# Epidemiological assessment of the occurrence of allergic dermatitis in workers in the construction industry related to the content of Cr(VI) in cement

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# INTRODUCTION

During the last 20-30 years, a decline in the occurrence of notified cases of cement dermatitis has been reported from many countries. There has been much debate over the causes of this decline. Some countries have since the 1980s had legislation which regulates the concentration of the chromium in the cement by adding ferrous sulphate and the reported decline have been attributed to this measure. It is also claimed that changes like use of prefabricated cement elements, less manual work in the construction industry and improved hygienic conditions and use of preventive measures (for example use of gloves) may have lead to a decrease, both of cement dermatitis and of the chromium allergy among workers in the construction industry. If fewer workers during the last years have been engaged in the construction industry compared to previous years, this will also influence trends based on the annual notifications of cement dermatitis to a national register. For instance, in France, a downward trend in the notification of the cement dermatitis has been reported, although no ferrous sulphate has been added to the cement in this country (Thomassen 2003, personal communication. Based on data from Caisse Nationale d'Assurance Maladie, France).

On this background, CEMBUREAU has expressed doubts regarding the epidemiological evidence related to the causal association between the reduced Cr(VI) content in cement and the reported decline in allergic dermatitis in construction workers. To approach this question further, it was decided to carry out a risk assessment based on the available epidemiological literature. Thus, at the end of 2002, CEMBUREAU asked the National Institute of Occupational Health (NIOH) in Oslo, Norway, to carry out a review of the available epidemiological documentation regarding the following two questions:

Does Cr(VI) in wet cement cause allergic dermatitis in construction workers?

Is there any causal association between the reduction of Cr(VI) in cement and the occurrence of allergic dermatitis?

The project group consisted of four experts, three physicians (two specialists in occupational medicine/epidemiology (Helge Kjuus and Kristina Kjærheim) and one dermatologist, specialised in occupational dermatoses (Joar Austad), and one expert in risk assessment (Kåre Lenvik).There were two meetings with representatives of CEMBUREAU: the February 18th (Willem van Loo, CEMBUREAU, and Thomas Thomassen from Norcem), and the April 28th (Willem van Loo, CEMBUREAU, Alain Capmas from Association Technique de l'industrie des liants hydrauliques, and Martin Schneider from Verein Deutscher Zementwerke e.V. Forschungsinstitut der Zementindustrie). A reference group consisting of three experts (Petter Kristensen, MD, Ph.D, epidemiologist at NIOH, Vidar Skaug, MD, toxicologist and expert in risk assessment at NIOH, and Jan-Øivind Holm, MD, Ph.D, dermatologist at Ullevål University Hospital, Oslo, expert on occupational dermatology) reviewed drafts of the manuscript.

The investigation was performed during the period January-April 2003.

# TERMINOLOGY AND DEFINITIONS

*Hexavalent chromium.* is the form of chromium which is of special interest in regard to this report. Synonyms which often are used for 'hexavalent chromium': Chromium(VI), Cr(VI) and $Cr^{6+}$.

*Water-soluble chromium*: In the context of chromium allergy from cement, the hexavalent salts of chromium are referred to as '(water) soluble chromium' since only these chromium salts are readily soluble in alkaline cement water. The occurrence of water-soluble chromium is crucial for the risk of sensitisation.

*The concentration of chromium in cement* is usually given in the units of ppm (= parts per million), mg/kg and µg/g. **Mg/kg** is used in this report, irrespective of the unit used in the original paper.

| 1 mg/kg = 1 µg/g = 1 ppm = 0.0001 % |
|---|

The German cement industry uses the phrase 'low-chromate' when the cement contains less than 2 ppm water-soluble chromate (Schneider and Lipus, 2002). The phrase 'low-chromate' is often used in papers without being defined, but it seems to be in the meaning that the concentration of water-soluble chromium is not higher than a couple of ppm.

*Chromium allergy:* 'Chromate allergy', 'chromium allergy' and 'chrome dermatitis' are terms which seem to have been used interchangeably in various papers. 'Chromium allergy' is used in this report, irrespective of the term that has been used in the referred paper.

There are two principal measures of disease occurrence:

*Prevalence:* The proportion of existing cases, old and new, in a defined population at a single point in time. The point prevalence is calculated as the number of existing cases in a defined population divided by the number of persons in the population.

*Incidence:* The number of new cases of the disease that develop in a population at risk during a specified time interval. The incidence rate is calculated as the number of new cases in a population in a defined period divided by the total person-time at risk during the same period.

# BACKGROUND

Cement and lime has long been known as a cause of contact dermatitis. Bernadino Ramazzini referred to it in his book, *De Morbis Artificia Diatriba*, first published in 1700, when he noted that "lime makes the hands of bricklayers wrinkle and sometimes ulcerates them. The first report on an epidemic occurrence was in workers building the Paris metro system (Marial,1908). The first modern cement, Portland cement, was made by Aspdin in Great Britain in 1825, and dermatitis has been described in almost every country since. The connection between chromate sensitivity and cement workers was first described by Bonnevie and Stauffer in 1939, but the connection was not proved until 1950 (Jaeger and Pelloni, 1950).

## CEMENT

Cement is a fine, grey powder which sets after a few hours when mixed with water, and then hardens in a few days into a solid, strong material. Cement is mainly used to bind sand and aggregates together in concrete. Four basic oxides in the correct proportions make cement hydraulic: calcium (65 %), silicon (20 %), alumina (10 %) and iron (5 %). These elements mixed in a homogenous paste called ‘raw meal’, will combine when heated by a flame at 2000 $^{o}$C. New compounds are formed, silicates, aluminates and ferrites of calcium.

Concrete is a solid material made of cement, sand, water and aggregates. When fresh it is thick fluid. Typically, concrete is the essential material used in construction.

The basic elements for cement are limestone and clay, containing calcium, quartz, alumina, iron, alkali and sulphates in certain proportions. Furthermore, small amounts of chromium are present, as well as minute amounts of cobalt, manganese, nickel and molybdenum. As there are natural variations in the chemical composition of the earth’s crust, the chemical composition of the raw materials will vary.

### *The manufacture of cement*

Basically, cement is produced in two steps: in the first cement clinker is produced from raw materials. In the second step cement is produced from the cement clinker.

The first step can be dry, wet, semi-dry or semi-wet process, according to the state of the raw materials. The raw materials are crushed, and homogenised into a paste which is fed into the kiln. This is a kind of enormous rotating pipe, 60 to 90 m long and up to 6 m of diameter. This ‘oven’ is heated by a 200 $^{o}$C flame to a temperature which can reach 1400-1600 $^{o}$C. The kiln is slightly inclined to allow for materials to slowly reach the other end, where it is quickly cooled to 100-200 $^{o}$C. The final product of this phase is called ‘clinker’.

The second phase takes place in a cement grinding mill, which may be located in a different place from the clinker plant. Gypsum (calcium sulphates) and possibly additional raw materials are added to the clinker. All elements are ground (crushed) to lead to a fine and

homogenous powder. The finished cement is then stored in silos before being delivered to users.

### *Chromium in cement*

The main sources of chromium in finished cement are the raw materials, refractory bricks in the kiln and chromium steel grinders. The relative contribution from these sources may vary, depending on the chromium content of the raw materials and on the manufacturing conditions (Puntke and Wassing, 2002; Klemm, 1994; Bergt,1963). In a study of clinker grounding with chrome alloy balls of 17-28 % chromium, the hexavalent chromium of the cement increased to over twice that present in the original clinker (Klemm, 1994). A study of East German cements (Bergt, 1963) showed that 28 % of the chromium originated from the raw materials, whilst burning process contributed 62 % and the remainder came from the mill liners and the grinding media.

Chromium occurs as trivalent chromium in the raw materials. During the manufacture of cement, the trivalent chromium is, at least partly, transformed into the highest oxidative state, hexavalent chromium, due to the alkaline environment, the high temperature and the presence of air in the kiln process. Thus, although there is no hexavalent chromium in the raw materials both, Cr(III)- and Cr(VI) compounds are present in the finished cement (Frias et al., 1993).

It has been demonstrated that the amount of soluble chromium is dependent on the content of soluble sulphate (Fregert and Gruvberger, 1973a; Fregert and Gruvberger, 1973b). Thus, the amount of chromate that is extracted together with the water is dependent on the alkali sulphate originally found in the cement. Also absorbed chromate can be released by use of sodium sulphate.It has also been demonstrated that the hexavalent chromium is independent of the total chromium in the cement (Fregert and Gruvberger, 1972; Ellis and Freeman, 1986). According to Klemm (1994), the hexavalent chromium of Portland cement are in the range 1 - 30 mg/kg, but is usually less than 20 mg/kg, and the content is usually less than 30 % of the total chromium.

Hexavalent chromium is a strong sensitising agent. It forms water-soluble compounds in cement and have the capacity to penetrate human skin (Fregert, 1981). In contrast the Cr(III) occurs in water-insoluble compounds in cement. It was realised several decades ago that the sensitising properties of cement were related to the content of hexavalent chromium. Much effort has therefore been made to get rid of the hexavalent chromium. Equipment in the manufacturing process has been changed in order to lower the contribution of chromium to the cement. It is reported from Australia that kilns containing magnesium-chrome refractories have progressively been changed to spinel (magnesium aluminate) (Tandon and Aarts,1993), and refractory bricks and grinders which contain chromium are not used today (information from CEMBUREAU on meeting the 28$^{th}$ of April). In Singapore, slag from blast furnace processes, which is free from hexavalent chromium, has been used as a substitute for clinker in the manufacturing of cement (Goh and Gan, 1996). Thus, by using 60 % slag instead of 5 % slag, the concentration of hexavalent chromate was reduced from 17.1 to 7.1 mg/kg.

In 1970, Burchhardt et al.(1970) showed that the addition of ferrous sulphate to the cement reduced the sensitising power. The method was further investigated with respect to commercial use at the end of the 1970's (Fregert et al.1979; Fregert, 1981), and this chemical

method have been used commercially in Scandinavian countries from the 1980's. When ferrous sulphate is added hexavalent chromium is transformed to trivalent chromium which forms water-insoluble compounds (Fregert et al.,1979; Fregert, 1981; Goh and Kwok, 1987). Chemically this process can be expressed as follows

$$Cr^{6+} + 3\ Fe^{2+} \rightarrow Cr^{3+} + 3\ Fe^{3+}$$

$Cr^{3+}$ is precipitated as $Cr(OH)_3$ due to the alkalinity of cement.

It has been demonstrated that the Cr(VI) can be reduced to less than 0,04 mg/kg by adding ferrous sulphate (Goh and Kwok, 1987).

The ferrous sulphate may lose some of its reducing capacity due to the high temperature and high humidity in the mill, and thus, some chromate may be present in the finished cement (Fregert et al., 1979; Klemm,1994; Puntke and Wassing, 2002; Schneider and Lipus, 2002). Furthermore, it has been demonstrated that the effect of the ferrous sulphate may decrease from the time of manufacture until the cement is used (Bruze et al., 1990; Fregert et al., 1979).

From a dermatological point of view, it is the quantity of Cr(VI) (i.e. the soluble chromium) in the cement which is of concern. Therefore it is hexavalent chromium, and not the total quantity of chromium, which is of importance and which has to be controlled in regard to the sensitising risk of cement.

From the above brief summary, it can be seen that there are a number of factors which have an impact upon the content of hexavalent chromium in the finished cement. Some measurement data are displayed in the tables below.

*Chromium content in different cements in mg Cr/kg cement*

| Country | Number of samples | Concentration | Reference |
|---|---|---|---|
| GDR | 280 | 0.05-3.3 (1) | Bergt, 1963 |
| Various in Europe | >185 | 0.003 - 20 | Høvding, 1970 |
| USA/Canada | - | <0.004 - 1.42 | Rebel and Delles, 1993 |
| USA | 7 | 0.3 - 6.9 | Denton et al., 1954 |
| USA | 42 | <0.1 - 5.2 | Perone et al., 1974 |
| Spain | 20 | 0.9 - 24.2 | Frias and Sanchez Rojas, 1995 |
| Australia | 24 | ≤1-18.5 | Ellis and Freeman, 1986 |
| Germany | 139 | <0.1 -20.3 | Kersting et al., 2002 |
| Australia | 8 | 0.2 - 8.1 | Tandon and Aarts,1993 |
| Asia | 10 | 3.6-25.1 | Goh and Kwok,1986a |

1) as mg $K_2Cr_2O_7$

*Adopted from Fregert and Gruvberger, 1972.*

| Country | Number of samples | Concentration of water-soluble Cr(VI) | Total Cr(III) and Cr(VI) |
|---|---|---|---|
| Sweden | 8 | 2-15 | 38-173 |
| Denmark | 5 | 1-5 | 35-60 |
| Norway | 3 | 6-40 | 42-173 |
| Finland | 4 | 5-17 | 48-80 |
| England | 3 | 3-4 | 57-80 |
| BRD | 7 | 5-12 | 64-69 |
| GDR | 5 | 1-13 | 56-75 |
| France | 15 | 1-9 | 57-102 |
| Italy | 2 | 1-4 | 48-71 |

The tables show that the concentration of water-soluble chromate varies between countries, but there are also considerable differences within the countries. It is to be noted that the figures are, in most cases, based on only a few samples. Moreover, the methods of sampling is often poorly explained, and a statistical description of the data is often lacking. Thus it is difficult to look upon the results as representative for a whole country.

The measurement results can also be affected by the method of determination, and this can sometimes explain measured variations.

## ALLERGIC CONTACT DERMATITIS

### *Contact dermatitis*

Contact dermatitis (contact eczema) is an inflammation of the skin due to topical exposure to chemical agents. The skin is erythematous (red) and scaly, often associated with fissures and secondary infection. There is always itch and often pain and burning.

Contact dermatitis is induced by two main pathways: *irritant* or *allergic*. Irritant contact dermatitis (ICD) is most common and accounts for about 80 % of all cases. This is a non-specific reaction due to agents which damage the skin barrier and interfere with the cells in the epidermis. Soaps, detergents, acids, alkalis and wet work are the most common causative agents. Allergic contact dermatitis (ACD) is a specific and immunological reaction, where sensitisation to a given allergen is required. Contact with the allergen in a sensitised person induces eczema in the skin. Three thousand allergens are known, the most common are metals and plant constituents.

Irritant and allergic contact dermatitis have the same clinical appearance. In occupational contact dermatitis hand eczema is most common. Often both types of dermatitis are seen at the same time, and many chemicals can act both as irritants and allergens. Irritant contact

dermatitis also predisposes for allergic contact dermatitis because of the reduced barrier function of the skin which facilitates the penetration of allergenic agents into the skin.

A specific diagnosis is based upon a patient history, a physical examination and allergy tests. Testing is performed as epicutaneous patch tests, where allergens in low concentration are applied to normal skin under occlusion for 48 hours. Both allergens and test procedures are standardised.

### *Chromium allergy*

The prevalence of chromium allergy in the general population is between 0,5 % and 1,7 % (Nielsen et al., 2000; Peltonen and Fräki, 1983). In consecutive patients with eczema, studies have shown prevalence figures from 1,8 % to 7,5 % (Johansen et al., 1999; Lestringant, 1999). Patients with chromium allergy diagnosed by patch tests do not need to have active dermatitis at the time of testing (common for all allergies).

In order to sensitise a person (induce allergic contact dermatitis) chromium has to penetrate the skin (epidermis) and stimulate cells of the immune system. Chromium(VI) has a high water solubility and is thereby able to penetrate the skin. It is classified as a potent allergen. Wet skin and increasing pH decrease the skin barrier function and increase chromium(VI) penetration. The lowest concentration of Cr(VI) which is needed to sensitise is not known. However both the concentration and the exposure time are crucial factors.

Cr(III) has low water solubility and only a small fraction will penetrate into the skin. Furthermore, high pH will precipitate Cr(III) as chromium hydroxide, which is virtually insoluble in water and sweat.

The level of hexavalent chromium which is necessary for eliciting an allergic reaction in sensitised persons varies. On normal skin, some individuals may react at a concentration down to 10 ppm in patch tests, while pretreating the skin with an irritant solution may give a positive reaction to 1 ppm (Basketter, 2001). Trivalent chromium can also elicit allergic reactions, but at a higher concentration. No lower threshold is known, but 46 % of chromium allergic patients reacted to 15000 ppm when patch tested (Barré Hansen et al., 2002). Metallic chromium is not allergenic. There is no penetration in the skin because of low solubility.

The main sources of chromium exposure are cement, tanned leather, printed and dyed textiles, anticorrosive oils and paints, photography chemicals and match heads.

Patch testing for chromium allergy is performed with 0,5 % (5000 ppm) potassium dichromate (Cr(VI)) in petrolatum. Another test system (TRUE test) may also be used. The tests are occluded to the skin for 48 hours. They are then read immediately, and after 24 and 48 hours. An eczematous reaction at the test spot is a positive test. The test substance and the occlusion may give an irritant reaction (false positive test). In USA, 0.25 % potassium dichromate is recommended for this reason. However, this concentration will not elicit an allergic reaction in all sensitised individuals (false negative test).

The International Contact Dermatitis Research Group (ICDRG) makes guidelines for patch testing which are followed by most countries world-wide. Test results are comparable when these guidelines are followed.

### *Cement eczema*

Cement eczema may be caused either by exposure to wet cement and high pH which induces irritant contact dermatitis, or by an immunological reaction to chromium which elicits allergic contact dermatitis. The observed eczema in many patients is a combination of these two mechanisms. An exact diagnosis is often difficult to assess.

## EPIDEMIOLOGICAL ASPECTS

Epidemiological research can be classified into three levels: descriptive epidemiology, etiological epidemiology and interventive epidemiology (Hernberg,1992). Descriptive epidemiology is concerned with the occurrence of disease in different populations without any view of causal interpretation of the relation. Etiological epidemiology investigates the association between an outcome (disease) and one or several determinants (exposure factors). Interventive epidemiology, when applied to solving etiological problems, examines the effects on morbidity or mortality of changing exposure conditions.

The papers reviewed in this report will primarily focus on etiological studies (does soluble Cr(VI) in wet cement cause allergic dermatitis in workers in the construction industry?) and interventive studies (does the reduction of Cr(VI) in wet cement lead to a reduced occurrence of allergic dermatitis?). It is important to realise that if an association is found between two phenomena, the connection cannot automatically be interpreted as causal. Thus, an observed association can, in addition to being causal, be due to bias (systematic errors) or chance (random errors), or it can occur seemingly (confounding).

Systematic errors are the most serious. They are inherent in the study design and cannot be corrected for. They can be either positive (leading to a false positive association where there is in fact none), or negative (masking a true, causal association). One type of systematic error, selection bias, occurs when the presence or absence of a disease systematically influences whether or not the subjects are included in the study. This selection bias is a serious problem in cross-sectional studies. E.g. subjects who develop allergic dermatitis due to exposure to wet cement, may tend to quit or change job, leading to a health-selective turnover in those most affected. Thus, the study will be restricted to the “survivors”. The result becomes biased, and the true health effects of the exposure in question are underestimated. So-called information bias occurs when there is asymmetry in the quality of information on the study groups and the reference groups, for instance if being diagnosed with the disease in question increases the chance of being classified as exposed.

Random errors arise if the precision of the measurement of either exposure or outcome is poor. Hence, random errors tend to mask a true difference between the populations. This is in contrast to systematic errors, which may act in either direction.

A seeming association may be due to confounding, i.e. another determinant (risk factor) for the disease which is also associated which the exposure factor in question. If the distribution of the confounding factor is known, it can be corrected for.

With regard to study design, cohort studies are often regarded as the most valid and informative type of epidemiological study. Cohorts are defined by a common event (employment in a specific industry, exposure to a common agent) and followed for a specified time, and new cases of the disease are measured during a time period (incidence). Cross-sectional studies examine an exposed and a non-exposed group at a particular point in time and compare the proportion of individuals with a disease or symptom in the two groups (prevalence).

For some diseases, e.g. cancer, some countries have reliable national registers which are used for epidemiological studies. Epidemiological outcome data related to occupational contact dermatitis (OCD) come from a variety of other sources which all have their limitations The most common sources are national survey data (annual statistics based on interview surveys or notifying registers or workers compensation systems), industry- or plant-specific data from workplace investigations, or clinic- or patchtest-based data on patient populations (for review, see Lushniak, 1995).

Thus, although a proper case definition is a prerequisite for the gathering of epidemiological data, the case definition can vary from one data source to another, and may be based on employer reporting, employee self-reporting, worker compensation claims or clinical diagnosis. The accuracy of the diagnosis is related to the level of skill, experience, and knowledge of those who make the diagnosis and its relationship to the workplace. Although guidelines are available for assessing the work-relatedness of dermatitis, they may be practised differently, making comparisons between groups, statistics or different studies difficult. Thus, problems with standard case definition may lead to the potential misclassification of OCD, resulting in over or underestimation of disease frequency.

Lushniak (1995) lists several other problems in assessing the epidemiology of OCD.
OCD is not a reportable disease in most countries which makes national statistics of limited use for valid comparisons. Based on national surveys in the United States, it has been estimated that occupational skin diseases may be of the order of 10 to 50 times higher than that which is reported by the U.S. Bureau of Labor Statistics (Mathias, 1985). As OCD does not commonly lead to hospitalisation, hospital records are not useful data sources. Physician-based data sources are also inefficient. As OCD often goes untreated and undiagnosed, many cases will never be documented in any data source. Individuals with OCD (or ACD) who seek medical care may be a unique subset of the population. This will lead to self-selection bias.

Furthermore, unique exposures may occur in different populations and different industries, so that the occurrence of the disease in one population cannot necessarily be generalised to other populations. Exposures change over time, and the affected worker may continue to have the disease ever though he is no longer exposed to the causative agent. The evaluation of past exposures may, in addition, be subject to recall and information bias. Most studies in the present review are cross-sectional studies. As already mentioned, these are subject to survivor bias. Persons with severe skin disease often leave the work force, leaving only those who are less affected or not susceptible to the disease to be included in the studies.

The fact that epidemiology is an observational discipline often puts restrictions on how specific research questions can be studied for both practical and ethical reasons. The control of study variables is therefore less than in classical experimental settings, and at the same time, the number of variables which possibly influence the association in question is immense. As an aid to the evaluation of an observed association, certain criteria for causal associations are often considered (Hill, 1965). Among the important criteria are the consistency, the temporality, the biological gradient (dose response), and the biological plausibility of the association. While none of the criteria, except the demand that the cause should come before the effect, are obligatory, they serve as useful guidelines in the discussion.

## AIMS OF THE STUDY

The aim of the study was the following:

> *To investigate and if possible establish, using the existing epidemiological literature, the probability that exposure to wet cement preparations containing soluble Cr(VI) cause allergic eczema to workers in the construction industry.*

The investigation was more precisely defined to be an evaluation and a discussion of the existing epidemiological literature regarding the following two questions:

- *Does Cr(VI) in wet cement cause allergic dermatitis in construction workers?*

- *Is there any causal association between the reduction of Cr(VI) in cement and the incidence/prevalence of allergic dermatitis?*

It has been outside the scope of this report to discuss the biological and toxicological evidence of the sensitising properties of chromium. The biological and toxicological properties are reviewed in several papers (National Institute for Working Life, 2000; Burrows, 1983; WHO, 1988; NIOSH, 1975).

## METHODS

The study was carried out in the following steps:

a) Literature search and retrieval of literature.

b) Screening of the literature
A read-through of all the papers and the selection of the important papers for in depth studies

c) In depth studies
The papers of importance to the question were subjected to thorough investigations and discussions, with regard to
- overall epidemiological design
- specific validity aspects related to possible systematic errors (selection bias, information bias, comparability, including assessment of real and potential confounders)
- external validity

d) Reporting

## RETRIEVAL OF PAPERS

A reference list received from CEMBUREAU (appendix 1) was assumed to be of relevance and almost all the papers were retrieved. Furthermore, computerised searches were carried out in order to trace relevant papers. These searches were supplemented by a hand-searching follow-up of reference lists of the articles retrieved.

Literature searches were performed in the following electronic databases:

Pubmed (MEDLINE)
Science Direct (Elsvier)
Science Citatian Index (ISI - Institute for Scientific Information )
NIOSHTIC (the version of OSHrom)

The search strategy was designed for finding papers on 'chromium allergy' in 'construction workers 'or related to cement, irrespective of the type and date of the study. As all papers regardless of the time of publication were of interest, no time limits were set in the searches.

The terms used in the searches:
*cement and (eczem? or allerg? or chrom? or derm? or skin)*
*chromate dermatitis*
*chromium allergy*
*construction workers and (allergy or dermatitis)*

Bibliographical details were downloaded, including abstracts when available.

Approximately 500 - 600 different references were hit, of which 130 papers were obtained.

### Papers selected for review

The only way to distinguish chromium allergy from other eczema is by patch testing with chromate. A criterion for including a study in the review was, therefore, that the paper explicitly states that such tests have been used in the assessment of chromium allergy.

Only a couple of papers focused on the occurrence of contact allergy related to the chromium concentration in cement. Nevertheless, cement eczema in construction workers was the topic in many of the papers, and these were therefore considered of relevance to this study.

### National registers of occupational diseases - workers' compensation statistics

Several countries have national statistics on occupational diseases, often connected to worker compensations. Unpublished statistics showing number of notified cases per year were available from several European countries for this review. The notification systems for the available statistics were either not or only poorly described in most cases. In the few cases the notification system was described, the statistics could perhaps under certain conditions be valid as to evaluate time trends within a country, but not for between-country comparisons. However, there might be serious selection bias in such statistics due to different routines for

registration/notification of cases. Based on the information given, it was not possible to perform a qualified evaluation of the available statistics, which, however, also was outside the scope of this study.

Overview of papers finally selected**.**

| Paper | Country | Time of investigation | Type of study | Population |
|---|---|---|---|---|
| Avnstorp, 1989a | Denmark | 83, 87 | Cohort | Construction workers |
| Avnstorp, 1989b | Denmark | 83, 87 | Cross-sectional | Construction workers |
| Avnstorp, 1991 | Denmark | 83, 87 | Cross-sectional | Construction workers |
| Basketter et al., 2001 | UK | - | Case series | Allergic subjects |
| Bruze, Fregert, Gruvberger, 1990 | Sweden | - | Case series | Allergic subjects |
| Bruze, Gruvberger, Hradil, 1990 | Sweden | - | Case series | Patients/construction workers |
| Coenraads et al., 1984 | Netherlands | - | Cross-sectional | Construction workers |
| Condé-Salazar et al., 1995 | Spain | 89-93 | Cross-sectional | Patients/construction workers |
| Freeman, 1986 | Australia | 85 | Cross-sectional | Patients/construction workers |
| Fregert, 1975 | Sweden | 60-69 | Cross-sectional | Patients |
| Geier and Schnuch, 1995 | Germany | 89-93 | Cross-sectional | Patients/general population |
| Goh et al., 1986 | Indonesia | - | Cross-sectional | Construction workers |
| Guo et.al., 1990 | Taiwan | 93 | Cross-sectional | Construction workers |
| Halbert et al., 1992 | Australia | 80-89 | Cross-sectional | Patients |
| Høvding, 1970 | Norway | 63, 68 | Cross-sectional | Construction workers |
| Irvine et al., 1994 | UK. | 90-92 | Cross-sectional | Construction workers |
| Johansen et al., 2000 | Denmark | 85/86, 97/98 | Cross-sectional | Patients/general population |
| Kiec-Swierczynska, 1990 | Poland | 67-79 | Cross-sectional | Construction workers |
| Olsavszky et al., 1998 | UK. | 82/83, 92/93 | Cross-sectional | Patients/general population |
| Peltonen and Fräki, 1983 | Finland | 72-76 | Cross-sectional | Patients |
| Perone et al., 1974 | USA. | 1970 | Cross-sectional | Construction workers |
| Reifenstein et al., 1986 | GDR | - | Cross-sectional | Construction workers |
| Roto et al., 1996 | Finland | 85/86 | Cross-sectional | Construction workers |
| Zachariae et al., 1996 | Denmark | 89-94 | Cross-sectional | Patients/general population |

# REVIEW OF THE LITERATURE

## I. STUDIES ON CR(VI) ALLERGIC DERMATITIS RELATED TO WET CEMENT IN CONSTRUCTION WORKERS

### *I a) BASIC INVESTIGATIONS*

**Basketter D et al.**
**Investigation of the threshold for allergic reactivity to chromium.**
**Contact Dermatitis 2001;44:70-74.**

Basketter et al. studied the threshold for allergic reactivity to chromium by investigating skin reactions to chromium. Closed patch tests and repeated open application tests were carried out on 17 chromium-allergic individuals. The data indicated a patch test threshold of 10 ppm chromium on normal skin. The threshold was closer to 1 mg/kg (1 ppm) in the presence of an irritant. The authors concluded that there was a very poor correlation between the patch test sensitivity and the sensitivity in the repeated test.

*Comments: This clinical investigation indicates that in daily work with long periods of exposure to low concentrations of chromium which are thought to be 'safe', allergic chromium dermatitis can still be induced. The threshold concentration for the elicitation in a sensitised person varies with the barrier function of the skin.*

**Bruze M et al.**
**Chromate sensitisation and elicitation from cement with iron sulfate.**
**Acta dermato-venereologica 1990; 70:160-162.**

This report describes three cases of the outbreak of allergic contact dermatitis from chromate in cement. The chromium concentration of cement was measured in each case. In the first case, the patient handled cement with a chromium-concentration of 2.0-4.6 mg/kg, in the second case a concentration of 0.3-7.3 mg/kg was found, and in the last case, the concentration was measured to be 3.0 mg/kg.

*Comments: The investigation shows that chromium allergy can be elicited at concentrations somewhere in the range of 0.3 - 7.3 mg/kg. The concentration was 3.0 mg/kg in one case. This is one of few studies which provides an indication of a threshold for the effect.*

**Bruze M et al.**
**Patch Testing with Cement Containing Iron Sulfate.**
**Dermatologic Clinics 1990; 8[1]: 173-176**.

Eight chromate-sensitive men were voluntarily patch tested with 0.5 % potassium dichromate in water, and all reacted positively to the tests. Furthermore, they were tested with cement

with or without iron sulphate and the same concentration of chromium, also in water solution. All the patients reacted to the cement tests without iron sulphate, but none of them to the tests with iron sulphate. Colorimetric analysis did not show any chromium in the cement fraction containing iron sulphate.

*Comments: This clinical study shows that wet cement without iron sulphate gives positive patch tests in chromium sensitive subjects, but not wet cement containing iron sulphate. This is a strong confirmation that the addition of iron sulphate transforms water-soluble hexavalent chromium into non water-soluble trivalent chromium. It also indicates that exposure to wet cement with iron sulphate will reduce the risk of allergic dermatitis.*

## *I b) INVESTIGATIONS BASED ON PATIENTS FROM DERMATOLOGICAL. CLINICS*

**Freeman S.**
**Dermatitis due to chromate in cement. Part II. Incidence of cement dermatitis in Australia.**
**Aust J Derm 1986**; **27:104-106.**

Members of the Australian College of Dermatologists were asked in April 1985 to keep a record of all patients seen during the next 12 months with allergic contact dermatitis due to cement. The number of cases, the occupations of the patients and the patch test results were recorded. Fifty-four cases of chromate-positive cement dermatitis were reported. A telephone follow-up in half of the cases was done. This revealed that 80 % were new cases. Extrapolated to all cases, this means that 43 out of 54 were new (incident) cases during one year.

Only 59 (31 %) of the dermatologists out of a total of 188 replied to the request. A telephone survey of a sample of 20 dermatologists indicated no cases of cement dermatitis among those who did not reply. The author therefore assumed that the response represented the correct number of cement dermatitis observed by the dermatologists. The 43 new cases represented only 0.012 % of all men in the construction industry in Australia and the author writes: ”However, these represent only the tip of the iceberg”.

*Comments: This selected population is not representative. The study does not provide any meaningful estimates of the incidence or prevalence of allergic dermatitis in cement workers.*

**Halbert AR et al.**
**Prognosis of occupational chromate dermatitis.**
**Contact Dermatitis 1992; 27: 214-219**

Occupational chromate dermatitis was diagnosed in 123 patients between 1980 and 1989 in a dermatological unit in Western Australia. In a follow-up study which was performed in the time period 1988 -1990, 89 of these patients were personally interviewed and examined, 24 were interviewed by telephone and 7 responded by filling in a questionnaire.

Seventy eight patients (65 %) had cement-induced chromate dermatitis. Seven to twenty cases of occupational chromate dermatitis were diagnosed each year in the time period 1980-89, of which 5 - 13 cases were cement induced. The occupations of the cement workers were

plasterers (26 %), concreters (24 %), bricklayers (22 %), and various others (28 %). Fifty-four of the workers handled bagged cement, 16 used bulk cement and eight used a combination of bagged and bulk cement. The authors states that the workers which used bagged cement were to be at the greatest risk of sensitisation.

*Comments: In this study the patients who were most commonly affected by chromate dermatitis were construction workers. The study concerns a selected population and no prevalence figures can be given.*

**Fregert S.**
**Occupational dermatitis in a 10-year material.**
**Contact Dermatitis 1975; 1:96-107.**

This is an analysis of clinical data from the examination of 1752 patients (1157 men and 595 women) at a dermatological unit in Lund, Sweden, during 1960-1969. The patients were referred on the suspicion of occupational dermatoses. Contact dermatitis was assessed by patch testing. This diagnosis was also based on the history, the localisation, the clinical picture, and the course of exposure in spite of negative patch test reactions.

Contact dermatitis was diagnosed in 92 % (501/545) of the women and 83 % (951/1157) of men. Cement casting and the building industry were the second and third most common occupations ranked according to the frequency of contact dermatitis (no figures given). Allergic contact dermatitis was assessed in 3 % of women and 2 % of men without positive patch tests.

The most common allergens in men were chromium, rubber and plastic, and nickel, rubber and chromium in women. Chromium was the most common allergen in men, and 50 % of 280 Cr-sensitised men were employed in the building and concrete industry. Of the 42 Cr-sensitised women, 20 % were employed in asbestos cement work.

A follow-up by means of a questionnaire to 846 patients (360 women and 486 men who had contact dermatitis) was done two-three years after the examination, and 555 responded. of the 176 men with continuing allergic dermatitis, 44 % were sensitive to chromium. Relatively few patients from the building industry and cement casting were without symptoms, and in men, the worst prognosis was in the cement casters. Permanent symptoms in the women occurred more often for allergic contact dermatitis than for irritant dermatitis. There was no such difference for the men. Twenty-nine percent (91/315) of the men had changed their occupation or stopped working

*Comments: The study is based on patient files of subjects with suspected occupational dermatoses, and is thus based on a highly selected population. Chromium allergy is predominant, and the occurrence is especially high in subjects with occupations where cement is used.*

**Peltonen I and Fräki J.**
**Prevalence of dichromate sensitivity.**
**Contact Dermatitis 1983; 9:190-194.**

In a population of 822 healthy adult volunteers, 2 % of the 410 men and 1.5 % of the 412 women showed a positive patch test to 0.5 % potassium dichromate. The population consisted of medical students, staff members of a hospital department, persons from a home of elderly people and employees at a newspaper office and at a printing plant, aged from 19 to 74 years. Furthermore, the results are presented from patch tests of 2981 clinic patients at a hospital in Turku, Finland, during the time period 1972-1976.

*Chromate sensitivity in patients of different occupations*

| Occupation | Sensitivity to chromium | |
|---|---|---|
| | Women (%) | Men (%) |
| Engineering | | 7.5 (16/213) |
| Building | | 15.5 (32/206) |
| Farming | 4.0 (6/150) | 5.8 (8/138) |
| Radio-/TV-industry | | 11.4 (4/35) |
| Graphics industry | | 15.3 (4/26) |
| Household work | 2.9 | |
| Medical personnel | 0.6 | |
| Office work | 1.8 | |
| Cleaners | 3.9 | |
| Textile industry | 2.7 | |
| Shop assistants | 1.2 | |
| Food industry | 1.7 | |
| Metal industry | 9.8 | |
| Leather industry | 15.4 | |
| Other occupations | 1.4 (7/504) | 1.5 (8/1158) |
| Total patients (n=2981) | 2.8 (51/1823) | 6.8 (80/1158) |
| Healthy volunteers (n=822) | 1.5 (6/412) | 2 (8/400) |

Ten of the positive reactions in the volunteers occurred in the 110 employees who were recruited from the printing industry.

*Comments: This is a study of a selected population (clinic patients). The highest occurrence of chromium sensitivity in men was in the building industry (15.5 %) and in the graphics industry (15.3%), and for females, in the leather industry (15.4 %). The most common cause of sensitivity in the building industry was exposure to cement.*

**Geier J and Schnuch A.**
**A Comparison of Contact Allergies Among Construction and Nonconstruction Workers Attending Contact dermatitis Clinics in Germany. Results of the Information Network of Departments of dermatology from November 1989 to July 1993.**
**American Journal of Contact Dermatitis 1995; 6[2]:88-94**

This paper is an evaluation of the data from patch testing of patients at dermatological hospitals in Germany during the period from November 1989 to July 1993. Two groups of patients were compared: male patients working in the construction industry (n=201) and all men not working in the construction industry (n= 5706). Approximately 90 % were patch-tested.

The age distribution was significantly different in the two groups, with more construction workers being in the group between 50 and 59 years, and fewer being more than 69 years.

*The main diagnoses assessed:*

| | **Construction workers** | | **Non-construction workers** | |
|---|---|---|---|---|
| | n | % | n | % |
| Allergic contact dermatitis* | 94 | 45.9 | 1524 | 26.7 |
| Irritant contact dermatitis | 30 | 14.6 | 650 | 11.4 |
| Atopic dermatitis | 20 | 9.8 | 621 | 10.9 |
| Dyshidrosis | 6 | 2.9 | 134 | 2.3 |
| Nummular eczema | 5 | 2.4 | 138 | 2.4 |
| Stasis dermatitis | 3 | 1.5 | 96 | 1.7 |
| Psoriasis | 3 | 1.5 | 62 | 1.1 |
| Other diagnoses | 29 | 14.1 | 1193 | 20.9 |
| Missing data* | 15 | 7.3 | 1288 | 22.6 |
| Total | 205 | 100.0 | 5706 | 100.0 |

* Statistically significant differences ($p < 0.001$)

There was significant difference between the construction workers and the others in the frequency of diagnosis of allergic contact dermatitis. The most common allergen in the construction workers was potassium dichromate.

*Positive patch test to potassium dichromate and cobalt salts:*

| | Dichromate | Cobalt salts |
|---|---|---|
| Construction workers | 61/191 (31.9 %) | 29/193 (15.0 %) |
| Others | 365/5143 (7.1 %) | 250/5154 (4.9 %) |
| Significance level | $p<0.001$ | $p<0.001$ |

A significantly higher frequency of sensitisation was found in the construction workers than the others for both potassium dichromate and cobalt salts. The authors state that contact with hexavalent chromium in cement is the main source of this allergen in the building industry.

According to the authors, cement with reduced chromate was not used in Germany at that time.

*Comments: It is not likely that the age-difference (for age > 50 years) between the groups is of importance in this study. However, this is a selected population. In spite of this weakness, the study strongly indicates that the occurrence of chromium allergy is high in construction workers compared to other occupations.*

## *I c) INVESTIGATIONS BASED ON WORKPLACE POPULATIONS*

**Coenraads JP et al.**
**Prevalence of eczema and other dermatoses of the hands and forearms in construction workers in the Netherlands.**
**Clinical and Experimental Dermatology 1984;9:149-158.**

Eczema on the hands and forearms was examined in 1691 construction workers out of a sample of 1789 workers from construction companies in the Netherlands. (Ninety-eight out of the 1789 workers were not available for examination). The examination took place at the work sites.

All workers were questioned as to their skin condition during the last three years. A person was registered as a case when he had had a skin disease for at least three weeks, recurrent skin diseases during the last three years or had a relevant skin disease at the time of examination. At the time of the examination, 113 workers had a dermatosis.

*Number of diagnosed skin diseases in the construction workers (n=1691):*

| | |
|---|---|
| Irritant dermatitis | 67 (4.0 %) |
| Irritant + allergic | 6 (0.4 %) |
| Irritant + atopic | 9 (0.5 %) |
| Allergic eczema | 23 (1.4 %) |
| Atopic eczema | 8 (0.4 %) |
| Others | 20 (1.1 %) |
| Total eczema | 133 (7.8 %) |

The 133 cases and a sample of 309 'non-cases', i.e. construction workers without hand eczema, were selected for further investigation and patch testing. Results stratified on occupation are given in the table below.

*The prevalence of eczema and allergy to dichromate, cobalt, thiuram mix and epoxy resin in five job categories*

| | Carpenters | Bricklayers plasterers, etc | Unskilled | Technicians, reinforcers | Administrative & supervision | Total |
|---|---|---|---|---|---|---|
| Examined (n) | 840 | 357 | 184 | 119 | 191 | 1691 |
| No of 'cases' | 51 | 45 | 16 | 7 | 14 | 133 |
| No of 'non-cases' | 789 | 312 | 168 | 112 | 177 | 1558 |
| No with positive patch test in the 'cases' | 3 (6.1 %) | 11 (24 %) | 3 (19 %) | 2 (28 %) | 0 (0) | 19 (14 %) |
| No with positive patch test in the 'non-cases' (*) | 34 (4.3 %) | 23 (7.6 %) | 5 (3.2 %) | 9 (7.7 %) | 15 (8.3 %) | 86 (5.5 %) |
| No of positive patch tests in the whole population. | 37 (4.4 %) | 34 (9.5 %) | 8 (4.3 %) | 11 (9.2 %) | 15 (7.6 %) | 105 (6.2 %) |

*(*) Coenraads et al. examined a sample of 309 individuals of 'non-cases'. The percentage prevalence of sensitised individuals is given in the parenthesis, and these figures have been applied in the calculation of the number of individuals with positive patch test in the whole sub-population of 'non- cases'.*

Patch testing was performed for dichromate, cobalt, thiuram mix and epoxy resin.

*Positive patch tests to some allergens:*

| | Dichromate | Cobalt | Thiuram mix | Epoxy resin |
|---|---|---|---|---|
| Prevalence in the 'cases' (n=133) | 11.1 % (14) | 2.3 % (3) | 3.0 % (4) | 0 |
| Prevalence in the sample of 'non-cases' (n=309) | 2.6 % (8) | 0.6 % (2) | 1 % (3) | 1.3 % (4) |
| Prevalence in the whole sub-population of 'non-cases' (n=1558) | 2.6 % (41) | 0.7 % (9) | 1.0 % (16 | 1.3 % (20) |
| Prevalence in the total population (n=1691) | 5.9 % ( 55) | 0.7 % (12) | 1.2 % (20) | 1.2 % (20) |

Contact allergy was found in 14 % (19/133) of the workers with eczema, and in 5.5 % (17/309) of the workers without eczema.

Positive tests for chromate were found in 11.1 % (14/126) of the 'cases' and in 2.6 % (8/307) of the 'non-cases'. (The patch test failed in seven cases).

*Comments: This cross-sectional study in construction workers is of high quality. The design is well described, and the sample population is large.*

*The study shows that chromium allergy was the most common type of allergy among the construction workers, a prevalence of 5.9 %. As regards to the prevalence in each occupation, the total occurrence of all types of contact allergy is given and not the exact prevalence of the different types of allergy. The prevalence of allergy is at the same level for the bricklayers/plasterers, technicians/reinforcers and in the occupation of administration/supervision Both bricklayers/plasterers and reinforcers are exposed to wet cement and therefore it can be assumed that most of the chromium sensitised individuals are found among these workers.*

**Irvine C et al.**
**Cement dermatitis in underground workers during construction on the Channel Tunnel,**
**Occup Med. 1994; 44: 17-23**

The material comprised approximately 1138 underground workers, out of approximately 5900 totally employed, mainly self-selected to the company medical centre for skin problems during 1990-92. A subgroup of about 800 grouters with frequent close contact with wet cement was systematically surveilled and invited to the investigation. The attendance rate was 58 % in the grouters. The rates for the occupational groups ranged between 5 and 16 %, except for a small group of tunnel hygiene workers where 62 % participated in the study.

In the total group seen, 332 (29.2 %) had past or present occupational dermatitis and 96 (53.3 % ) of the 180 who were patch tested were chromate sensitised. Two thirds of those allergic to chromate had been exposed to chromate for more than ten years. Almost one in four had less than two years of exposure. Of all grouters seen, 23.8 % had occupational dermatitis currently or previously. Of those patch tested, 65.1 % were sensitised to chromate. Multiple sensitisation was very frequent, and a positive test for cobalt occurred in 65.1 %, for nickel in 19.8 % , for chromate and cobalt simultaneously in 58.1 % , and for Cr/Co/Ni in 12.8 % . Only 26.7 % were non-sensitised to all metals. Sensitisation for epoxy was found in 29.1 % . Results are also presented for fitters, locomotive drivers, miners, electricians, plant operators, and tunnel hygiene workers.

*Comments: Inclusion in the study is based on self-selection to a medial clinic, giving prevalence estimates not representative for the background population (i.e. increasing the estimates). In the subgroup of grouters, for whom the establishing of a representative sample was attempted, only 58 % responded to the invitation. The authors also discuss the problems regarding dermatitis and the fear of job loss, resulting possibly in a selection bias in the opposite direction (i.e. decreasing the estimates). Compared to other estimates from similarly selected groups, the prevalence estimates which are presented are very high, perhaps indicating that patients were tested in periods with active dermatitis, which possibly gave high rates of false positive test results ("angry back"). When the calculation of the prevalences was based on the total number in the different groups and subgroups, it was found that 1.6 % of all underground workers, and 7.0 % of the grouters were sensitised to chromium. It is stated in the discussion that individual protective measures were found to be beneficial. No data are however shown to illustrate this.*

**Goh CL et al.**
**Occupational dermatitis in a prefabrication construction factory.**
**Contact Dermatitis 1986;15:235-240.**

Altogether 272 workers in a construction factory were interviewed, examined and patch tested. Occupational dermatitis was diagnosed in 38 workers (14 %). Twenty-two had irritant dermatitis, 15 had allergic contact dermatitis due to chromate. The overall prevalence of chromate sensitivity was 8.5 % . Eight of 23 had asymptomatic chromium allergy.

*Comments: These prevalence figures numbers are comparable to those reported in other studies in construction workers.*

**Guo YL et al.**
**Dermatoses in cement workers in southern Taiwan.**
**Contact Dermatitis 1999; 40: 1-7.**

The aim of this cross-sectional study was to investigate the prevalence, causal agents, work exposure and risk factors for occupational dermatoses in construction workers in southern Taiwan.

The target population was all 2054 listed members of The Cement Workers' Association in Taiwan City in 1993. A total of 1233 were successfully interviewed by telephone, and of these, 1147 were current construction workers who worked with cement regularly. Fifty percent (573) were randomly selected and invited to a clinical examination, 196 (34.2 %) were examined, and 166 (29.0 %) were finally patch-tested.

There was a good correlation between self-reported and clinically diagnosed dermatoses. Chromate sensitivity was significantly associated with both self-reported and clinically diagnosed hand eczema.

The one-year prevalence of skin problems related to work was 11.2 % in male workers and 3.2 % in female workers, showing an increasing trend with the number of years of exposure. Also the number of hours tiling was significantly associated with the occurrence of work-related skin disease. Chromate sensitivity was found in 16.5 % of the male and 7.2 % of the female workers who had been patch tested. Differences due to gender and task specific differences in exposure and protective measures (gloves) and duration of exposure were seen. There was a strong association between sensitisation to chromium and cobalt with 4 of 21 chromate-sensitised workers also being cobalt-sensitised, while only three of those non-allergic to chromate were cobalt sensitised ($p=0.0003$).

*Comments: This cross-sectional study seems to have a good control on inclusion/exclusion, but a high degree of selection to the clinical examination and patch testing is probable, which may have resulted in elevated estimates of sensitisation rates.*

**Kiec-Swierczynska M et al.**
**Occupational dermatoses and allergy to metals in Polish construction workers manufacturing prefabricated building units.**
**Contact Dermatitis 1990; 23:27-32.**

The prevalence of dermatoses and allergy to chromium, cobalt and nickel was determined in 1782 workers exposed to cement (dry and wet) in Poland. The workers exposed to dry cement were all from one plant, employed on mills and cement kilns, and cement loaders and packers. A total of 905 subjects in five factories were employed in producing concrete from wet cement. A control group consisted of 74 male carpenters and 37 female seamstresses.

The prevalence of dermatitis and oil acne was significantly different between the exposed group and the controls. (The workers were exposed to machine grease and to oils applied to moulds). Of the controls with skin problems, 10 subjects suffered from dermatoses (one woman and nine men).

*The occurrence of skin diseases*:

| | **Exposure** | **Positive Cr-test n (%)** | **Dermatitis n (%)** | **Oil acne n %)** |
|---|---|---|---|---|
| Exposed group (n=1054) | Cement (n=1054) | 250 (23.7) | 297 (28.2) | 130 (12.3) |
| | Dry (n=149) | 39 (26.2) | 42 (28.2) | 0 |
| | In concrete (wet) (n=905) | 211 (23.3) | 255 (28.2) | 130 (14.4) |
| Controls (n=111) | | 11 (12.2% | 10 (9.0) | 0 |

*Comments: The occurrence of chromium allergy is remarkably high in both the cases and the controls. Chromium allergy is not reported as being associated with oils and grease, and can therefore most probably be attributed to the cement. No demographic data was given except for the occupation, and such differences between the cases and the controls cannot be excluded. However, the study discloses a very high prevalence of chromium allergy in workers exposed to cement, both wet and dry.*

**Condé-Salazar L et al.**
**Occupational allergic contact-dermatitis in construction workers.**
**Contact Dermatitis. 1995; 33:226-230.**

The paper reports the patch test results of 449 construction workers (male) who were patients at a dermatological clinic in Madrid in the period 1989-93. Patients having cutaneous lesions or a clinical history of occupational dermatitis were tested. Thus, 90.8 % (408) were tested. Of these, 65.2 % (268/408) were found to have been sensitised in their work. Chromate (42.1 % , 172/408) was the main allergen, followed by cobalt (20.5 %) and nickel(10 %). The mean age of the patients was 45 years (range: 18-65 years). About one in three (31.1 %) were sensitised between 2 and 19 years in their occupation. The author attributes the allergic contact dermatitis to cement.

*Comments: The study discloses a very high occurrence of chromium allergy in construction workers.*

**Høvding G.**
**Cement eczema and chromium allergy: An epidemiologic investigation.**
**Thesis. University of Bergen, Bergen 1970.**

Høvding studied the prevalence of chromium allergy in masons and assistants (hodmen) in the city of Bergen, Norway. The primary aim was to evaluate the association of cement eczema with chromium allergy, but the study also revealed some interesting data on the prevalence of the skin disease. All masons and assistants were member of the local trade unions, and the workers were contacted by use of the member files. The membership lists showed 237 and 157 active masons and hodmen, respectively, totalling 394 workers. Out of these, 221 (93.3 % ) masons and 145 (92.4 % ) assistants were traced and included in the study. A questionnaire survey including 367 workers was carried out in 1962. Ten percent (37/367) reported skin problems.

Altogether, 366 of the workers participated in a field study carried out on the building sites in 1963. This investigation included clinical examination of the skin, patch testing with potassium dichromate, and history recording.

*Outcome of the clinical examination:*

| | **Masons (n=221)** | **Assistants (n =145)** | **Total (n=366)** |
|---|---|---|---|
| Positive patch test n (%) | 25 (11.3 %) | 8 (5.5 %) | 33/ (9.0%) |
| Clear skin | 194 (87.8%) | 127 (87.6%) | 321 (87.7 %) |
| Irritant effects (symptoms interpreted as first stage of dermatitis) | 11 (5.0%) | 13 (8.9%) | 24 (6.6%) |
| Symptoms of eczema | 16 (7.2%) | 5 (3.5 %) | 21 (5.7%) |
| Average age | 41.8 y | 48.6 y | 44.5 y |

A positive reaction to the patch test was twice as frequent in the masons than in the assistants. The author suggests this difference could be due to a more intensive exposure to wet cement in the former.

*The distribution of positive patch test by years in occupation:*

| Years in occupation | 1-10 | 11-20 | 21-30 | 31-40 | 41-50 |
|---|---|---|---|---|---|
| Masons, % | 6.3 (3/48) | 10.7 (8/75) | 8.5 (4/47) | 12.5 (3/24) | 36.8 (7/19) |
| Assistants, % | 5.3 (2/38) | 5.0 (3/60) | 4.2 (1/24) | 6.3 (1/16) | 14.3 (1/7) |
| Total, (%) | 5.8 (5/86) | 8.1 (11/135) | 7.1 (5/71) | 10.0 (4/40) | 30.8 (8/26) |

The average time in the occupation was 21.7 years for masons and 18.1 years for assistants. Twenty-three percent had been in the occupation for less than 10 years, and about 40 % had been for more than 20 years. A statistically significant association was found between the

prevalence of chromium allergy and the duration of exposure. An increase of sensitised individuals with increasing age was also indicated, but could not be further assessed due to the high correlation between age and exposure time.

*Clinical findings related to the patch test with 0.5 % dichromate*.

| | Positive patch test | Negative patch tests | Total |
|---|---|---|---|
| Clear skin | 14 (42.4 %) | 307 (92.2 %) | 321 (88 %) |
| Irritant effects | 2 (6.1 %) | 22 (6,6 %) | 24 (6 %) |
| Symptoms of eczema | 17 (51.5%) | 4 (1.2 %) | 21 (5 %) |
| Total | 33 (100%) | 333 (100 %) | 366 (100 %) |

This table shows that there were 16 cases of latent allergy (i.e. cases without eczema, but with a positive test), of which 14 were completely without skin problems. The table shows a striking difference between the occurrence of eczema in the positive and negative subjects, 51.5 % and 1.2 % respectively. The table further discloses a close association between eczema and dichromate sensitivity, with 80.9 % (17/21) of the eczema in those with a positive test.

All subjects with skin problems in 1963 were contacted 5 years later (1968). They were asked to answer a questionnaire with the focus on prognosis. A clinical examination was carried out on the workers who

- had a positive patch test in 1963 and who had occupational eczema (17 cases).
  Thirteen out of 17 were tested at the re-examination, and all tested positive.

- had a negative patch test in 1963 and who had eczema at the point of examination, (four cases)
  All were still in the occupation at the re-examination. One patch tested positive, one negative and two refused testing.

- had a positive patch test in 1963 and a history of no skin problems (nine cases).
  All had continued in occupation at the re-examination and had been exposed to cement as previously. Eight reported having had no skin problems. Seven tested positive on chromate and two negative (positive in 1963).

- had latent allergy in 1963 and who had history of eczema (seven cases).
  Six were still exposed to cement in the occupation at the re-examination. Five were tested and tested positive.

- had a negative patch test in 1963 and who reported eruptions during 1963-68 (four cases).
  Three tested negative and one positive at the re-examination. (One having lichen planus was not tested).

Eight masons and 15 assistants had changed occupation since 1963 and 35 had died/retired.

During the time period 1963-1968, the cumulative incidence of dichromate sensitive cases of cement eczema was found to be 7.3 % (27/366), and of dichromate negative to be 1.3 % (5/366). Only 6 % had changed their work. The study suggests a favourable prognosis with

regard to the capacity for work, but the medical prognosis did not seem as favourable. It is worth noting that most workers expressed strong reservations with regard to the benefit of wearing protecting gloves during work, and almost all of them only wore gloves occasionally.

*Comments: This study is of high quality, and is considered as an early pioneer study. Various factors related to wet cement work and skin problems are discussed. A high prevalence of chromium allergy in masons and assistants was found. It was highest in the masons. A statistically significant association was found between the prevalence of chromium allergy and exposure time, indicating an exposure-response relationship. A high proportion of the subjects with dermatitis ("symptoms of eczema") were dichromate sensitive (81%). Only 1% of those with a negative patch test had dermatitis, and 6.6% had irritating effects (first stage dermatitis). The study indicates that the disease may take many years to develop. Høvding found no significant change of occupation due to the chromium allergy. This study gives a relatively strong support to the hypothesis of a relationship between Cr(VI) in wet cement and allergic dermatitis in construction workers.*

**Perone VB et al.**
**The Chromium, Cobalt, and Nickel Contents of American Cement and their relationship to Cement Dermatitis.**
**Am Ind Hyg Assoc J 1974; 35: 301-306.**

The paper describes analyses of chromium, cobalt, and nickel in cements, and their etiological roles in causing the dermatitis which was observed in cement workers in USA.

Medical histories and patch testing were undertaken in 95 workers who regularly handled cement. They were interviewed and examined for past history of skin diseases and present evidence of dermatitis. All were patch-tested for potassium dichromate, 0.25 % . Readings were made once only at 30 minutes after the removal of patch

Chromium was measured in 42 cement samples, both in the raw cement, and in solutions. The total chromium in the solutions ranged from < 0.5 mg/kg (5 samples) to 10.1 mg/kg; the mean was 3.7 mg/kg (exclusive the 5 samples of less than 0.5 mg/kg). Only 18 of the 42 samples contained measurable quantities (0.1 mg/kg or higher) of hexavalent chromium; the highest concentration was 5.4 mg/kg. The range of chromium in the raw cements was 5.0 - 124 mg/kg with a mean of 29.5 mg/kg.

The 95 workers were members of the following crafts: cement masons, plasterers, hod carriers, bricklayers and labourers. More than 50 % of the workers had worked with cement for 15 years or more.

Twenty-five workers had a history of cement dermatitis or cement burns. At the time of patch-testing, one third of the workers had evidence of mild to moderate dermatitis.The patch tests were negative except for one with a '1+' reaction. The authors concluded: "The patch-test shows a very low degree of latent contact sensitisation".

*Comments: The prevalence of chromium allergy is remarkably low in this study compared to other studies, and so is the content of chromium in the cement. Provided the workers have been exposed to low chromium cement all the time, this study shows a low prevalence of chromium allergy in workers exposed to cement of low chromium content.*

## II . STUDIES RELATED TO DIFFERENT LEVELS OF CR(VI) IN CEMENT

### *II a) INVESTIGATIONS BASED ON PATIENTS FROM DERMATOLOGICAL CLINICS*

**Johansen JD et al.**
**Changes in the pattern of sensitisation to common contact allergens in Denmark between 1985-86 and 1997-98, with a special view to the effect of preventive strategies.**
**British Journal of Dermatology 2000; 142: 490-495.**

This is a prevalence study where patch test results from members of the Danish Contact Dermatitis Group were collected. Consecutive eczema patients over a 6-month period in 1985-86 and 1997-98 at the same clinics were tested by identical methods and with patch-test allergens. The significant changes were:

1) A reduction in nickel allergy in children 0-18 years from 24.6 % to 9.2 %
2) Fragrance allergy increased from 4.1 % to 9.9 %
3) Allergy to potassium dichromate decreased from 3.0 % to 1.2 % .

*Comments:. The observed decreased "prevalence" of chromium allergy in consecutive eczema patients from 1985-86 to 1997-98 in Denmark is statistically significant. A lower rate of sensitisation in the years after the reduction of Cr(VI) in the Danish cement may be one explanation for this reduction. However, changes in exposure and occupation in the members of the source population are not known.*

**Olsavszky R et al.**
**Contact sensitivity to chromate: comparison at a London contact dermatitis clinic over a 10-year period, Contact Dermatitis 1998; 38:329-331.**

The aim of the study was to examine the role of the reduction of chromate sensitisation through the addition of ferrous sulphate to cement by comparing the sensitisation rates of patients attending a dermatitis clinic between 1982 and 1992. Ferrous sulphate has not been added to cement in the UK. All patch tested patients attending the clinic were tested for chromate sensitisation.

Prevalences were equal in the two periods, with 4.0 % and 4.3 % in men and 1.6 % and 2.0 % in women in the former and latter period, respectively. The gender distribution was equal, but fewer older workers were sensitised in the last period (suggested to be due to earlier retirement in this period). The source of sensitisation was not evident in this large proportion of the chromate-allergic persons. Only 12 and 13 % were workers in the building trades in the respective periods. Cobalt was the most common co-sensitiser. Of those with Cr allergy, 41 % and 34 % had Co allergy in the respective periods, and more than 20 % had nickel allergy.

No difference in chromate sensitisation rates was observed between the two periods, neither for men nor for women. The constant gender ratio was interpreted as indicating that there had been no significant change in cement sensitisation during the ten years. Neither was there any

difference in the prevalence of cobalt co-sensitisation, which is seen as an indicator of cement exposure.

*Comments: The study is based on the self-selection of patients from the general population to a dermatitis clinic. Population prevalence rates can therefore not be calculated. The number of patients patch tested is not given, but can be calculated from the results (In 1982-3 N=3830, in 1992-3 N=3178). The results indicate a stable risk of chromate sensitisation at the general population level, but is should be noted that only a small proportion of the samples are from workers in the building industry. The possible changes in the catchment area or industry/employment are not discussed, but may have biased the results.*

**Zachariae COC et al.**
**Chromium allergy in consecutive patients in a country where ferrous sulphate has been added to cement since 1981.**
**Contact Dermatitis 1996; 35: 83-85.**

The aim of the study was to establish the likely cause of chromate sensitivity in consecutive eczema patients at a dermatology clinic in an area where the water-soluble chromium content in cement had been significantly reduced. The material comprised 4511 patients seen with eczema at the clinic in Denmark between January 1989 and December 1994. All patients were patch tested.

Altogether 79 patients were sensitised to chromium, i.e. 1.5 %. Based on the patient's history the source of sensitisation was identified. The source was cement for 10 patients, leather for 19, chromium from other sources for 7, and in 45 cases the source remained unknown. Of the chromium sensitised patients, 6 % had hand eczema, while 41 % had foot eczema. Seven of the 10 with allergic contact dermatitis from cement had been sensitised before 1981 (five in full time exposed occupations – bricklayer or cement worker), and one by occupational contact since 1981 (concrete renovation). Two out of three cases who were sensitised after 1981 occurred in leisure-time bricklayers.

Information is given in the discussion section on the ~3000 workers constructing the combined bridge/tunnel over the Great Belt straits in Denmark, after which only four cases of dermatological disease was reported in the work period 1992-93. Two of these had contact dermatitis associated with hydraulic oil and machine oil, and none were related to chromium.

*Comments: This study reports that only 10 out of 4511 patients seen at the clinic had cement-related sensitisation to chromium, of whom only three were sensitised after 1981. Although it is not possible to evaluate the population prevalence from the clinical material like the present, it should be noted that the finding of three new cases of allergic dermatitis is remarkably low. Compared to corresponding figures in other clinical materials, it seems unlikely that this low figure is due to selection exclusively.*

## *II b) Investigations based on workplace populations*

**Avnstorp C,**

**a) Prevalence of cement eczema in Denmark before and since the addition of ferrous sulphate to Danish cement.**
**Acta Derm Venereol 1989; 69: 151-155**

**b) Risk factors for cement eczema.**
**Contact Dermatitis 1991; 25: 81-88**

**c) Follow-up of workers from the prefabricated concrete industry after the addition of ferrous sulphate to Danish cement.**
**Contact Dermatitis 1989; 20: 365-371**

Avnstorp has published a series of papers regarding the risk of chromate dermatitis and hand eczema before and after the addition of ferrous sulphate to cement in Denmark in 1981.

In paper a), workers from five factories producing prefabricated concrete building components were included. Workers were patch tested for chromate, cobalt and nickel sensitisation, subjected to a clinical examination, and their occupational and medical histories were recorded. In 1981, a total of 190 of 196 workers with daily exposure to wet cement were investigated, and 227 of 229 exposed workers were investigated in 1987. Fifty-five of the group tested in 1987, had been exposed to wet cement in other companies before 1981, and 159 had been exposed after 1981 only. No comment is made on the 15 workers who are lacking. One hundred and fifty-eight unexposed workers of 172 workers investigated in 1981 served as the control group.

The cross-sectional prevalences and relative risks at the two points in time were compared. In 1981 the prevalence of hand eczema was 11.7 % , and in 1987 it was 4.4 % (p-value 0.008). The respective prevalences for chromium allergy were 10.5 % and 2.6 % (p-value 0.002). These differences did not change essentially when restricting the analyses to those workers who often used gloves. In 1981, 14 % of the workers who often used gloves were sensitised to chromate, while only 3.5 % of those who often used gloves tested positive to chromate (p=0.006) in 1987 (Avnstorp 1992). The distributions of age and duration of exposure were different in the two groups, with the 1981 group being older and with a longer exposure time. The author states that when matching "with respect to an exposure time of 7 years", the differences were still significant for hand eczema (8/77 *vs.* 6/181, p-value 0.022), but only borderline significant for chromium allergy (4/75 *vs.* 2/172, p-value 0.05).

In a final analysis, the risk of chromate sensitisation was compared according to the level of exposure in four groups: the unexposed in 1981, those with low exposure in 1987, those who had had both high and low exposure in 1987, and those highly exposed in 1981. The following results were seen:

*The risk of chromate sensitisation compared between different groups.*

| | RR | 95% CI | Comment |
|---|---|---|---|
| Control group, tested 1981, (the reference group) | 1.00 | | 2/158 sensitised |
| Tested 1987, exposed to ≤2 ppm, ≤6 years | 1.00 | | 2/159 sensitised |
| Tested 1987, exposed to ≤10 ppm and ≤2 ppm, 7-31 years | 5.7 | 1.3-25.1 | 4/55 sensitised |
| Tested 1981, exposed to ≤10 ppm, 1-46 years | 8.3 | 2.6-26.9 | 20/190 sensitised |

In paper b) the possibility that changes in the work process or the individual use of protective equipment have caused the observed reduction in chromate dermatitis is discussed. Specifically, three topics were analysed: 1) The prevalence of hand eczema and chromate sensitivity in two groups with different levels of chromate exposure. 2) The influence of chromate sensitivity on the severity of skin cement eczema. 3) The influence of wet cement on irritative eczema and the effectiveness of individual preventive measures.

The material is essentially the same at that analysed in previous publications (190 of 196 workers tested in 1981, 227 of 229 tested in 1987, and 67 tested both in 1981 and 1987 and found non-sensitised in both years).

The prevalence of objective cement eczema in 1981 was higher than in 1987 (47/190 vs. 28/227, $p=0.002$). The prevalence of allergic cement eczema was higher in 1981 than in 1987 (17/47 vs. 3/28, $p<0.001$), while the prevalence of irritant cement eczema did not significantly change from 1981 to 1987 (30/47 vs. 25/28). When non-sensitised workers in the two groups (170 in 1981 and 221 in 1987) were divided into four groups with respect to the severity of skin changes, no significant differences were found. When the sensitised workers were compared with the non-sensitised, a significant difference in the severity of skin affection was found ($p<0.0001$). The group of 67 non-sensitised workers assessed in 1981 and 1987 were studied in order to analyse the impact of wet cement on irritative eczema. Eleven (16.4 % ) reported cement eczema during the follow-up period. Neither reported risk factors (degree of concrete pouring, levelling, finishing, repairing, avoiding contact with wet cement, use of gloves, use of creams, handwashing) nor the duration of exposure did significantly predict the development of skin symptoms. However, exposure to wet cement predicted cement eczema with borderline significance ($p=0.06$). No additive effects of the individual preventive measures were found.

In paper c) an analysis of medical status and employment status in 1987 was made based on the 196 exposed workers available in one of the five participating companies in 1981. The study showed that those sensitised in 1981 had chronic hand eczema more often and had taken an early retirement more often in 1987. The study indicates a more severe prognosis of allergic chromate eczema than of irritant eczema, where the allergic eczema occurred more frequently and more often needed topical steroid treatment.

*Comments: This group of studies is among the few which have partly been able to investigate the same workplace population at two points in time, with different exposure levels. The main problem of these studies is the possible influence of age and/or duration of exposure on the risk of sensitisation and hand eczema. It is not quite clear how the duration of exposure was controlled for, and the results after such adjustment were of borderline significance or non-*

*significant, possibly because the number of workers available for this analysis was not sufficient. However, in a later analysis of the same material, the duration of exposure to wet cement was categorised into five strata, but did not significantly predict objective cement eczema or chromate sensitivity (Avnstorp 1991).*

*Also, the author makes a non-documented statement that no other changes in work process and occupational hygiene took place. In a later publication, not presented in the present report (Avnstorp, 1992) it is, however, stated that, mechanisation of the work processes was performed in Denmark during the late 1950's and early 1960's, and that further modifications took place up to the early 1970's. No essential changes have occurred since then nor during the study period. Due to the short interval between the two study periods this may well be correct.*

*The inclusion rate is very high, and a questionnaire answered by those who were not clinically investigated showed no differences in the reported exposure or skin complaints. The problem of possible selection bias, present in all cross-sectional studies, should however be considered. This is also discussed more thoroughly by the author in another publication (Avnstorp, 1992) where it is found that the most probable bias, a selective loss of sensitised workers before the 1981 study, would actually reduce the differences between the compared groups.*

*Altogether, the Avstorp's studies are definitely among the better-performed studies, indicating a marked effect of the reduction of water-soluble chromate on the risk of sensitisation and dermatitis.*

**Reifenstein H et al.**
**Zur Häufigkeit des Zementekzems bei der Verarbeitung chromatarmer Zemente**
**Z Gesamte Hyg 1986; 32[9]: 559-560.**

The occurrence of cement eczema was compared in workers at12 concrete plants which used cement with different concentrations of chromium(VI). The number of notified cases of occupational chromium allergy, the number of exposed workers and exposure time from each plant was obtained for a time period of up to 15 years. The average number of chromium allergies per year and per exposed worker was calculated (transformed to incidence per 1000 person-years in the table below).

Depending on the manufacture of the cement, the concentrations of chromium(VI) was 24 mg/kg ('high') and < 0.4 ('low') mg/kg. Some plants used the cement of low chromium content, some used cement of 'high' content, and some plants used both types.

*Occurrence of allergic cement eczema in plants using different types of cements*

| Chromium in cement | Exposed workers (n) | Exposure time (year) | Cases of cement eczema (n) | 'Incidence' (*) | Total cement eczema |
|---|---|---|---|---|---|
| | 50 | 15 | 0 | 0 | |
| Low | 32 | 11 | 0 | 0 | 3/640 |
| (<0.4 mg/kg) | 38 | 12 | 0 | 0 | (0.5%) |
| (4 plants) | 520 | 8 | 3 | 2.9 | |
| | 300 | 8 | 3 | 1.3 | |
| Low and high | 18 | 11 | 4 | 20 | 13/398 |
| (3 plants) | 80 | 4 | 6 | 18 | (3.3%) |
| | 250 | 6 | 64 | 42 | |
| High | 80 | 6 | 10 | 21 | |
| (12-24 mg/kg) | 90 | 6 | 5 | 9.3 | 85/765 |
| (5 plants) | 45 | 6 | 4 | 15 | (11.1%) |
| | 300 | 2 | 2 | 3.3 | |

*) 'Incidence' - here defined as new cases per 1000 person-years, based on a stable number of exposed workers.

Based on the calculations of the quotients, the 'exposure time' (in the table) seems to be the duration of observation, and not the actual exposure time of the workers. Thus, workers in the 'low chromate' cement plants have been observed for 8-15 years, and workers in the 'high chromate' plants for 2-6 years.

A statistically significant association was found between the Cr(VI) content and the number of sensitised workers. The authors concluded: "The risk of an occupational disease is definitely lower in the concrete plants processing low-chromate cements".

*Comments: The study is poorly described. The work processes are not well defined. Nor is the test used to identify sensitised individuals. Furthermore, if, for instance, different surveillance routines were being practised, say less attention was given to chromium allergy at the 'low-chromate' cement plants owing to the anticipation of low risk, this may have introduced a bias. However, if there were variations between the plants, variations not only between plants using different types of cement, but also between the plants using the same type, would have been expected. However, the results within both the 'low-chromate' and 'high-chromate' cement plants seem to be fairly consistent.*

*The actual exposure time of the workers is not known. Long observation times in the 'low chromate' plants, 8-15 years, show that these plants have been active for several years and it can be assumed that workers may have been exposed to cement for a fairly long time. Thus, the observation time in the 'high chromate' cement plants, 2-6 years, is less than half that of the 'low-chromate' plants. If this suggests that these plants have been active for only a shorter time period, the workers may have had a shorter exposure time. If so, the number of sensitised workers is underestimated compared to the 'low chromate' plants, and the contrast between the two types of plants is actually greater than observed.*

**Roto P et al.**
**Addition of ferrous sulphate in cement and risk of chromium dermatitis among construction workers. Contact Dermatitis 1996; 34: 43-50.**

The aim of this study from Finland was to determine whether the reduction of water-soluble chromium in cement by the addition of ferrous sulphate reduced the risk of chromium-induced dermatitis in construction and prefabrication workers. The prevalence of chromium dermatitis was investigated in a representative sample of exposed workers in 1986/87, the year before the reduction of water-soluble chromium in cement by the addition of ferrous sulphate was introduced in Finland. In addition, the occurrence of allergic chromate dermatitis in construction workers reported to the Finnish Occupational Disease Registry for each year from 1978 to 1991 was investigated, and the two periods 1978-87 and 1988-1991 were compared.

A total of 1478 house construction workers and concrete element prefabrication workers were included. They were clinically investigated and interviewed on their history of work and skin disease. The response rate in the construction workers was 92 % (836/913), and 91 % 642/707) in the prefabrication workers.

The prevalence of hand dermatitis (irritant and allergic together) was 6.8 % in the construction workers and 8.9 % in the prefabrication workers. The prevalence of chromium allergy which was confirmed by patch testing in workers with dermatitis was 4 % (4/105). Of 16 previously established cases of allergy, 12 were re-tested, and 5 were found to be positive, giving a total prevalence of 7.7 % (9/117).

*Dermatitis reported to the Finnish Occupational Disease Registry*

| | **Number of cases of chromium allergy** | | **Number of cases of irritant dermatitis** | |
|---|---|---|---|---|
| **Time period** | Total | Average per year | Total | Average per year |
| 1978-1986 | 210 | 23 | 104 | 11.6 |
| 1987[1] | 21 | 21 | 7 | 7 |
| 1988-1992 | 42 | 8.4 | 63 | 12.6 |

1*) The year of implementing the use of ferrous sulphate*

Multivariate analysis of the data from the disease registry showed a significantly decreasing risk of chromium contact dermatitis by period of diagnosis with an odds ratio (OR) of 0.4 (95 % confidence interval (CI) 0.2-0-7). When the duration of exposure was added to the model, the decrease in risk associated with the period of exposure did not essentially change (OR 0.3 (95 % CI 0.1-0.6). Age was not significantly associated with chromate dermatitis. An enquiry by the authors revealed that the number of workers exposed to cement in the construction industry remained practically unchanged and no change in the reporting system occurred throughout the study period. Possible sources of bias which are mentioned are changes in diagnostic procedures, with a higher risk of false positive tests in early years, and an increasing number of occupational health physicists, possibly increasing the rate of reporting.

*<u>Comments:</u> The problem of allergic contact dermatitis in Finland seemed to be relatively small already before the addition of ferrous sulphate to cement, as a very small proportion of patients with dermatitis had a positive test. Still, the analyses of the disease registry indicated that allergic contact dermatitis in construction workers in the second period was reduced to less than one third of the initial level, while no such decrease was seen for irritant dermatitis. The study is partly based on a national notification system with the aforementioned inherent limitations.*

# DISCUSSION

Available epidemiological studies on the occurrence of allergic dermatitis related to exposure to Cr(VI) in wet cement have been reviewed in this report. Of the about 130 papers originally considered, 24 were selected for separate evaluation. Thus, although the majority of the papers provided relevant background information, they were not regarded as sufficiently informative for inclusion in the studies which were to be subjected to in-depth review. The selected studies were of varying types of design. The majority was cross-sectional studies, either based on clinical materials (Condesalazar et al.,1995; Johansen et al., 2000; Freeman, 1986; Fregert, 1975; Geier and Schnuch, 1989; Halbert et al., 1992; Olsavszky, 1998; Peltonen, 1983; Zachariae, 1996) or populations of workers (Coenraads, 1984; Irvine, 1994; Goh et al., 1986; Guo, 1999; Kiec-Swierczynska, 1990; Høvding, 1970; Perone, 1974; Avnstorp, 1989a, 1989b, 1991; Reifenstein, 1986; Roto et al., 1996). Two of the studies were of a more basic, experimental test design (Basketter et al., 2001; Bruze & Fregert, 1990), and were included for their high relevance to the topic in question. Five studies used repeated cross-sectional measurements and evaluations (Avnstorp, 1989a, 1989b, 1991; Reifenstein, 1986; Roto et al., 1996). The studies by Avnstorp and Høvding (1970) were the only studies attempting to follow the same population over time.

All the selected studies have their weaknesses, as described previously. However, several studies, regardless of design and geographical area, report a higher occurrence of chromium allergy in construction workers exposed to cement than in other occupations (Halbert et al, Coenraads et al., Fregert, Peltonen et al., Geier et al.), and in workers exposed to cements with a high content of Cr(VI) compared to those who were exposed to a low concentration (Avstorp, Reifenstein, Perone, Johansen et al., Zachariae et al.). Thus, the question is whether these observed associations are causal or only spurious associations due to systematic errors.

With regard to the validity, and thus the interpretation of the available studies, some common main aspects should be discussed, related to exposure characterisation, the definition of the outcome variable, and the overall study design.

Exposure characterisation

The risk of allergy is dependent on both the concentration of Cr(VI) in the cement and the duration of exposure to the cement. Therefore both these factors are used to characterise the exposure load. In the present studies, cement is considered to be of two types as regard to the concentration of hexavalent chromium: cements with a concentration of less than a couple of ppm are often referred to as ‘low chromate’ cement. Except for one study (Bruze et al.1990), the exact content of Cr(VI) has not been measured with respect to the study in question. The chromium content has been assumed to be the same as that which is generally found in the cements of the country of concern. However, analyses have shown that the content may vary and may not always be ‘low’ or ‘high’ as assumed from general considerations. Furthermore, the workers have been exposed for many years and the chromium content may have been different in different time periods. This gives rise to an uncertainty in the presumed exposure contrast. However, to the extent that the main problem is less contrast between the exposed groups (e.g. if the low-grade cement contain a higher concentration of Cr(VI) than

anticipated), this would have led to reduced outcome differences, and cannot explain the differences observed.

Furthermore, in all the studies the 'exposure time' which is used as a surrogate for 'dose' has been expressed in the number of years the workers have been employed in the construction industry. The operational term 'time employed in the construction industry' is a very crude proxy for the duration of skin contact with wet cement, which perhaps is what we would prefer to measure. It is therefore difficult to use time in construction work as an indicator of 'dose', as some groups may have had intense contact with wet cement, while other construction workers may have had a very limited direct contact with cement. However, to the extent that such a misclassification of exposure has occurred and is expected to be non-differential, it cannot explain the observed outcome differences between groups.

Another challenge is that the individual worker's direct skin exposure to wet cement may have been reduced during the last decades, owing to automatisation, more large scale use, more use of technical devices, improved preventive routines and also less construction work performed.. Thus, it is difficult to compare prevalence estimates which originated in different time periods, let us say, before and after an intervention (e.g. lowering of the Cr(VI) content in the cement), without establishing a proper reference group. However, the observation of a reduced prevalence of allergic dermatitis, while the prevalence of irritating dermatitis has remained constant (Avnstorp, 1991; Roto et al.,1996), supports the hypothesis of a causal association between lowered Cr(VI) content in the cement and allergic dermatitis.

Definition of the outcome variable

Contact dermatitis is normally located only on the exposed skin areas. There is no valid practical test procedure for diagnosing irritant contact dermatitis. This diagnosis is based upon the patients' information on exposure to skin irritants which are known to cause eczema and negative allergy tests for contact allergy. The diagnosis 'allergic contact dermatitis' is given when exposure to allergens is followed by eczema and confirmed by a positive allergy test (patch test).

When construction workers are exposed to wet cement, there is a concomitant exposure both to irritants and allergens. Workers who are sensitised to chromium (positive patch test) and who show signs of contact eczema are diagnosed as having allergic contact dermatitis to chromium. However, this group of patients may also include a number of persons with irritant contact dermatitis – for instance previously sensitised workers now exposed to wet cement without Cr(VI). The best method for evaluating the correlation and magnitude of these two types of contact dermatitis would be a prospective study of the incidence of sensitised workers (both workers with and without eczema). No such studies have been undertaken. The sample size of such a study may be a problem, however, taken into consideration that the major proportion (70-80%) of dermatitis among cement workers are of the irritant type. Thus, a fairly large population is required to be able to demonstrate a possible reduction in allergic dermatitis related to reduced Cr(VI) content in the cement.

Thus, the definition of disease status related to (allergic) dermatitis is difficult to study epidemiologically, which is illustrated in the present studies. However, the extent to which the lack of a precise definition of the outcome variable is considered to be non-differential (i.e. affects the exposed and the non-exposed group in a similar way), will not bias the measure of association (risk ratio, prevalence ratio etc

Overall study design

Many of the studies are of limited value due to a too poor description of the design. All available studies were cross-sectional, and thus vulnerable to selection bias. This comprises both 'selection in', of subjects into the study population (hospital patients, group of construction workers), and 'selection out', e.g. subjects who leave work due to health problems (here: dermatitis). Many of the reviewed studies are based on volunteers. Such studies are obviously subject to bias by self-selection. Persons who volunteer for a study are likely to differ from the general population; they may either be healthier or sicker, depending on their expectations. Individuals who (voluntarily) seek medical care represent a form of volunteers. Thus studies on OCD and ACD which are based on patient files from hospitals or physicians are likely to be biased. In addition, such data is seldom related to the size and type of the population from which they are selected. When no data on the sizes of the populations are given, the prevalence of chromium allergy cannot be calculated. In particular, there is a lack of relevant exposure contrasts, i.e. comparisons between cement-exposed workers and a properly defined unexposed group. The frequency of chromium allergy in different occupations is mutually ranked in some of the studies, but a proper reference group has only been established in few of the studies.

Evaluation of causality

After having considered chance and bias as possible explanations for an observed association in epidemiological studies, the criteria for causal associations, mentioned on page 13 in the section of "Epidemiological aspects", are often considered. For the present evaluation, the question of *biological plausibility* is of particular importance, i.e. how plausible is it that Cr(VI) in wet cement causes allergic dermatitis in construction workers, and how plausible is it that a reduction of Cr(VI) in wet cement would reduce the occurrence of allergic dermatitis in construction workers? As a medical condition, allergy and sensitisation to allergens is well described and well understood. Chromium is one of a series of well-known allergens. The reduction of allergenic exposure is a well-known strategy for the reduction of allergic reactions. Thus, the epidemiologically observed associations between Cr(VI) content in cement and allergic dermatitis are actually biologically very plausible.

Regarding the *consistency* of the epidemiological evidence, it should be noted that all studies indicate results in the same direction: a high prevalence of chromium allergy is found in construction workers (Goh et al., 1986; Kiec-Swierczynska, 1990; Guo et al., 1999; Høvding, 1970; Geier et al., 1995) as compared to results from dermatological clinics (Johansen et al., 2000; Olsavszky et al., 1998; Zachariae et al., 1990). Also, the prevalence in construction workers has been found to be higher than among other occupational groups in studies based on general population samples (Fregert, 1975; Peltonen and Fräki, 1983; Geier et al., 1995).

One of the stronger indications of a causal relationship is found when the withdrawal of an exposure results in a decrease in the incidence of a disease. This is seldom possible to investigate directly, but it has been tried in some of the studies included in the present report. In a study from Denmark (Avnstorp,1989a) the risk of chromate sensitisation in those exposed to high levels of chromate (10 mg/kg) was found to be eight times higher than in those who were never exposed. The group of workers exposed to low levels of chromate (<2 ppm) had the same risk as those who were never exposed. The study by Reifenstein et al.(1986) also compared the prevalence of chromium allergy between plants using different

types of cement. Reifenstein found the lowest prevalence in the plants with cements of low chromium content. However, it is difficult to assess these results because the study is poorly described. But with all reservations on the possible bias that may have been inherent in the study, the results do indicate a reduced occurrence of allergic dermatitis associated with lowered concentration of Cr(VI) in the cement. The study by Roto et al. (1996) also provides some support to this association. This also seems to be in accordance with the conclusions in a recent Nordic criteria document on chromium (National Institute for Working Life, 2000).

Another important criteria of causality in epidemiological studies is the demonstration of an *exposure (dose)-response relationship* (the number with an observed effect increases with increasing exposure ('dose') (Hill, 1965).

There is relatively sparse epidemiological documentation on dose-response relationships related to Cr(VI) content in cement and the risk of allergic dermatitis. With regard to duration of exposure, Høvding demonstrated a significant increase in allergic dermatitis with duration of exposure. In addition , the lack of such a relationship in many of the studies may be due to the 'selection out' of unhealthy workers from the occupation.

With regard to the 'dose' defined in terms of the concentration of Cr(VI), Perone et al., (1974) demonstrated very low degree of latent contact sensitisation in workers exposed to cement of very low chromium content. Furthermore, the observation by Bruze and Fregert in 1990 that 8 chromate sensitive subjects reacted to cement without iron sulphate, while none reacted to cement containing ferrous sulphate, also gives strong support to the hypothesis of a causal relationship between the occurrence of allergic dermatitis and the reduction of Cr(VI) in cement. More papers throw light on a threshold for allergic reactivity. Basketter et al. (2001) found a threshold for allergic reactivity to chromium of 10 mg/kg on normal skin and a threshold closer to 1 mg/kg in the presence of an irritant. In cases of outbreaks of chromium allergy reported by Bruze et al. (1990), elicitation was recognised at 3 mg/kg. Stern et al. (1993) estimated an effective threshold of about 10 mg/kg for the elicitation of allergic contact dermatitis in sensitised populations. Furthermore, based on literature on cement dermatitis, they found a threshold concentration of 10 mg/kg Cr(VI)) in the material. Damaged skin is more penetrable and vulnerable to hazardous substances than normal skin and a lowered threshold is to be expected. Thus, an effective threshold of about 1- 4 mg/kg chromium in construction workers who may often suffer from cement eczema, seems to be likely according to the reported studies.

Independent of the available epidemiological documentation, it is biologically highly plausible that exposure to a high concentration of a potent allergen (Cr(VI) will lead to a higher risk of allergic dermatitis than exposure to a low concentration of the same allergen. For dermatologists, this relationship seems to have been so obvious that further epidemiological documentation may not have been considered necessary.

In spite of this, in retrospect, it seems rather surprising that the opportunity to systematically follow a defined, suitably exposed cohort with regular surveys and identification of incident cases, before and after a reduction of Cr(VI) content in the cement, compared with a corresponding cohort where the Cr(VI) content was stable, was not properly utilised. We recommend that such a study should be performed in the future.

# CONCLUSION

Owing to the lack of a proper exposure characterisation, problems with identifying homogeneously diagnosed, unselected cases and a lack of prospective follow up of populations with relevant exposure contrasts, all the epidemiological studies reviewed in this report have more or less serious limitations. The papers can therefore only contribute to a limited degree to the documentation of causality between the occurrence of allergic dermatitis in construction workers and the content of Cr(VI) in wet cement. Furthermore, only limited epidemiological documentation on dose-response relationships related to the Cr(VI) content in cement and the risk of allergic dermatitis has been provided. However, the available documentation seems rather consistent with regard to reporting fairly strong associations between the Cr(VI) content in cement and the occurrence of allergic dermatitis. It seems unlikely that all these associations reported in the reviewed papers are due to systematic errors only.

One of the recommended criteria for assessing causal relationships in epidemiological studies (Bradford Hill, 1964) is biological plausibility. Independent of the available epidemiological documentation, it is biologically highly plausible that exposure to a high concentration of a potent allergen (Cr(VI)) will lead to a higher risk of allergic dermatitis than exposure to a low concentration of the same allergen.

Related to the two specific questions given in the aims, we will conclude with the following:

1. The available epidemiological literature provides documentation that supports the hypothesis of a relationship between Cr(VI) in wet cement and allergic dermatitis in construction workers.

2. The available epidemiological literature is not sufficient to conclude that there is a causal association between the reduction of Cr(VI) in cement and the reduced occurrence of allergic dermatitis. However, although the documentation is relatively sparse, the available documentation indicates such a relationship.

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# APPENDIX 1.

## List of literature received from CEMBUREAU.