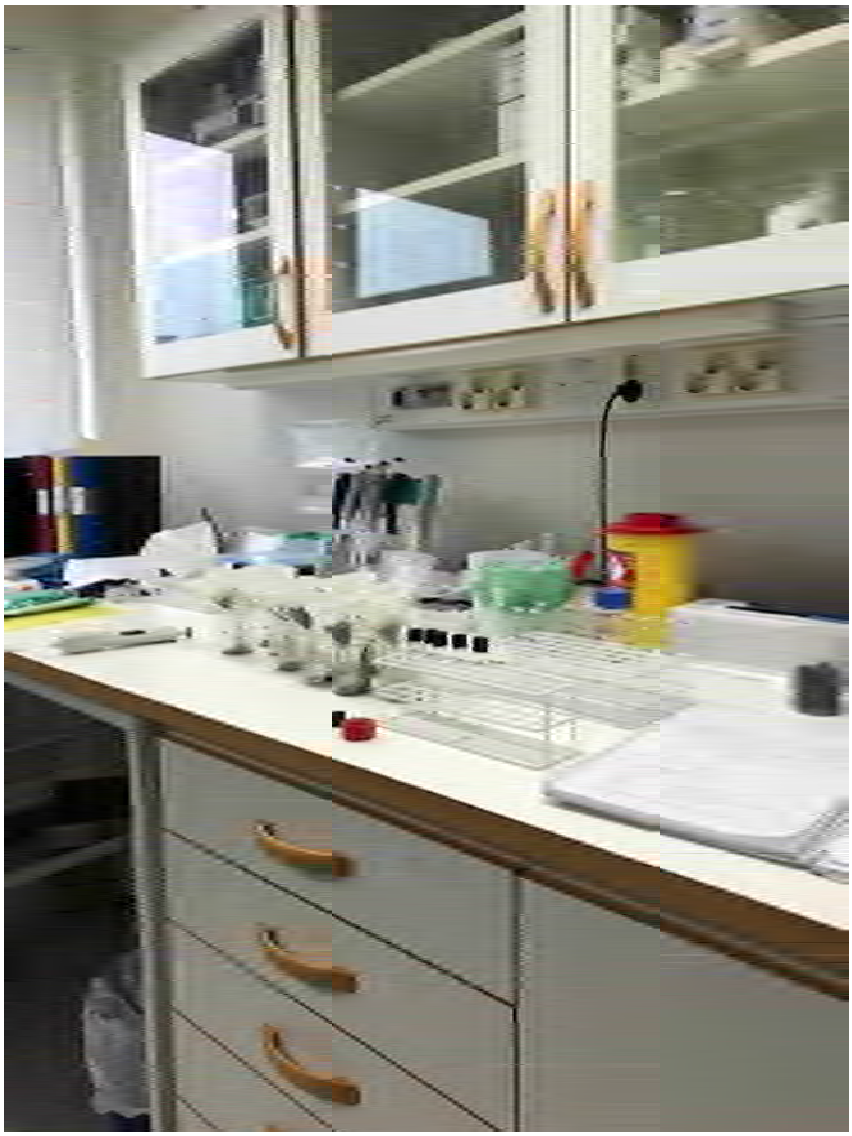


Figure 35. Filtering of the cement samples.

3.4.3 Spot tests of the cement samples

The cement samples were investigated regarding their contents of hexavalent chromium using the diphenyl carbazide spot test as described in paragraph 3.2.4. The concentration of the reference solutions used in spot test of the cement samples were 10 ppm (10 µg/mL), 5 ppm, 2 ppm, 1 ppm, 0.5 ppm, 0.1 ppm and 0.05 ppm.

4 Results

4.1 Study I

During the study period 6482 patients were tested: 2339 men and 4143 women. The mean age was 48 years. Among these, 233 HCA individuals were found, corresponding to a frequency of 3.6%: 76 (3.2%) men and 157 (3.8%) women (p=0.27). The proportion of HCA individuals was significantly higher among those aged ≥40 years than among those younger than 40 (146/3493 versus 87/2989) (p=0.006), both in men (49/1260 vs. 27/1079, p=0.046) and in women (97/2186 vs. 60/1957, p=0.022). A significantly higher proportion of atopic dermatitis was found among the HCA individuals. Eighty-eight of the HCA individuals had, or had had, atopic dermatitis, versus 65 of the controls (p=0.03).

In the logistic regression analysis, the association between hexavalent chromium allergy and atopic dermatitis remained significant after adjustment for sex and age, hand, face, leg and foot dermatitis, nickel allergy and cobalt allergy. There was a significantly higher frequency of foot dermatitis among HCA women than among controls (29 vs. 14) (p=0.02), and there was a significantly higher frequency of leg dermatitis in HCA men than in controls (20 vs. 7) (p<0.001). No differences were found with regard to hand or face dermatitis. Among the 233 HCA individuals, 6 were listed as construction workers. All 6 were men, had dermatitis at more than one location, and had leg dermatitis. None had a family history of atopy, but one had a previous diagnosis of atopic dermatitis. In addition to the 6 construction workers, another 9 individuals were found with known former exposure to cement. Among the controls, one man worked in construction, and another had formerly worked in construction. Simultaneous allergic reactions to potassium dichromate and cobalt chloride were found in 63 individuals: 41 women and 22 men, corresponding to 27% of the HCA individuals. Among the controls, allergic reactions to cobalt were found in 12, all women, corresponding to 5% of the controls. The difference in the frequency of cobalt allergy between HCA individuals and controls was statistically significant (p<0.0001). More HCA individuals than controls reacted to nickel, but the difference was not statistically significant. Among the HCA individuals a statistically significant difference was found between individuals with an isolated cobalt allergy (cobalt-positive but nickel-negative) and controls (p<0.0001). In the logistic regression analysis, the association between hexavalent chromium allergy and cobalt allergy remained significant (p<0.01) after

adjustment for sex, age, atopic dermatitis, hand, face, leg and foot dermatitis, nickel allergy and cobalt allergy (OR 14.2; 95%CI: 4.9-41.2). The logistic regression analysis also showed that individuals with combined allergy to nickel and cobalt were less likely to also be HCA after adjustment for sex, age, atopic dermatitis, hand, face, leg and foot dermatitis, nickel allergy and cobalt allergy.

Figure 36. The demolition of old concrete building at Skane University Hospital, Malmö.

4.2 Study II

All the reducing compounds investigated showed a hexavalent chromium-reducing capacity. Iron(II) sulfate showed the strongest reducing capacity in both test solutions, i.e. in water solution and in cement extract, and also the most long-standing capacity. Some of the reducing compounds were difficult to dissolve. Cysteine in cement extract was excluded from the analysis due to difficulties in dissolving it. It was not possible to dissolve 10% acetylcysteine in either solvent, so this could not be analysed.

Figure 37. Excavation in preparation for new a construction at Skane University Hospital, Malmö.

4.3 Study III

All 18 volunteers completed the study according to the protocol, and no adverse effects were observed. The most prominent reactions were seen on untreated skin, followed by almost as prominent reactions on the skin treated with the Essex cream vehicle alone. Three of the 18 volunteers showed positive reactions to trivalent chromium on untreated skin. All of these showed a strong reaction (++/+++) to hexavalent chromium at the highest concentration. No reactions were seen to

trivalent chromium in volunteers with weak or negative reactions to hexavalent chromium (3 of 10 versus 0 of 8; p=0.22). Formulas containing glutathione and iron(II) sulfate inhibited ACD in HCA individuals tested with a dilution series of hexavalent chromium and cement extract. The differences were significant for both these reducing additives. The volunteers also showed less reactivity on the areas of their backs treated with the petrolatum vehicle alone. The reactivity to cement extract of skin treated with any formula was similar to the reactivity pattern in the dilution series of potassium dichromate.

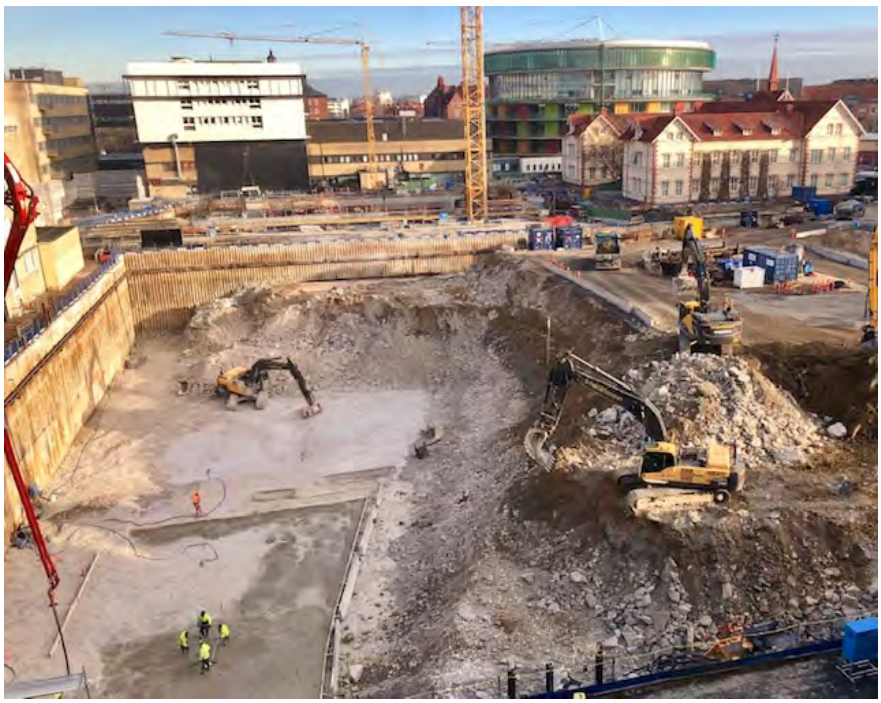


Figure 38. Further preparation work, Skane University Hospital, Malmö.

4.4 Study IV

Sixteen of the 18 volunteers showed reactions on skin treated with the commercially available barrier cream, whereas only 13 showed reactions on untreated skin at the first test reading on Day 3 or 4, or at the second test reading at Day 7. Skin treated with petrolatum or Essex cream alone showed fewer and less prominent allergic reactions than skin treated with the commercially available barrier cream.

Figure 39. The new concrete building is taking form at Skane University Hospital, Malmö.

4.5 Study V

40 cement samples from countries within and outside the EU were investigated. The samples contained amounts of hexavalent chromium ranging from <0.1ppm to >70 ppm. Eighteen cement samples contained >2ppm hexavalent chromium, whereas 22 contained less. Four of 17 samples from within the EU contained >2ppm hexavalent chromium, i.e. higher amounts than stipulated in the EU directive, as compared to 14 of 23 samples from countries outside the EU (p=0.027).

Figure 40. The new concrete building at Skane University Hospital, Malmö with the exterior in place.

5 Discussion

5.1 Study I

This retrospective study covered a 10-year period starting 20 years after the decision to add iron(II) sulfate to cement in order to reduce the concentration of hexavalent chromium, and thus the risk of sensitization and the possible consequence of ACD in construction workers. As expected, few cases of contact allergy to hexavalent chromium were seen in patients exposed to cement through work. Six construction workers and another nine individuals with known former exposure to cement were identified. The ages of the 6 individuals still working in construction during the study period were 21, 38, 39, 39, 47 and 55 years. Three of them were employed at the same plant, which produced precast concrete elements (188). Some of these men might have developed hexavalent chromium allergy before 1983, when the addition of iron(II) sulfate to cement started in Sweden (it was made mandatory in 1989). Although measures have been taken to reduce hexavalent chromium to trivalent chromium in cement, construction workers may still be exposed to hexavalent chromium, as some hexavalent chromium will always remain in the cement. Furthermore, trivalent chromium can be re-oxidized to hexavalent chromium in cement if it is exposed to weathering (187-189).

A reported increase in the prevalence of chromium allergy in Denmark has been attributed to exposure to leather (59, 144, 172, 206). Trivalent chromium is used during leather tanning to give the leather properties such as smoothness, softness, flexibility, and water resistance. In contact with air, trivalent chromium in leather can be oxidized to hexavalent chromium, and thus the skin may be exposed to hexavalent chromium despite the fact that hexavalent chromium is not used during tanning (74, 207). In the period from 1989 to 1994, Danish investigators found that the majority of their HCA patients were women. They therefore concluded that occupational contact with cement had become a less important cause of hexavalent chromium dermatitis as a direct result of the regulation on the addition of iron(II) sulfate that was implemented in Denmark in 1983, and that there was a shift from mainly cement exposure among men to leather exposure among women (172).

We found 157 HCA women in the present study population, corresponding to 3.8%, and 76 HCA men, corresponding to 3.2%. Hence, HCA individuals also were predominantly women in our study population, although the difference was not statistically significant. Furthermore, a significantly higher frequency of foot

dermatitis was found among HCA women than among controls. The cause of foot dermatitis in women is thought to be the wearing of chromium-tanned leather shoes in direct contact with the skin. Interestingly, there was an overrepresentation of HCA men with leg dermatitis, compared to the controls ($p<0.01$). In fact, all 6 of the HCA individuals identified as construction workers had leg dermatitis, whereas neither of the 2 construction workers in the control group had leg dermatitis. No increase was seen in the frequency of hexavalent chromium allergy in this study population, as was observed in the Danish studies mentioned above. However, after 2015 an increase in the frequency of hexavalent chromium allergy was noted at our department, although these data were not included in the current study. During the period 2015-2020, the frequency of hexavalent chromium allergy at our department has varied between 2.9% and 6.2%.

In this study population, 27% of the HCA individuals also reacted to cobalt, in contrast to the controls, only 5% of whom were allergic to cobalt. This is in line with previously published results (116). A significant association was observed between hexavalent chromium allergy and isolated cobalt allergy (but no concomitant nickel allergy) in the logistic regression analysis.

Concomitant sensitization to hexavalent chromium and cobalt is common (208-211). Cobalt allergy has been mentioned as being of unclear relevance, and is often regarded as a result of co-exposure to other metals (212, 213), co-sensitization (214) or cross reactivity (215). It is known that the response to a combination of allergens can be both additive and synergistic. Sensitization by combinations of metals can result in increased elicitation to specific allergens within the mixture (209, 216), which could also explain concomitant allergy to chromium and cobalt.

Compounds based on both chromium and cobalt are used in leather production (208, 217). Studies have shown hexavalent chromium allergy to be the most common contact allergy in patients with foot dermatitis, followed by cobalt allergy (116, 144). However, ACD can also result from cobalt exposure alone (218). High amounts of cobalt were identified in a leather sofa that caused dermatitis in an individual, and it was concluded that this was attributable to the use of pre-metallized dyes, which provided better washing- and light-fastness than traditional dyes (114, 208, 217).

Cobalt and chromium sensitivity also occurs simultaneously more often in individuals with cement dermatitis (219), than in non-construction workers (220). There are no indications that cobalt sensitization is, or has been, an important factor in the development of the long-standing ACD associated with cement exposure (219).

A significantly higher proportion of atopic dermatitis was found among the HCA individuals than among the controls. Eighty-eight of the HCA individuals had atopic dermatitis, compared to 65 in the control group. The reason for this is unclear. Some previous studies have suggested a positive association between atopic dermatitis and

contact sensitization (221, 222). One study showed that children with atopic dermatitis affecting the hands and feet had a significantly higher frequency of contact allergy than children with atopic dermatitis not affecting the hands and feet (55). Some experimental studies have shown that individuals with atopic dermatitis have suppressed contact sensitivity as a result of their disease (223), and the risk of protracting contact allergy is not increased in those with atopic dermatitis, as opposed to claims by other authors (30). In another study, the prevalence of atopic dermatitis was not found to differ significantly between the case and the control groups (172). It is believed that several aspects affect the association between individual factors such as age, atopic dermatitis and contact sensitization (223, 224). The individual variation in the effectiveness of the skin barrier has been discussed with regard to the penetration of hexavalent chromium into the skin (225). Workplace exposure, age, sex, use of consumer products and genetic predisposition have been identified as the most important risk factors for contact allergy (31). Some claim that individual susceptibility to sensitization probably results more from environmental factors than genetic ones (213). Contact allergy most likely develops as a result of both endogenous and exogenous factors, and it can be difficult to determine which dominates in individual cases (178).

Figure 41. Concrete in an aquatic park, Brisbane Australia.

5.2 Study II

The objective of this study was to identify chemicals with the capacity to reduce hexavalent chromium which would be suitable in a barrier cream, and to find a cosmetic formula that would ensure good compliance and no adverse effects. Any kind of cream applied to the body must have certain qualities, such as good absorption, a tolerable odour, not cause discomfort and not be too expensive. It is known that a bad odour can develop from formulas containing glutathione, and attempts have been made to solve this problem (226). In addition, glutathione is assumed to have a bleaching action on the skin (227). Dihydroxyacetone has a characteristic odour, and tans the skin, and is widely used for this purpose (228). Bad odour is unacceptable in any cream, and the properties of tanning and bleaching of the skin in a barrier cream are also undesirable. Despite this, these chemicals were included in this study because of other properties, i.e., their reducing capacity and being innocuous to the skin.

Iron(II) sulfate showed the most promising hexavalent chromium-reducing capacity in the laboratory investigation. The results also indicated that glutathione might be an alternative for further investigation as an ingredient in a barrier cream, despite its possibly bad odour. Furthermore, it has been shown that glutathione protects against hexavalent chromium-induced cytotoxicity in human keratinocytes by reducing it to trivalent chromium (87).

The practical purpose of the study was to alleviate symptoms in construction workers, by reducing their exposure to hexavalent chromium in extreme conditions. It was therefore important to investigate cement extracts to investigate whether the chemical properties of cement could interfere with the reduction of hexavalent chromium. The reducing capacity of the chemicals was also demonstrated in the cement extracts.

Although the other chemicals investigated showed an acceptable reducing capacity, iron(II) sulfate and glutathione were chosen for further investigations in a barrier cream study.

5.3 Study III

In this study, the protective properties of the barrier cream formulas were investigated under standardized conditions. The physical barrier function was investigated by testing a lipid-based vehicle (petrolatum) and an oil-in-water emulsion (Essex cream). Petrolatum alone gave some protection without the addition of a reducing chemical. Formulas containing either glutathione or iron(II) sulfate inhibited ACD in HCA individuals tested with a dilution series of potassium

dichromate, $Cr_2K_2O_7$, and cement extract. The differences between the formulas containing the active reducing chemicals were small. A lipid-based vehicle seems to be preferable, as the formulas with petrolatum appeared to be slightly better, with lesser skin reactions.

When considering the effect of a barrier cream, it is necessary to take into account how the cream is intended to be used. If the purpose is secondary prevention, i.e. to protect already sensitized individuals, the protective effect must be greater than if the purpose is primary prevention, as a lower dose of an allergen is needed for elicitation than for sensitization. This means that a barrier cream can be useful even if the reactivity in treated skin is only halved compared with untreated skin.

A barrier cream reducing the total exposure to hexavalent chromium may offer protection against both sensitization and elicitation. A weakness of this study is that the volunteers tested all had a known contact allergy to hexavalent chromium. Consequently, it was not possible to demonstrate protection against sensitization. However, this appears plausible because, as discussed above, even a minor decrease in hexavalent chromium results in protection in most cases. Further studies must be performed to investigate whether any of these barrier creams have both a primary and a secondary preventive effect.

In countries lacking regulations on exposure to hexavalent chromium, construction workers are at risk. There are recent studies from several countries including Australia, Singapore, Turkey and Taiwan confirming this (168, 174, 192, 214, 229, 230). Some individuals become sensitized and develop ACD, even in countries with regulations (187-189). Cement to which iron(II) sulfate has been added may also contain hexavalent chromium, as the reduced chromium in the cement can oxidize if the cement is exposed to air (159). The situation of construction workers differs depending on local conditions, and the worst-case scenario is working without any physical protection at all, and handling cement containing high amounts of hexavalent chromium.

The function of barrier creams in reducing the level of skin penetration has been evaluated previously (231), and many studies have investigated the preventive effect of barrier creams on ACD caused by different allergens (231-240) and specifically hexavalent chromium (80, 127, 150-152). Some of these studies showed some, or even good, protective effect, but it has been difficult to find a barrier cream that works well against hexavalent chromium. However, regardless of the presence of active substances, the use of moisturisers and emollients has a positive effect, at least in irritant occupational hand dermatitis (23). Reducing the exposure of the skin to hexavalent chromium is health promoting (3, 153, 184, 241). The situation of workers can be improved at various levels, using different means, not least educational interventions concerning personal protection and prevention (242). In the present study, the barrier creams containing glutathione and iron(II) sulfate

showed protective properties, despite the fact that the concentrations of hexavalent chromium were considerably higher than in real-life situations.

Only seven of 18 volunteers showed a positive reaction to cement extract, all of them showing strong to extreme reactions to potassium dichromate ($Cr_2K_2O_7$). The limited reactivity to cement extract can probably be explained by the relatively low content of hexavalent chromium in the cement extract used (about 50 ppm), which is much less than in the $Cr_2K_2O_7$ dilution series (up to 6700 ppm).

Reactivity to trivalent chromium was demonstrated in three of the volunteers. Trivalent chromium is recognized as having less potential to sensitize and cause ACD, being less toxic and evoking less skin irritation than hexavalent chromium. However, trivalent chromium might still have an influence on the skin, perhaps not only in those allergic to hexavalent chromium. Despite this, and based on the results of this study, it was concluded that a barrier cream designed to offer protection against hexavalent chromium is of use.

Reduction of hexavalent chromium in cement is the easiest ant the most effective way to reduce the risk of ACD caused by hexavalent chromium in cement, but this measure has unfortunately not been implemented universally. The results of this study are sufficiently promising to motivate further studies, such as a ROAT study, and if the results are promising, a field study would be warranted.

5.4 Study IV

In this study a commercial barrier cream claimed to offer protection against exposure to certain metals including chromium, was investigated. A barrier cream is intended for use under certain conditions, and it can be argued that its use in a patch test is not appropriate. The commercially available barrier cream assessed in this study is not claimed to offer protection against hexavalent chromium explicitly, but it might be difficult for an individual who is allergic to chromium to make this distinction, especially since it is the hexavalent chromium compounds that are harmful to the skin.

The time frame is not mimicking a real life situation as the study was performed as in normal patch testing and with the use of dilution series. However, even during normal exposure to cement, some of the circumstances investigated in the study appear. For example, there is often prolonged use of gloves that tend to become wet (occlusion) and exposure to the allergen is intermittent.

The results presented in Study IV were derived from the same tests as those presented in Study III. The finding that the commercially available barrier cream showed a lower protective capacity than the other formulas tested, and even untreated skin was unexpected.

The sample size in this study is a limitation. However, the number of volunteers was sufficient to calculate some basic statistics, on which some conclusions can be drawn concerning the protective properties of the formulas evaluated. The results were interesting as both the untreated skin and skin treated with petrolatum or Essex cream alone showed weaker patch test reactions to both hexavalent chromium and cement extract, than the skin treated with the commercially available barrier cream.

Some objections were raised by the manufacturer of the barrier cream regarding its evaluation by patch testing. This is a valid objection, and continued evaluation is planned in future studies (the ROAT study, as mentioned above). We agree that the efficiency of a barrier cream should optimally be assessed in a real-life situation, or at least in a situation simulating a real-life situation and we have suggested collaboration with the company in such a study. However, a patch test study was considered necessary, before continuous studies were undertaken.

5.5 Study V

In this study, it was found that 45% (18/40) of the cement samples contained more than 2 ppm hexavalent chromium, hence implying a risk of sensitization. Four of 17 cement samples (24%) from countries within the EU contained high amounts of hexavalent chromium, despite the addition of a reducing agent. Fourteen of 23 (61%) cement samples from countries outside the EU contained high amounts of hexavalent chromium.

According to a recent Finnish study, construction is a sector associated with major risks of developing occupational skin disease, about 70% consisting of ACD. Chromium was found to be the second most important allergen, despite the addition of iron(II) sulfate in Finnish cement. In general, chromium allergy was reported to be derived from wearing chromium-tanned leather gloves, but it was also pointed out that it is difficult to differentiate between these two sources of exposure in the clinical setting (243). Others have found that hexavalent chromium still causes ACD, despite the addition of iron(II) sulfate to cement (187-189). ACD resulting from chromium allergy in the Scandinavian countries, where iron(II) sulfate is added to cement, could possibly be further reduced if better information was provided on the shelf-life of cement, and educational measures were implemented for construction workers on the hazards that still exist (244).

As seen in this study, and in others, several kinds of cement are available on the market, some of which contain high amounts of hexavalent chromium while others do not (173, 245, 246). It is logical to assume that the risk of high amounts of hexavalent chromium in cement is higher in countries without regulations on cement reduction than in countries where the regulation has been implemented. The risk of ACD due to hexavalent chromium in cement is high in countries lacking such

regulations and the implementation of legislation similar to that in Europe has been called for in various parts of the world (2, 171, 174, 191, 192).

Figure 42. Sandal maker, Kerala south west India.

In one of the countries lacking such regulations on cement, Australia, an increase in the numbers of workers being affected by occupational ACD due to hexavalent chromium has been reported. A recent investigation reported 24-28 new cases of ACD due to hexavalent chromium in cement per year, compared to data for the previous 21 years, where the corresponding number was 20-24 (174). Repeated investigations have highlighted the situation in Australia (168) and there is a call for change. Singapore is another country lacking legislative measures concerning hexavalent chromium in cement. Recent data show chromium to be among the three most common allergens in occupational skin disease between 2009 and 2018 (247). A recent study in Turkey showed that chromium in cement is still among the main allergens, and occupational ACD was reported in 45% of construction workers (192). In India, a less recent study showed a similar situation, where 45% of symptomatic construction workers in the investigated population showed positive reactions to hexavalent chromium at patch testing, which indicated hexavalent chromium to be the most frequent allergen among construction workers in that part of India. It is almost impossible for those working in construction in India to change profession, due to the poor level of technical skill among construction workers. Safety guidelines in the workplace are less strictly enforced in many developing countries, including India, and specific government guidelines intended to protect workers from developing occupational skin disease are virtually non-existent (2). Suggestions for regulations to reduce the amount of hexavalent chromium in cement in India were made recently in connection with investigations of the content of hexavalent chromium in cement from India, which was found to be high (191).

The importance of preventing sensitization is emphasized by the fact that ACD due to hexavalent chromium tends to be both severe and chronic (37, 123, 154, 171, 172, 174-176). This is often explained by the difficulty in avoiding exposure to chromium, since it is ubiquitous in the environment (37, 47, 85).

Many attempts have been made to prevent ACD resulting from hexavalent chromium, including education in personal protective measures and barrier creams, etc. (127, 150-152, 155). However, no measures have proven to be as effective as the addition of iron(II) sulfate to cement. Since no significant individual factors related to sensitization to hexavalent chromium have been found (224) it is impossible to propose a universal solution. Hence, general prevention must be the objective, and if primary prevention cannot be achieved, due to ignorance, or unwillingness to implement measures and regulations concerning the reduction of hexavalent chromium in cement, secondary prevention must be implemented. Preventive measures are needed to avoid clinical disease among sensitized individuals and to avoid further sensitization (213).

Much has been done to reduce the negative effects of cement on humans and the environment, but further measures are necessary. The cement industry is facing environmental challenges that will force future changes. If these changes could include the reduction of hexavalent chromium in cement much would be won.

5.6 General discussion and perspectives

There is seldom a simple solution to complex questions involving many actors. However, in this case there is. Contact allergy to hexavalent chromium caused by cement can effectively be prevented by adding iron(II) sulfate to the cement during production or on-site, without reducing the functionality of the product. Decades of scientific work and practical experience have proven this.

Figure 43. Construction worker, Paqueta, Brazil.

Occupational skin diseases are very common. They represent more than 30% of all occupational diseases in Europe (86, 248) and in much of the rest of the world (59). Among occupational skin diseases, ACD caused by chromium and other metals is

frequent (79, 192, 214, 220, 230, 249). Occupational diseases affect millions of workers every year. Many occupational diseases are difficult to predict and prevent: ACD to hexavalent chromium is not. Nevertheless, construction workers are still becoming sensitized and developing ACD. In the developing world, families face poverty and despair resulting from the loss of their main source of income. Occupational skin diseases often have a poor prognosis and a negative economic impact on both the individual and society (250). Even dermatitis without an allergic component is handicapping, resulting in sick leave and job avoidance (251). Hand dermatitis has a serious impact with far-reaching personal consequences, regardless of its origin (252, 253). ACD due to hexavalent chromium has a poorer prognosis than other forms of hand dermatitis, and there is little hope for those affected. The group of workers with disabling hexavalent chromium allergy is consequently growing. However, most forms of ACD can be prevented by reducing exposure (254). This has already been proven in the case of chromium in the Scandinavian and European countries. We also know that legislation and educational efforts make a significant difference (153, 156, 184, 244).

In the work described in this thesis, I have investigated contact allergy to hexavalent chromium and the resulting ACD, and described how research can improve the situation. It is my hope that the research performed in this field, and the results of regulative measurements will be an eye opener to stakeholders, as such preventive measures are easily implemented. Barrier creams can be of use to both the individual and the industry where, for some reason, the preventive measure of adding iron(II) sulfate is not enforced or is inadequate. Science and increased knowledge can influence legislative bodies and stakeholders to make changes. The question is how to impart this knowledge to leaders and the construction industry globally. Reducing the exposure of construction workers to hexavalent chromium will prevent further sensitization and ACD, but it will not help those already affected. Small amounts of chromium in other materials can also lead to ACD. Even reduced cement may contain hexavalent chromium as a result of oxidation. It is thus necessary to search for alternatives such as barrier creams that can offer protection to already sensitized and affected individuals.

Greater attention is being devoted to global environmental issues, including those in the construction industry. Attempts are being made to find more sustainable methods of producing cement and ways of using it. In the construction industry, there is an excellent opportunity to simultaneously raise awareness of the occupational risks and ways in which they can easily be reduced by adding iron(II) sulfate to cement.

Figure 44. Cristo Redentor in Rio de Janeiro, Brazil, made of cement from Limhamn in Sweden.

6 Summary and concluding remarks

6.1 Concluding remarks – Study I

A relatively high frequency of contact allergy to hexavalent chromium, 3.6%, was found in HCA patients in southern Sweden. Historically, occupational exposure to cement has been the primary cause of hexavalent chromium allergy in Sweden, however, the cause of contact allergy to hexavalent chromium, at least in Europe, has shifted from exposure to cement to other materials, such as leather. Over a quarter (27%) of these patients also reacted to cobalt, whereas only 5% of the controls were allergic to cobalt. A significant association was found between allergy to hexavalent chromium and isolated cobalt allergy in the logistic regression analysis. A significantly higher proportion of HCA patients had atopic dermatitis than among the controls.

6.2 Concluding remarks – Study II

Iron(II) sulfate showed the most promising hexavalent chromium-reducing capacity in these laboratory investigations. However, some of the other compounds investigated also showed an acceptable reducing capacity. As the main aim of this study was to identify candidates for further investigation concerning barrier creams, other aspects were also considered, such as solubility, tanning of the skin, and bad odour. Iron(II) sulfate and glutathione were chosen for further investigation in a barrier cream study.

6.3 Concluding remarks – Study III

Barrier creams containing glutathione and iron(II) sulfate inhibited the elicitation of ACD in HCA individuals tested with a dilution series of hexavalent chromium and cement extract. The differences in reactivity between treated and untreated skin

were significant for both reducing compounds. The lipid-based vehicle petrolatum alone was also found to have a protective effect.

6.4 Concluding remarks – Study IV

A higher number of volunteers (16/18) showed reactions on skin treated with the commercially available barrier cream than on untreated skin (13/18). Skin treated with petrolatum or Essex cream showed fewer and less prominent allergic reactions than skin treated with the commercially available barrier cream. Further studies simulating the real-life situation are needed to clarify the results of this study.

6.5 Concluding remarks – Study V

Almost half (45%) of the cement samples studied contained over 2 ppm hexavalent chromium, implying a risk of sensitization. Four of 17 cement samples from within the EU contained high amounts of hexavalent chromium, even after the addition of a reducing agent. Fourteen of 23 cement samples from countries outside the EU contained high amounts of hexavalent chromium. Worldwide implementation of iron(II) sulfate addition to cement, concomitant with efforts to produce more environmental sustainable cement, would benefit the construction industry and individual workers.

Figure 45. Chromium in various forms, Havana, Cuba.

7 Summary and concluding remarks in Swedish

7.1 Sammanfattning studie I

En relativt hög frekvens av kontaktallergi mot sexvärt krom, 3.6%, påvisades. Historiskt har arbetsrelaterad exponering för cement varit den huvudsakliga orsaken till kontaktallergi mot sexvärt krom i Sverige. Idag har orsaken åtminstone i Europa skiftat från cementexponering till andra exponeringar, sannolikt framförallt läder. 27 % av patienterna med kontaktallergi mot sexvärt krom reagerade också för kobolt, till skillnad från kontroller, där endast 5 % var allergiska mot kobolt. Det fanns en signifikant association mellan kontaktallergi mot sexvärt krom och isolerad koboltallergi i den logistiska regressionsanalysen. En signifikant högre andel atopisk dermatit påvisades bland patienterna med kontaktallergi mot sexvärt krom än bland kontrollerna.

7.2 Sammanfattning studie II

Järnsulfat visade den mest lovande reducerande kapaciteten av sexvärt krom i dessa *in vitro* försök. Emellertid noterades även en acceptabel reducerande kapacitet hos de övriga kemikalierna som undersöktes. Eftersom huvudsyftet med studien var att finna kandidatkemikalier för fortsatta undersökningar avseende barriärkrämer, togs även hänsyn till andra aspekter så som löslighet, färgförändring av huden och dålig lukt. Järnsulfat och glutation valdes ut för vidare undersökningar i en barriärkrämsstudie.

7.3 Sammanfattning studie III

Sammanfattningsvis utvärderades den skyddande kapaciteten hos barriärkrämer preparerade för studien. Barriärkrämer som innehöll glutation och järnsulfat inhiberade elicitering av allergiskt kontakteksem hos individer allergiska mot sexvärt krom när de testades med en spädningsserie av sexvärt krom och

cementextrakt. Skillnaden i reaktivitet mellan behandlad och obehandlad hud var signifikant för båda reducerande tillsatser. En skyddande effekt av den fettbaserade bärarmatrixen vaselin som sådan noterades också.

7.4 Sammanfattning studie IV

I den här studien utvärderades effekten av en kommersiellt tillgänglig barriärkräm mot krom. Ett större antal forskningspersoner (16/18) uppvisade reaktioner på hud behandlad med den kommersiella barriärkrämen jämfört med obehandlad hud (13/18). Hud behandlad med vaselin eller Essex kräm uppvisade också färre och mindre prominenta allergiska reaktioner än hud behandlad med den kommersiella barriärkrämen. En lappteststudie efterliknar inte en verklig exponeringssituation och kan därför inte anses vara en optimal metod för att utvärdera den kliniska effekten av en barriärkräm, men det är en standardiserad metod och kan ses som ett första steg i en utvärdering. Framtida studier som efterliknar verklig exponering behövs för att klargöra resultaten i den här studien.

7.5 Sammanfattning studie V

I den här studien påvisades att 45% av cementproverna innehöll mer än 2 ppm sexvärt krom, vilket innebär en risk för sensibilisering. Fyra av 17 cementprover från länder inom EU innehöll högre halt av sexvärt krom än den reglerade halten, trots tillsats av järnsulfat. Fjorton av 23 cementprover från länder utanför EU innehöll halter över 2 ppm sexvärt krom. Beslutet att tillsätta järnsulfat för att minska halten sexvärt krom i cement och risken för sensibilisering och allergiskt kontakteksem beskrivs som en av de mest framgångsrika preventiva insatserna som tagits inom yrkesdermatologins historia. Kvalitén på cement påverkas inte negativt och varken kostnaden eller ansträngningen är betydande. En parallell ansats att tillsätta järnsulfat, tillsammans med det kontinuerliga arbetet att producera cement med mindre negativ miljöeffekt, vore ur flera perspektiv ett gynnsamt prospekt för lagstadgande organ och cementtillverkare.

Figure 46. Concrete buildings, Buenos Aires.

Acknowledgements

In alphabetical order

All my companion workers at YMDA for Your friendship and support, and for being there doing also my share of the work during my absence from the clinic during parts of the PhD work.

Cecilia Svedman, my supervisor, for never ending commitment and support. This work would not have been done without You.

Erik Zimerson, my co-supervisor, for invaluable teaching and listening.

Helen Sheppard, for language review.

Jonas Palm Media Tryck Lund, for technical and graphical support.

Kajsa Davidson Källberg, for always being there and for offering artistic and technical skills.

Lena Persson, my co-author, for tireless commitment and reliable work in the laboratory.

Magnus Bruze, my co-supervisor, for scrutinizing and for asking those important questions that would otherwise not have passed my mind.

Malin Engfeldt, my former supervisor, for guiding me into the PhD work and for continuing support.

Marléne Isaksson, my co-supervisor, for carrying me through the first hard part of the work and for continuing support.

Martin Mowitz, my co-supervisor, for indispensable support in every critical step of the work, from the very start to the very end.

Volunteers in study III and IV, for trusting us and our intentions and offering Your valuable time and commitment.

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Contact Allergy to Hexavalent Chromium

The work described in this thesis has enabled me to combine my love for India with a fight for social equality and a reduction of occupational diseases.

There is seldom a simple solution for complex questions involving many actors. In this case there is. Contact allergy to hexavalent chromium in cement, impairing thousands of construction workers globally, can effectively be prevented by adding iron(II) sulfate to cement during production or on-site, without reducing the functionality of the product. Decades of scientific work and practical experience have proven this.

Great attention is being devoted to global environmental issues, including those in the construction industry. As the industry is facing challenges that will force future changes there is an excellent opportunity to raise awareness of the occupational risk of allergic contact dermatitis and to strive for a universal implementation of hexavalent chromium reduction in cement.

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Printed by Media-Tryck, Lund 2021 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Occupational and Environmental Dermatology

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2021:97
ISBN 978-91-8021-104-8
ISSN 1652-8220