



VIDENCENTER *for* ALLERGI

2001-2011 (10 years)



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1. Background and frame

The National Allergy Research Centre was established in 2001 by The National Environmental Protection Agency, Ministry of Environment, as part of a strategy to reduce adverse effects from chemicals.

The background for establishing a Centre for especially contact allergy and associated diseases was that it is a frequent and well documented adverse effect of chemicals affecting at average 20% of the European population carrying consequences as chronic eczema, decreased quality of life and may affect the work ability of the individual. The diseases associated with contact allergy may have severe social and economical consequences for the individual and society, but may also be prevented.

The main task of the Centre was prevention of allergy from chemical substances- especially in consumer products, which is a frequent cause of contact allergy. Occupational allergy/eczema was not directly included as occupational exposures are under the framework of another Ministry.

Initially the role of chemicals in producing allergy-like airway symptoms was part of the mandate of the National Allergy Research Centre. In 2006 an independent centre addressing chemical sensitivities by inhalation was established. Since then The National Allergy Research Centre has focused on skin/contact allergy.

The grant for creation of the National Allergy Research Centre was in public tender and was awarded The Department of Dermatology, Gentofte Hospital in collaboration with The Department of Dermatology, Odense University Hospital.

The Centre was officially opened 18.October 2001.

1.1 Concept

The Centre was the first of its kind in Denmark and is established in close relation to the units in the hospital sector, which treats patients with allergic diseases. Patients with allergic diseases caused by chemicals are the point of departure for the research and work of the Centre. It is the strategy of the Centre to determine the causes of allergy to chemicals, i.e. substances, products, exposure scenarios, concentrations and to establish limits for exposure to contact allergens, which are safe for the majority of allergic individuals. Investigations in the general population, register-based research, general exposure analysis and basic research contribute to the over all aim of prevention of contact allergy. Prevention means both to effectively prevent new cases of allergy (primary prevention) and to reduce the burden of disease among allergic individuals (secondary/tertiary prevention). In this context both early detection of disease, improved diagnosis, identification of risk groups and improved information regarding contact allergy and associated disease are important.

The Centre works by project-based knowledge building in an interdisciplinary environment with broad national and international networking to other researcher and institutions.

Other centres have subsequently been formed based on a similar concept.

1.2 Organisation

The National Allergy Research Centre was formed by The Department of Dermatology and The Department of Lung and Respiratory Medicine at Gentofte Hospital, University of Copenhagen together with Department of Dermatology, Odense University Hospital. The Centre was/is situated at Gentofte Hospital, where it is an integrated part of the Department of Dermato-allergology. The department was until March 2011 under the leadership of Professor Torkil Menné, who has been followed by Dr Claus Zachariae.

Since 2006 the Centre has been run only by the departments of dermatology, as an independent Centre addressing inhalation of chemicals and sensitivities was formed by a former researcher from the National Allergy Research Centre (Dr Jesper Elberling).

The organisation of the Centre aims at creating optimal research conditions and flow of knowledge so that shortest possible time passes from new knowledge arises until the results are passed on to patients and implemented in the clinical setting as well as passed on to the authorities and/or industry, who is going to transform the research results to practical measures, as regulations or recommendations.

Staff

The National Allergy Research Centre is run by a director of research (Professor Jeanne Duus Johansen) and an academic staff, which primarily has consisted of PhD.-students with different academic backgrounds as medical doctors, biologists, pharmacists, ingenious, health pedagogies etc. In the recent years former ph.d.students have become senior researchers.

In the period 2001 -2011 (10 years) 22 researchers have been/are employed as PhD-students resulting in 14 finished PhD.-Theses and 8 ongoing. Two of these PhD.-studies have been performed at the Department of Dermatology, Odense University Hospital.

The Centre has been involved in additional 4 PhD.-studies primarily performed in other institutions (see appendix 1). Currently 5 former ph.d.students work full or part time as senior-researcher at the Centre. They perform research themselves and supervise PhD.-students. Several medical students are also involved in research.

A full time computer scientist (Søren Gade) takes care of the databases of the Centre and help out the researcher in extracting and analysing data.

A full time secretary (Susanne Schweitz) is in charge of the reception, making accounts and assists in performing research.

Steering committee

The steering committee of the Centre consists of representatives from the clinical departments, The National Environmental Protection Agency and The National Board of Health. The steering committee approves the yearly work plan and evaluates the progress four times á year.

Networks

The Centre has many co-operation partners and interfaces, nationally and internationally. There is a close co-operation with patient and consumer organisations, scientific institutes in chemistry, molecular biology, immunology, epidemiology, occupational medicine and philosophy as well as a net-work of dermatologists in private practice and different specialities at university hospitals.

1.3 Resources

The Centre has since the opening in 2001 had a yearly grant of 5 mio. Dkr. from the state (equals 675.000 Euro/600.000 £ /6.150.000 SEK). The amount has been unchanged in this 10 year period.

In the period of 2005 – 2009, the grant was given jointly by The National Environmental Protection Agency and The National Board of Health, but from 2010 the full amount comes from The National Environmental Protection Agency only, this means that some tasks, which is primarily of interest to the Health authorities are no longer given priority.

Other funding

The staff of Centre is continually applying for additional funding. At least 2 major applications and 10-15 minor are made each year. The major applications e.g. to the Strategic Research Council, takes at least 1 months of academic work time to prepare.

In the past couple of year a major effort has been made to put the topic of contact allergy on the agenda in EU in order to get a call covering the topic in the FP's. This work has been done in collaboration with The Capital Region Denmark EU office in Brussels. It has resulted in a meeting on skin allergies and research

needs in Brussels Feb. 2011, with the participation of a wide range of international experts, legislators and scientific officers from the Commission.

From 2002-2004 the yearly external funding from other sources were between 425.000-1.7 million Dkr. and from 2005-2010 between 2.0 – 3.5 million Dkr.

The major contributors have been:

- The Research foundation of the Copenhagen County (3.6 mio. Dkr.)
- The Foundation for Professional Development in Private Practice (6 mio. Dkr)
- The Foundation of the Ministry of Health and Internal affairs (1.4 mio. Dkr)
- The TrygFoundation (1.8 mio. Dkr.)
- The Foundation for Occupational Health (2 mio. Dkr.)

In addition the research group working on the health of hairdressers (lead by senior researcher Heidi Søsted) has funding of 2.0 -2.5 mio Dkr. per year.

Added value

The unpaid manpower of professors and senior doctors/researchers is added in their capacity as research leaders. The networking with other research institutions means that a large part of the research expenses is not payable but is part of the research collaboration e.g. in large scale epidemiological investigations, chemical analysis etc. This adds up to a considerable extra value of several million kroner.

1.4 Main tasks

The main tasks for the Centre are to prevent allergy to chemical substances in consumer products by:

- Surveillance
- Research – new knowledge
- Information

2. Projects and achievements

2.1 Surveillance and quality of care

2.1.1 National database for contact allergy

A national surveillance system for contact allergy has been established in order to provide data regarding the prevalence/incidence of contact allergy and to measure effects of interventions.

In Denmark such data has not been available before now, as the diagnosis of patients seen by dermatologists in private office is not registered collectively anywhere.

It is estimated that 75% of patients undergoing patch testing are seen by dermatologists in private office and 25% in the outpatient care units at hospital departments in Denmark.

The national surveillance system for contact allergy has therefore been established in co-operation with the members of the Danish Contact Dermatitis Group, who are dermatologists in private office, representing the primary health care system. Further data are collected from three hospital departments (Gentofte, Odense and Århus), representing the secondary health care system.

Data collection started 1. October 2002 since then the network has been expanded and the database contained data of 3.500 persons with contact allergy for 2003 and 5.107 in 2010 (figure 1). This corresponds to about 20% of patients tested in Denmark.

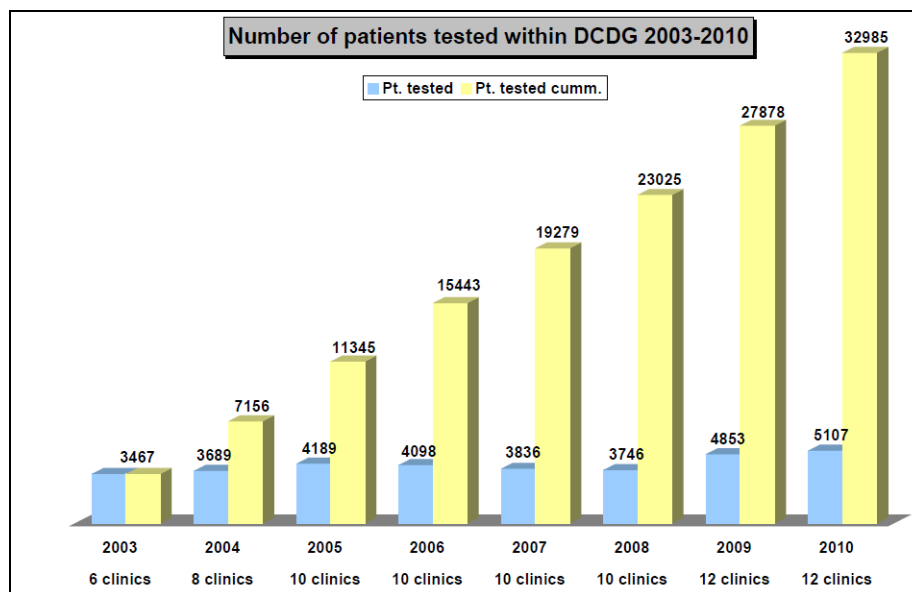


Figure 1: Number of patients patch tested by members of The Danish Contact Dermatitis Group and reported to the National Allergy Research Centre.

The data from the surveillance system is published on the home page each year with comments.

The size of the database is now considerable as it contains data from more than 30.000 individuals, which make a reasonable basis for scientific publications regarding trends and causes of contact allergy e.g.:

- Trends in allergy to methylidibromo glutaronitrile (publication no. 121)
- Added diagnostic value of testing with FMII (publication no. 181)
- Allergens associated with severe symptoms of hand eczema (publication no.) 146

A historical database on patients tested exclusively in the Department of Dermato-Allergology, Gentofte Hospital from 1980 and on comprising data from 25.000 patients is also managed by The National Allergy Research Centre. This database is also used for analysis in case more detailed data is needed or long time trends are analysed. Examples of scientific publications:

- Trends in allergy to nickel (publication no. 165)
- Leather as primary cause of chromium allergy (publication no. 162)
- Allergy to formaldehyde and causative exposures (publication no. 183)

Data from this database is transferred on an aggregated level to The European Surveillance System of Contact Allergy based in Germany (publication no. 64).

2.1.2 Quality of care in contact allergy

The database is also the basis for work in systemising and equalising the quality of health services concerning contact allergy. The database is approved by the National Board of Health as a quality database, which means that a range of formal requirements have to be fulfilled regarding steering group, data management and reporting. The yearly report has to be approved by representatives from the Danish Regions and it is evaluated every 1-3 years if the database still fulfils the requirements.

Representatives from The National Board of Health and Danish Regions are in the steering group of the Database and supervise the work. Professor Niels Veien from Ålborg is in charge of co-ordinating the work and data collection from private practice and comes ever 14 days in the Centre to review data.

A guideline including standards and indicators of quality in the diagnoses and treatment of contact eczema has been developed and is the basis for the measurement of the quality of care.

At the same time more detailed standard operating procedures (SOP) are developed in collaboration with the Danish Contact Dermatitis Group e.g. for diagnosing latex allergy, hand eczema and information about skin-care programs to patients. These SOPs are made available to other dermatologists at the homepage of the Centre (www.videncenterforallergi.dk). Further more than 30 new patient information sheets have been made in collaboration with the Danish Contact Dermatitis Group- also available at the home page.

The performance of each clinic/department in relation to each standard of quality of care is measured every 6 months and the clinic/department has the possibility to review the data before it is published. The data is also discussed at the meetings of the Danish Contact Dermatitis Group.

Eight standards exist. An example is the standard for investigating patients with hand eczema and professional use of natural latex gloves. At least 90% of these patients need to fulfil the standard of having a skin prick or RAST test for latex-allergy. It can be seen from the figure 2 that the network has improved their performance over the years in fulfilling this standard and thus improved the quality of care.

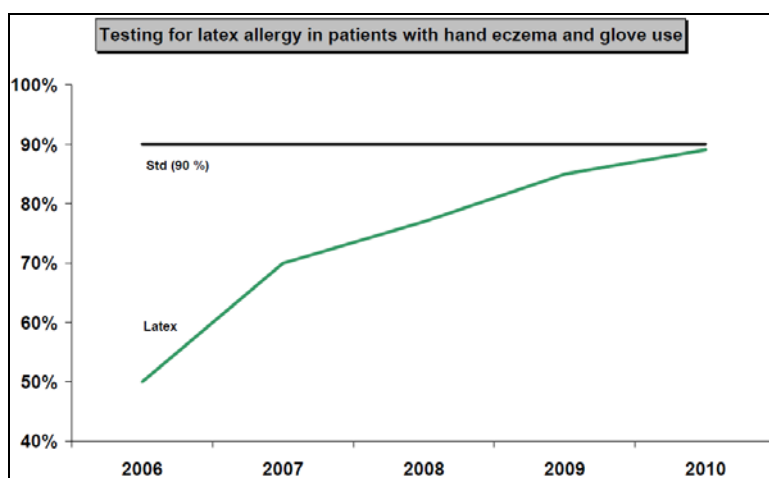


Figure 2: Proportion of patients with hand eczema and professional use of natural rubber gloves, who are being investigated for latex-allergy (skin prick/RAST) by members of The Danish Contact Dermatitis Group. The standard has been set to 90% of patients should fulfil the requirement. The performance in fulfilling the standard has improved over years.

As part of the work on quality of care educational seminars are offered to the staff of the participating clinics every second year.

The co-operation in the national database between hospital departments and dermatologists from primary health care is unique in Denmark. It is regarded a model project for co-operation in the health sector and for development of other databases.

A further expansion is planned, as a mini-version of the database has been developed which will be offered to all dermatologists in private practice, who also as part of the programme will receive newsletters and will be offered education in patch testing/contact allergy.

2.2 Research projects

A number of research projects have been established within the framework of The National Allergy Research Centre. In total 22 of these as PhD.-studies, 14 finished and 8 are on-going (appendix 1). In addition many smaller or larger research projects have been undertaken by medical students or senior researchers.

Several projects are/have been partly or fully financed by external resources.

The projects are all aimed at preventing allergic disease. They deal with exposure evaluation in relation to consumer products and allergy, establishing limits for exposure to contact allergens, improving diagnostic tools and compliance, as well as giving insight into mechanisms and identification of risk groups. A number of externally funded projects address occupational exposures, risks and prevention.

2.2.1 Main themes of research

Apart from the PhD.-theses a total of 229 scientific papers have been published and additional 16 accepted for publication bringing this up to 245 papers (appendix 3). An overview of these can also be found on the webpage of the National Allergy Research Centre (<http://www.videncenterforallergi.dk/scientific-articles.html>), where it is also possible to make a search on different topics.

Overview of papers by main category

Category	Number of publications
Nickel	39
Perfume/fragrance	37
Hand eczema	36
Cosmetics	34
Hair dye	26
Occupational dermatitis	23
Preservatives	22
Diagnostics/procedures	16
Risk assessment	15
General population epidemiology	14
Cobalt	12
Chrome	12
Methyldibromo glutaronitrile	11
Filaggrin mutations	10
Multiple allergies	8
Empowerment	6
Atopic dermatitis	6
Plants	6
Methyl isothiazolinone	5
Combination effects	5
Allergy to rubber chemicals	4
Hairdressers	3
Nanoparticles	3
Tattoos	3
Irritants	2
Exposure analysis at the work place	2
Adhesives	2
Parabens	1
Latex	1

Papers may appear in more the one category.

Some of the main finding of this scientific production will be mentioned below. The numbers in parenthesis refers to the list of publications (appendix 2).

2.2.1.1 Epidemiology of contact allergy

General

A review has been published on contact allergy in the general population (no. 108), which analyse all the published data so far and shows that the median prevalence of contact allergy in the general population in Europe is at least 20%.

Original research has also been performed. In 2006 a random sample of 3.500 adult Danes in the Copenhagen area was patch testing and answered a questionnaire. The study was performed in collaboration with The Research Centre for Prevention and Health, Glostrup Hospital. The results were compared with similar investigations performed in 1990 and in 1998 given a unique possibility to study trends (167) and a number of papers have been published concerning specific allergens. Further papers on the clinical epidemiological aspects of contact allergy have been published based on data from the historical database at Gentofte Hospital and the surveillance system.

New study:

- A study focusing on children with contact allergy/dermatitis has been initiated.

2.2.1.2 Nickel allergy

Epidemiology and effect of intervention

Nickel is the most frequent subject of the investigations performed.

It was shown by analysing the above mentioned population-data that nickel allergy has decreased in young females from around 20% in 1990 to 10% in 2006, probably due to the Nickel regulation, which was introduced in Denmark in the early 1990'ies. At the same time nickel allergy was shown to increase in older females as they had already acquired the nickel allergy in their early years (no. 166). The association between hand eczema and nickel allergy was also weakened (no. 168). These findings were supported by analysis of data from the historical database at Gentofte Hospital (no. 165).

The value of the reduction in number of new cases of nickel allergy in Denmark was previously estimated by COWI consult to 9.7 billion Dkr. over a 20 year period.(<http://www2.mst.dk/common/Udgivramme/Frame.asp?>).

'Validation' of limit in the Nickel Directive

The nickel release from metal object in close contact with skin is set to 0.5 µg/cm²/week in the Nickel Directive. An analysis of 8 previously published occluded Ni dose-response studies were made. The statistical analysis showed that 5% of a sensitized population reacts to 0.44 µg Ni/cm² and 10% react to 1.04 µg Ni/cm² (no. 47) This is in the range of the limit of the Nickel Directive, but not directly comparable as the patch test conditions differs from use conditions.

Exposure assessment

In spite of the decrease in nickel allergy, it is still very common affecting 10% of young females and studies have been undertaken to pinpoint current exposures to nickel from consumer products and at the work place.

In the first place the spot-test, dimethyl glyoxime test, for detection of significant nickel release from metal items were validated and found to have a high specificity (97.5%) but a fairly low sensitive (59.3%) (no. 205). Based on a case-report, an investigation of nickel release from mobile phones on the Danish marked was undertaken and showed significant nickel release from 19.5% of the investigated phones (no. 130). This lead to a contact to the Danish EPA/Ministry of Environment and following to the EU-Commission, who decided, mobile phones were covered by the nickel directive (no. 164).

A number of investigations on nickel release from consumer items have been performed (no.132, 163,170,202 and 242). A high frequency of nickel release from hair claps for children was found (no. 163). In EU countries covered by the nickel regulation between 0 (Sweden) and 18.4% (Warsaw) of earrings released nickel (overview in 242). In countries without nickel regulations as Bangkok, China and USA, the frequency of nickel release from earrings was about 30% (no. 242). Earrings bought in market places carried a higher risk of releasing nickel (no. 242).

Study year	City	Type of store and DMG test-positive earrings, % (no. pos./no. tested)				Total
		Clothing (chain)	Accessory (chain)	Other*	Market	
<i>Present study</i>						
2010	London, UK	4.3 (4/93)	0 (0/21)	25.0 (15/60)	38.7 (12/31)	15.1 (31/205)
2010	Warsaw, Poland	3.8 (3/78)	2.5 (1/40)	39.7 (23/58)	36.7 (11/30)	18.4 (38/206)
<i>Results from other studies performed in EU member states</i>						
1999	Stockholm, Sweden ²¹	0 (0/11)	0 (0/15)	11.1 (2/18)	–	4.5 (2/44)
2002–2003	Stockholm, Sweden ²²	0 (0/18)	0 (0/10)	0 (0/33)	–	0 (0/61)
2010	Stockholm, Sweden ²⁰	0 (0/11)	0 (0/57)	8.6 (3/35)	25.0 (1/4)	3.7 (4/107)
2009	Copenhagen, Denmark ³	4.8 (4/84)	0 (0/36)	31.0 (9/29)	57.1 (12/21)	14.7 (25/170)
<i>Results from studies performed outside of Europe</i>						
2007	San Francisco, USA ²⁷	8.3 (8/97)	26.6 (25/94)	42.9 (12/28)	69.0 (40/58)	30.7 (85/277)
2009	Chengdu and Beijing, China ²⁶	–	–	–	–	31.5 (99/314)
2009	Bangkok, Phuket, Hatyai, Thailand ²⁶	–	–	–	–	29.2 (71/243)

Figure 3: Overview of results from studies investigating nickel release from ear-rings from publication no. 242.

A paper on The EU nickel directive on how to achieve better protection against nickel allergy in the future has been written with international partners (no 245).

Nickel and cosmetics

In theory, all pigmented make-up products may contain metal allergens including nickel. Eyelid dermatitis has previously been observed among nickel allergic dermatitis patients following exposure to nickel containing mascara and eye shadow. Questions about this risk are often raised by consumers/patients. Analysis of results from the general population showed no overall association between having nickel allergy and reporting cosmetic dermatitis from mascara or eye shadow use. This does not exclude a causal relationship in selected cases (no. 199).

Nickel at the work place

Another source of nickel exposures are in the work place. A case-study of 6 patients was undertaken in an international collaboration (no. 215). An acid wipe sampling technique was employed to quantify nickel exposure on the hands of patients with an occupational nickel exposure. Occupational exposure to nickel-releasing items raised the nickel content on exposed skin as compared with a non-exposed control site. Nickel-reducing measures led to complete symptom relief in all cases. Nickel may be released from work tools such as scissors. In a study (no. 173) random hairdressers' stores in Copenhagen were visited. The dimethyl glyoxime (DMG) test was used to assess excessive nickel release. Nickel release was found in 1 of 200 pairs of scissors and 7 of 13 crochet hooks.

New studies:

- Random samples of tools are being investigated for nickel release

Susceptibility

Studies on individual susceptibility of nickel allergy have been performed (see under risk groups).

Cobalt

Epidemiology

As nickel release from consumer items has been restricted, it has been speculated, if cobalt had replaced the use of nickel and thus if a change in cobalt allergy could be detected. This was investigated in eczema patients over a 23 year period. It was seen that cobalt followed the downward trend of nickel allergy (165).

Exposure assessment

Cobalt allergy is still frequent and a spot-test for cobalt exposure has been developed to analyse exposures (no. 203). Cobalt release from inexpensive jewellery was investigated with the spot test. Cobalt release was only found in a minority (1.1%) of the 354 investigated items (no. 194).

New studies:

- Investigations of random samples of tools for cobalt release.
- Investigations of mobile phones, dental and orthopaedic implants

Chromium

An increasing trend of contact allergy to chromium due to leather exposure was demonstrated among Danish eczema patients (no. 162). A previous investigation from The Danish Environmental Protection Agency had shown that chromium was released from 35% of consumer leather products. Both hexavalent and excess trivalent chromium were detected (reported in a review no. 3). A PhD.-study addressed aspects of epidemiology (no. 72), improved diagnosis (no. 10), thresholds of response (no.71) and exposure to chromium via leather (no.71).

The problem has not been addressed by regulators yet partly due to lack of relevant exposure measures i.e. release of chromium over time from leather and therefore difficulties in setting and controlling limits.

New studies:

- The National Allergy Research Centre has recently engaged in a new analysis of chromium release from shoes together with the Force Institute.

Fragrances

An increasing trend in contact allergy to FMI was seen from 1990 to 1998 in the women aged 18-41 years population, with a decrease to the same level as in 1990 in 2006. The analysis also showed that sensitization to FMI was associated with reporting cosmetic dermatitis and seeking medical attention due to cosmetic dermatitis (no. 169). The same trend was seen in eczema patients (no. 127).

New fragrance allergens was detected in an international collaboration, these were compiled into a new diagnostic test FMII (no. 48, 49). Also a number of natural oils were identified as allergens. The added value of testing with the FMII was just recently analysed (no. 181). FMII was found to contribute significantly to the diagnosis of fragrance allergy.

The main allergen in FMII is hydroxyiso 3-cyclohexene carboxaldehyde (HICC). The Fragrance Industry introduced voluntarily a limitation in its use due to its prevalence as an allergen in 2003.

The trend of this allergen was followed in Danish eczema patients from 2003-2007 without any sign of effect of this intervention (no.113). A study on HICC and threshold for allergic responses has been performed; based on the results it was concluded that 0.02% should be the maximum allowed concentration (no.21). Subsequently The Fragrance Industry has lowered the permitted concentration of use to this level in perfumes.

Identification of new allergens

In an international, EU-funded, co-operation the main allergens in the natural extract, oak moss absolute, was identified in a bio-guided fractionation procedure (no.8), this makes it at least theoretically possible to remove/reduce the allergens e.g. by chemical procedures and thereby achieve primary prevention and secondary prevention.

Dose-response relationships

The dose-response relationship has been investigated for a number of fragrance allergens by serial dilution patch testing, by repeated open application test with solutions of allergens and with dummy products (no.9, 11, 20, 23, 21, 42, 95, 143). The data is available to industry to be considered in their risk assessment and has also been provided to the EU-Commission.

Causative exposures

Analysis of the causative cosmetic products in eczema patients with fragrance allergy show that deodorants play a big role in fragrance allergy, followed by lotions and perfumes (no. 214).

Combined exposures and immunology

New studies

- A research programme has been developed together with the Section of Experimental Immunology, Faculty of Health Sciences, University of Copenhagen, which aim at studying the effect on the immune system of combined exposures to fragrance ingredients.

Exposure analysis

Products from patients and randomly sampled products from retailers have been analysed for levels of different allergens, which provides important knowledge concerning current exposures to important fragrance allergens. Isoeugenol derivatives were found in a study in one third of products, which may cause reactions in isoeugenol sensitive subjects (no.125) and the presence of chloroatranol and atranol in cosmetics were investigated in another study (no. 34). In another study the composition of old perfumes with newly launched was investigated and a different composition i.e. fewer known allergen was seen in the new perfumes compared to the old ones (no.22).

These studies have been in collaboration with The National Environmental Research Institute.

Hand eczema and fragrance allergy

A PhD.-study was performed on the relationship between hand eczema and fragrance allergy as part of an EU-funded project. A review of the literature was made (no.14), a clinical study including a questionnaire (no.12), an experimental provocation on the hands of sensitized individuals (no.13) and an investigation in combined exposures to irritants and fragrance allergens (no.11).

Quality of life

A questionnaire study was made of 147 patients with fragrance allergy (no. 151). A large proportion (45%) reported that their quality of life was significantly negatively influenced by their fragrance allergy.

New studies:

- A larger study is planned to further describe how and why the life quality is affected.

Effects of inhalation of fragrance

A PhD study has been performed on the characterization of individuals who experience symptoms from eyes and air-ways, when exposed to fragrance ingredients. A statistical relationship between contact allergy and the risk of reporting air-way symptoms to air-borne chemicals was found (no.45, 46). This is thought to be caused by an increased general sensitivity in the skin and mucous membranes in these individuals. Certain fragrance ingredients was shown to release histamine (no. 86), but no evidence of type I allergy in these patients was found (no. 45).

Preservatives

General trends

The trend in allergy to preservatives was investigated over a 24 year period (1985-2008) based on data from the historical Gentofte database (no. 193).

Formaldehyde allergy was persistently prevalent over the study years. The overall prevalence of preservative allergy increased significantly (P (trend) = 0.001), mainly because of patch testing with additional preservatives in recent years.

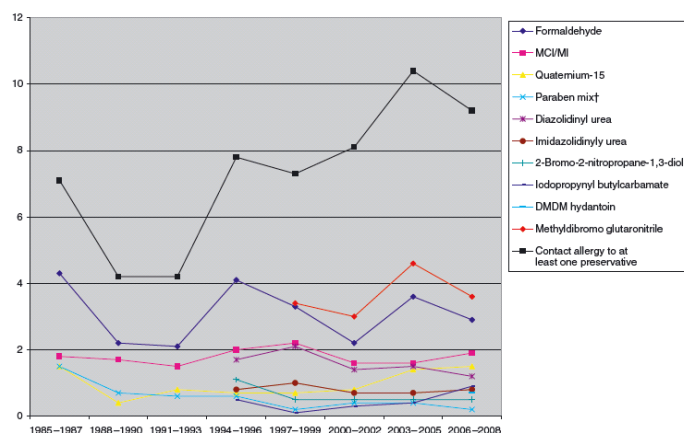


Figure 4: Temporal trends of preservative allergy among eczema patients in Denmark (Gentofte) (1985-2008) from publication no. 193.

Specific preservatives

Methyldibromo glutaronitrile (MG)

Methyldibromo glutaronitrile (MG) was permitted as a preservative in cosmetics in 1980'ies in too high concentrations. This resulted in an increasing number of cases of contact allergy to MG were seen among eczema patients tested by dermatologists in Europe, including in Denmark, The National Allergy Research Centre focused on this topic at an early stage. The first paper on this topic from the Centre concerned the clinical experience and was published in 2003 (no. 25). MG allergy was found in 4.9% of patients tested at Gentofte Hospital and in 60% of cases a relevant exposure was found primarily to cosmetic products.

Exposure and thresholds

A PhD. study (in Odense) was initiated on the subject MG allergy and prevention. Investigations done here and as a part of another PhD.-study showed that low levels of MG elicited allergic reactions in sensitized individuals (no 31). Further elicitation could also be produced by exposure to a liquid soap with the maximum permitted concentration of MG (no 28), that repeated exposures, as with liquid soaps, gave the same effect as if the one large dose had been administrated (no. 54). It was also shown that the combination with an irritant, as in soaps, increased the skin response (no.32). One study also focused on the characteristics of patients seen by dermatologists in private practice in 1 year. In total 5% of the patch tested patients had a positive response to MG. In half of the cases the patch test reaction to MG was judged to be of current relevance. Creams and lotions accounted for one-third of the identified causative products and liquid soaps for one fourths (no. 55).

Intervention

These findings together with the international experience made a basis for a new risk assessment performed by the Scientific Committee advisory to the EU-Commission, which again lead to the ban of the use of MG in EU first in stay-on cosmetics, implemented in 2005 and later in rinse-off products, implemented in 2008. A follow-up paper was made showing a significant decreasing trend of MG-allergy in Denmark following the interventions made (no.121), which is also illustrated in a later study (no 193) (see figure 4 above).

Methylisothiazolinone (MI)

Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) has been one of the most frequent sensitizers since the 1980s. In 2005, the use of MI alone was approved for the preservation of cosmetic and household products in the EU. Before that, MI was used in industrial products, and the first cases of isolated MI contact allergy were published.

MI was included in the baseline series at Gentofte Hospital from 2006. The analysis of the patch test data from 2006-2010 showed that MI contact allergy was already at the same level as that of other sensitizing preservatives, which have been on the market for several years. MI contact allergy was associated with both occupational and consumer products. Painters were the most frequent occupational group, with MI-allergy (no. 184). In several cases airborne/systemic contact dermatitis and asthma/rhinitis were seen in patients with MI-allergy, who had lived in rooms, newly painted with MI containing paint (no. 235).

A study was made concerning thresholds and showed that patients sensitized to MI may react to even very low levels of MI (5 ppm) (no. 235).

New studies:

- An investigation regarding products, numbers and types, on the marked containing MI and chemical analysis of the levels used.
- A study has been initiated to measure the levels of MI in indoor-air after having applied paint and follow changes in concentrations over time. This study is done in collaboration with indoor-air engineers at the Technical University.
- A study concerning skin problems and contact allergies in painters have been initiated together with the painters' union.

Formaldehyde and releasers

Addressed in the general paper (no. 198) mentioned above. Exposures to formaldehyde and causes of formaldehyde allergy were also analysed (183).

PPD

An overview of Epidemiological data on consumer allergy to p-phenylenediamine has been published on behalf of The European Society of Contact Dermatitis (no.135). In Europe a decrease in the 1970s of PPD allergy was replaced by a plateau with steady, a high prevalence ranging between 2% and 6%. It was concluded that contact allergy to PPD is an important health issue for both women and men.

In a new study PPD patch test results from dermatitis patients tested between 2003 and 2007 in 10 European patch test centres were analysed. The weighted average prevalence of PPD-allergy was 4.6% among 21 515 patients, showing that PPD is a frequent allergen. PPD sensitization occurred more often in centres located in Central and Southern Europe than in Scandinavian centres.

The overall proportion of positive patch test reactions to PPD that were registered as being of either current or 'past' relevance was high (weighted average 53.6% and 20.3%, respectively). Consumer hair dyeing was the most prominent cause of PPD sensitization (weighted average 41.8%). Furthermore, occupational hair dye exposure (10.6%) and cross-sensitization to textile dyes (12.6%) were frequently reported (no.159)

An increasing prevalence of PPD was found from 1.4% in 1989 to 2.4% in 2007, when analyzing the Danish data (no.128). A further analysis showed that this could not be explained by cross-reactivity to other para-compounds such as IPPD, and thus indirectly supporting that the major causative factor for PPD-allergy is hair dyeing (no. 227).

Hair dyes

The focus on hair dyes was started by a case study of 55 consumer complaints in 2002 (no.6). This was followed by a PhD.-study consisting of an epidemiological interview based survey in a random sample of the general population demonstrating that most women have at one time dyed their hair and that around 5% of those who have dyed their hair report adverse skin reactions (no. 61). Recently in a random sample of adolescents it was found that 82% had dyed their hair at some point and that 10% had experienced an adverse reaction (no.207), which indicates an increasing problem in comparison with the former study in adults (no. 61).

In one paper focus was set on children with allergic reactions to hair dyes (no.85). Further the dose-response relationships of PPD were studied (no.86) and case-based exposure analysis performed (no.40), as also investigations into the effect of oxidation (no.84). A QSAR analysis was also undertaken to identify other relevant hair dye allergens apart from PPD (no.39).

Animal experiments of exposure to PPD-containing hair dyes have shown that such exposure causes severe immune activation, which is worse than exposure to PPD, even if the hair dye is removed after 30 min. of exposure (175). Oxidation of the hair dye increased the response.

A new study in animals with repeated exposures to hair dyes over a longer period showed that hair dyes in addition to being potent skin sensitizers also induced anti-inflammatory mechanisms, i.e. tolerance. This might explain why many consumers can use hair dyes repeatedly without developing noticeable allergies, but it also raises the question whether the immune modulatory effects of hair dyes might influence the development of autoimmune diseases and cancers (187).

New studies:

- Patch testing additional hair dyes substances to improve diagnosis
- A ph-d study has been initiated in order to study further the effects on the immune system of PPD/hair dyes and other strong allergens.

Thiurams

A decrease was described in thiuram allergy, which may be an effect of legislation (no. 80).

2.2.1.3 Risk groups and individual susceptibility

Risk groups – individual susceptibility

The analyses for the two most frequent filaggrin mutations (R501X and 2282del4) were established at the department of biochemistry at Gentofte Hospital. This means that the analysis is offered to relevant patients in the clinic and that typing has been performed on different populations – patients and general in order to describe the possible effects of a disrupted skin barrier on the risk of allergy and eczema.

Currently genotyping has been performed on 6.000 individuals from the general population and 500 eczema patients.

Main findings:

- 8% of the general population carries one of the two filaggrin mutations (no. 196).
- A positive and significant relationship between filaggrin gene defect and nickel allergy was found among those who had never been pierced (no.196). Published as the by-pass theory (no.126).
- Filaggrin null mutations may lower the age of onset of nickel dermatitis in those who are not ear-pierced (223).
- No relationship was found to other frequent allergens (no. 196), neither to multiple allergies in eczema patients (no.176), which supports that the major risk factors for contact allergy are environmental.
- FLG mutation status and atopic dermatitis were positively associated with neomycin and ethylenediamine sensitization (no. 196).

New studies:

- The nickel-binding in the skin is being studied especially in relation to filaggrin.
- Dose-response relationships are being investigated in nickel-sensitive individuals stratified for genotype.

Persons with multiple allergens

In a PhD study focus was on patients with multiple allergies. Multiple contact allergies were found in 5.1% of standard tested patients, primarily women, and 90% got diagnosed by the first test. Frequency of multiple allergies increased with age, which again indicates the environmental exposures are strong risk factors (no. 88).

This was confirmed in an experimental induction study using diphenylcyclopropenone, where no difference was seen in sensitization ratios between a group of poly-sensitized, mono-sensitized and healthy controls (no.174). Hand dermatitis was associated with polysensitization (no.140).

2.2.1.4 Risk assessment and thresholds for contact allergy

Acceptable risk

A paper on acceptable risk has been produced in an international collaboration (no.172). The clinical epidemiology (CE) and drug utilization research (DUR) method was used (in a reverse manner) to make delineations between the 10-year prevalence of contact allergy in the general population and the corresponding prevalence of contact allergy observed among patients with dermatitis in Denmark and Germany. The detection limit of the method was 1/10.000 with contact allergy, which was deemed 'low level' epidemic category. It corresponds to 0.04%-0.05% of patch test positive Danish eczema patients and 0.02%-0.1% of German eczema patients. It was suggested that this level was used as an alert for dermatologists and policy makers of potential significant problems of contact allergy.

General thresholds/exposure limits

The general characteristics of the dose-response relationships of elicitation of contact allergy have been investigated in a PhD.-study. Three model substances were chosen (nickel, MG, HICC). Patients with the specific allergy and controls without were exposed to serial dilutions of the allergen by single occluded exposure (patch testing) and by repeated open application (no 91,117,143).

It was shown that:

- More reacted to repeated exposure than to the single occluded exposure for identical doses per application.
- The dose-response curve for accumulating doses i.e. 2 weeks of accumulated exposure was almost identical to the single occluded exposure curve.
- A conversion factor between threshold concentrations at patch testing and use testing could be given (no. 144).
- The conversion factor was smaller for the volatile allergen HICC (no. 144).

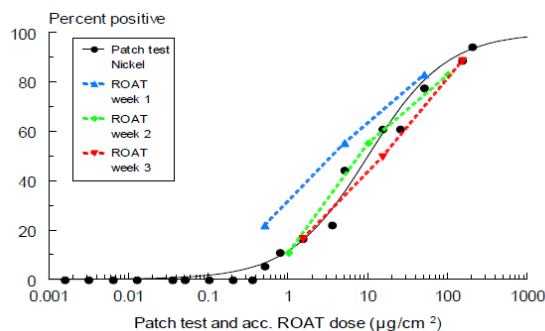


Figure 5: Dose-response curves for nickel for patch test and 1, 2 and 3 week repeated open application tests (from publication no. 91)

It was observed that the dose eliciting a response in 10% of the sensitized individuals, called ED10 was very similar for the 3 allergens.

This prompted a review of the literature and a re-analysis of dose-response data (no 212). The literature was searched for patch test elicitation studies that fulfilled six selection criteria. The elicitation doses were calculated, and fitted dose-response curves were drawn. Sixteen studies with eight different allergens were selected. The median ED10 value was $0.835 \mu\text{g}/\text{cm}^2$. The ED10 patch test values were all within a factor of 7 from the lowest to the highest value, leaving out three outliers.

No obvious patterns between the sensitization and elicitation doses for the allergens were found.

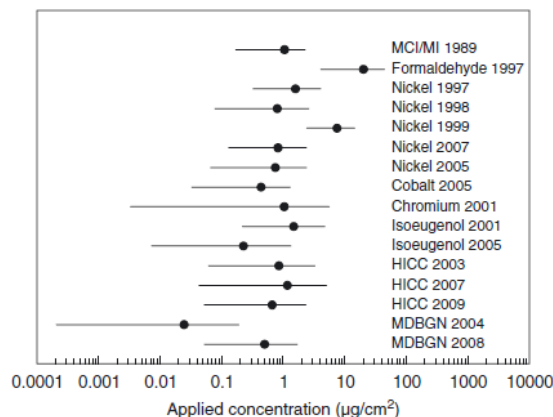


Figure 6: ED10 values and 95% confidence values calculated from 16 studies from publication no 212

These findings have implications for risk assessment as a generic approach for limitations of exposure to allergens, which already have caused significant disease, may be used, if no specific data exists.

Thresholds for specific substances

The dose-response relationships of the following allergens have been studied by serial dilution patch and/or use tests:

Cinnamal (no.9)

Chloroatranol (no.20)

Chromium (no. 10)

Hydroxycitronellal (no. 11; 23)

Hydroxyisohexyl 3-cyclohexene carboxaldehyde (no. 21; 95; 143)

Isoeugenol (no. 42)

Methyldibromo glutaronitrile (no. 28; 31; 32; 54; 74)

Methylisothiazolinone (no. 219)

Nickel (no. 91)

PPD (no.86)

Micro-vesicles and change in risk of contact allergy.

Micro-vesicles such as ethosomes are used in cosmetics. As part of a PhD-study performed in Odense animal experiments showed that ethosome formulations of known contact allergens can increase their sensitizing capacity (no. 186), and in a clinical study it was shown that they may enhance patch test reactions in patients (no. 185). However the effect depends on the allergen and on the type of micro-vesicles. It was concluded that formulation of lipophilic allergens in some vehicle systems may enhance the sensitizing and eliciting capacity and that the potential effect of vehicle systems should be considered in risk assessment.

2.2.1.5 Disease patterns and contact allergy

Contact allergy is a functional change in the immune system induced by exposure to reactive chemicals. Allergic contact dermatitis is an inflammatory disease which may be chronic. In both cases it could be hypothesized that such changes in the immune system/chronic inflammation could lead to a change in disease patterns. Register-based studies linking the historical contact allergy database with patient registers have shown inverse relationships with auto-immune diseases such as diabetes type I (no. 70), inflammatory bowel disease (90) and psoriasis (137). Animal experiments have been undertaken and the first results indicate that the relationship could be causal as repeated exposure to a potent allergen interfered with the incidence of diabetes in mice (178). This is under further investigation in a post.doc study.

The contact allergy database was also linked with the Danish Cancer Register. It was shown that patients with contact allergy had a decreased risk of certain cancers such as skin cancer and breast cancer, which may be due to the active immune system (immune surveillance theory). An increased risk of bladder cancer was found, which may be hypothesized is due to secretion of metabolites of allergens through urine (no. 210).

The perspective of such research is that it shows the implications of contact allergy/allergic contact dermatitis as a systemic disease. It indicates that exposure to reactive chemicals (contact allergens) can lead to a complex interference with the human body and with unpredictable consequences.

2.2.1.6 Systemic exposures to contact allergens

Contact allergens may be part of different medical devices, such as orthopaedic implants, dental braces and stents, which are inserted in the body and exposed to body fluids, so that contact allergens may be released. Relative few investigations exist on the possible consequences of systemic release of contact allergens in those already sensitized or the consequences of being sensitized by internal exposure to contact allergens. It also raises the question on how to adequately diagnose such a state. A review of human biomonitoring in relation to contact allergy has been made and is under publication.

A review has also been made on cutaneous and systemic hypersensitivity reactions to metallic implants (no. 206). It has been investigated if nickel or chromium allergy gave an increased risk of in-stent restenosis after percutaneous coronary intervention, and no overall increased risk was found (no. 224). Likewise when studying the risk of implant failure after total hip arthroplasty (no. 161).

2.2.1.7 Hand eczema

Classification

A guideline for diagnosis and treatment of hand eczema was made in collaboration with the Danish Contact Dermatitis Group and on behalf of the Danish Dermatological Society (no.221).

The guideline contains a scheme for classification of hand eczema in different clinical and etiologically types. This classification scheme was tested in 710 hand eczema patients and the results recently published (no. 216).

Severity assessment

A scoring system, called hand eczema severity index (HECSI), for assessing severity of hand eczema was developed and validated (no. 51). A photo-guide with photos of different grades of hand eczema developed for doctors was modified and tested for use by hand eczema patients (no.94). This makes it possible to investigate the severity of hand eczema in questionnaire studies.

Epidemiology, individual and environmental risk factors

A review of the epidemiology of hand eczema has been made (no. 195).

As part of a PhD.-thesis a population-based questionnaire study was performed in the Copenhagen Region based on a random sample of 6.000 adults. The 1-year prevalence of hand eczema was 14%. Twenty-three per cent rated their hand eczema as moderate to very severe. In total, 67% had consulted their general practitioner and 44% had consulted a dermatologist because of hand eczema. Multivariate analysis showed a positive association between severity of hand eczema and medical consultations. Of those individuals who had not consulted a dermatologist 26% had experienced moderate to very severe hand eczema within the previous 12 months (no.119).

A study on hand eczema patients was undertaken and 799 consecutive hand eczema patients seeking dermatological advice were included. A follow-up was made 6 months after the primary consultation (no. 145-147). It was shown that severe hand eczema at baseline was associated with older age, atopic dermatitis and contact allergy.

Being an unskilled worker was a predictor for a poor prognosis at follow-up (no. 147).

New studies:

- A PhD. study has been initiated with a focus on irritants as a risk factor for hand eczema and the interaction with individual susceptibility.

Medical attention

In the study mentioned above, it was shown that the risk of a poor prognosis increased by a factor of 1.11 [95% confidence interval (CI) 1.02-1.21] per month of patient delay in seeking medical attention and by 1.05 (95% CI 1.00-1.10) per month of healthcare delay in referring the patient to a dermatologist (no. 145). This finding can have implications for the organisation of healthcare system as regard to hand eczema patients.

Prevention

The benefit of alcohol-based disinfectant used on normal skin was debated five-ten years ago. This prompted two investigations by The National Allergy Research Centre showing alcohol-based disinfectants caused less irritation of the skin than hand washing (58, 59). This contributed to the overall decision of recommending hand washing replaced by alcohol disinfection, if possible. A PhD-study on prevention of hand eczema among hairdressing apprentices have been performed (see below).

New studies:

- A PhD-study on compliance and empowerment in patients with hand eczema has been initiated.

2.2.1.8 Occupational dermatitis

General

Analysis of all recognized cases of occupational hand eczema was done as part of a PhD-study. It was shown that hairdressers, bakers and food handlers were the occupational groups with the highest incidences of hand eczema (37, 44, and 66).

Hairdressers

A special focus has been on hairdressers through the co-operation with The Research Centre for Hairdressers and Beauticians. Two PhD.-studies have been performed, one was an intervention study performed on the vocational schools of hairdressing apprentices and the other- still on going -concerns a cohort of all hairdressers graduated since 1985, their prevalence of hand eczema, reporting of occupational eczema and reasons for leaving the trade.

In the first study it was shown that hairdressing apprentices have less skin problems (atopic dermatitis) before entering the trade (208), in the first year of education 30% develops hand eczema. With a simple educational programme it was possible to reduce the incidence of hand eczema significantly. (<http://www.videncenterforallergi.dk/publications-phd-theses.html>).

These results will provide the basis for introducing the educational programme as a standard at the vocational schools.

In the second study (236) it was found that 40 % of hairdressers report having had hand eczema, in most cases it started as apprentice, 45% leave the trade and hand eczema is the most frequent reason next to muscular pain. In the next analysis underreporting of hand eczema as an occupational disease to the Board of Occupational Health will be addressed.

Painters

It was shown in the analysis of MI data that painters were the most affected occupational group (184).

New studies:

- An analysis of patch test data on painters is ongoing
- A protocol has been written to make an investigation of hand eczema among all painters.
- Exposure analysis is planned of MI in air samples from newly painted rooms

New studies:

- Exposure analysis in occupational contact dermatitis is a PhD study with the aim of systemizing how exposure is analysed in cases of occupational contact dermatitis, document the adequateness of information given via safety data sheets and improve the diagnostic work-up. Further it is planned to map the presence of well-known allergens in products used in different occupations via the product register.
- *Food handlers:* Data from the past 10 years of prick-prick testing foodhandlers with foods is under analysis. The investigation includes a questionnaire regarding the course of disease.
- *Epoxy allergy:* A questionnaire study has been performed among all patients with epoxy allergy seen the past 5 years. The main purpose is to pinpoint exposures and elucidate the course of disease.

2.2.1.9 Information/empowerment

A number of studies have been performed to investigate the need of information of different patients groups and whether the current ways of information also matched these needs e.g. studies was made on the ability of patients with contact allergy to read ingredient labels (no. 30;102), wheter patients followed the advice given concerning skin care and treatment (no. 101,152) if patients with fragrance allergies used the newly introduced ingredient labelling of specific fragrance ingredients (no. 151).

New study:

- A PhD-study is currently being performed addressing the needs of hand eczema patients for individualized information and testing new ways of providing information in order to enhance compliance and empowerment.

3. Relevance and impact of results and investigations

3.1 In regulations

The investigations made by the National Allergy Research Centre are all relevant for prevention and thus also in some cases for regulation, as basis for evaluation of current regulations or as indications of need of new regulations.

The results from the surveillance system is important for regulators to be able to follow trends, document effects of interventions made or as alerts for emerging problems.

Examples of the direct or potential use of results in regulations:

In a number of studies the effect of the Nickel Directive has been investigated. Solid epidemiological evidence has been provided that this intervention has had a power-full effect on the epidemiology of nickel allergy in the population. This supports that such interventions could be made in other relevant areas such as chromium in leather or in specific risk groups such as occupational settings.

The investigations made by The National Allergy Research Centre regarding allergy to methyl dibromo glutaronitrile (MG) provided essential evidence, which was used in the re-evaluation of the substance in the Scientific Committee advisory to the European Commission regarding the risk of contact allergy. Subsequently MG was banned from use in cosmetic products in EU, fully implemented in 2008.

The National Allergy Research Centre was the first to make a systematic investigation of nickel release from mobile phones on the market. The idea came from seeing a patient in the clinic with a chronic facial dermatitis, which turned out to be caused by nickel release from her mobile phone. This illustrates the relevance of the concept and organisation of the Centre. The investigation showed that one out of five of mobile phones on the market released significant amounts of nickel. This led to a contact to the Danish EPA/Ministry of Environment and following to the EU-Commission, who decided, mobile phones were covered by the Nickel Directive.

The investigations done on PPD and hair dye allergy have highlighted the problem and increased awareness also in EU. A memorandum of risk of hair dye allergy was produced by the Scientific Committee on Consumer Products, advisory to the European Commission (December 10th 2006).

A working group of skin allergies were formed. As a first step better labelling and warnings on products were agreed by member states in EU. It was also agreed to emphasise that permanent hair dyes are unsuitable for children, which was inspired by a publication from the Centre, which provided the age limit of 16 years.

Potent and hitherto unknown allergens have been identified in a natural fragrance extract (*oak moss abs.*), in an international collaboration. Dose-response investigations have been made, which show that patients react to extremely low levels of these substances. This information was sent to the European Commission leading to an assessment by their Scientific Committee and a recommendation that these substances should not be present in cosmetics. Other investigations on fragrance ingredients, e.g. HICC have also been basis of opinions from the SCCP (December 2003/2004). These opinions have not yet been implemented in legislation, but fragrance industry has used the thresholds suggested for HICC in their safety guidelines.

A model of acceptable risk of contact allergy has been developed, which may be used as an alert of potential significant problems of contact allergy for use by policy makers.

The understanding of factors of importance for contact allergy/allergic contact dermatitis has been improved by investigations in the dose-response relationships. This means an improved basis for risk assessment and eventually for regulations, if relevant. A standardized model for determining threshold of response has been developed, which may be used as the basis for regulations. A model providing generic thresholds has also been developed for use if no substance specific data exist. This will ease the handling of significant contact allergens in the future.

The results from the investigation of MI allergy have been sent to the Commission by the Danish EPA to be considered in relation with the Biocide directive (REACH) and the Cosmetic Directive.

Investigations have also highlighted insufficiencies in regulations e.g.:

- The lack of limitations concerning release of CrVI from leather (shoes)
- Regulations are lacking addressing the problem of hair dye allergy
- The potential excessive exposure to nickel allowed by the Nickel Directive due an adjustment factor allowing 10 times the limit.
- The use of complicated names for labelling of cosmetics making it difficult for patients to read the label, especially for formaldehyde allergic patients.

3.2 Potential preventive effects

Trends in contact allergy and disease burden

It is documented that the investigations done on MG and the subsequent intervention have had a preventive effect. There are also indications of a decreasing trend for some of the fragrance substances in focus (not published). Many of the other investigations may have both specific preventive effects concerning allergy to certain substances and general preventive effects. A specific example is the new investigations on MI allergy, while more general preventive effects may be obtained by the acceptable risk model providing alerts for potential significant problems of contact allergy and the model providing generic thresholds for significant contact allergens. The strategy behind these investigations is to establish limits for exposure to contact allergens, which are safe to the majority of allergic individuals, in order to reduce the burden of clinical disease among allergic individuals (secondary/tertiary prevention). At the same time such measure will be effective in preventing new cases of allergy (primary prevention). The value of the reduction in number of new cases of nickel allergy in Denmark was previously estimated by COWI consult to 9.7 billion Dkr. over a 20 year period. The value of the already performed and suggested interventions are considerable both seen in a Danish and a European context.

Identification of allergens and improved diagnostics

Prevention is dependent on that the relevant allergens are identified. If proper diagnostics are not performed, the causative exposures go undetected and the patient will continue to be exposed leading to chronic disease. Further it is not possible to take general action against an undetected problem.

The Centre has participated in and performed a range of investigations, often in an international collaboration, aimed at identifying new or emerging contact allergens e.g.:

- The main allergens (chloroatanol/atranol) in the natural extract, oak moss absolute, has been identified, which could make it possible to remove/reduce the allergens e.g. by chemical procedures and thereby achieve primary and secondary prevention.
- Hydroxyisohexyl 3-cyclohexene carboxaldehyde has been established as an important allergen.
- The significance of oxidation products of limonene as contact allergens in Europe has been shown.
- Methylisothiazolinone has been identified as a significant 'new' allergen.

This has led to improved diagnostics and thereby provided the basis of preventive actions in relation to the patient in question and in a more general context.

The Centre has also been active in establishing and validating a new diagnostic test for fragrance allergy, the fragrance mix II, which detect about 20% more patients with fragrance allergy and which has become a part of the European baseline series – for the benefit of European eczema patients.

Risk groups

Identification of individual susceptibility and risk groups are important for aimed preventive actions and targeted information. The Centre has established the analysis of filaggrin mutations in Denmark. The filaggrin mutations lead to deficiency of the stratum corneum and an increased risk of (atopic) eczema. The analysis is offered to all relevant patients with eczema and makes it possible to focus the advice, preventive actions taken and choice of therapies. The Centre has genotyped the largest cohorts in Europe, general population and patients, which provides more general knowledge about individual susceptibility. In new studies the Centre is focusing more on characterizing the full skin barrier including other proteins and lipids. A study on the binding of nickel in the stratum corneum and the relation to risk groups may in the future give rise to targeted prevention. Another focus of the Centre will be characterizing children with contact allergy.

Exposure assessments

Understanding exposure and performing relevant exposure assessments is a corner stone of risk assessment and prevention. The Centre has provided a validation of the nickel assessment tool, the dimethyl glyoxime test, which provides confidence in results obtained using the test. A new spot test for cobalt exposure has been developed and made commercially available.

The mapping of significant nickel release from consumer items on the European market and in non-European countries focuses attention on the relevant problems and makes it possible to target prevention and improve regulations and control measurements.

The studies providing knowledge on exposure levels to different fragrance allergens and preservatives are of equal importance.

The work on assessing deposit of nickel on the skin in the work place – done in an international collaboration-is important for the understanding of causes of hand eczema and for prevention and regulations

The studies on exposure of the general population including youngsters to potent allergens e.g. by hair dyeing put the need for prevention into a context.

A study is ongoing, which will systematically investigate the means and possibilities of exposure assessment of individual occupational cases. This will display insufficiencies in regulations for providing relevant information without serious delays.

Increased awareness, information and education

The investigations provide information which makes it possible to increase awareness on risk exposures e.g. use of permanent hair dyes, semi-permanent tattoos, and fragranced products/deodorants. Such behavioural modifying information will contribute to prevention.

The Centre has provided evidence that alcohol based disinfection is less irritating to the skin than hand washing and in this way contributed to the change in recommendations for healthcare workers.

In one of the PhD.-studies, done in collaboration with the Research Centre for Hairdressers and Beauticians an educational programme for hairdresser apprentices was shown to reduce the incidence of hand eczema significantly and will now be implemented in the routine.

A PhD-project is ongoing, which aims at increasing compliance and empowerment of all patients with hand eczema and thus reducing the burden of disease.

3.3 Usability

3.3.1 The healthcare system

Contact allergy/contact dermatitis and hand eczema are frequent diseases, seen in primary healthcare by general practitioners and dermatologists in private office, some times by occupational physicians and in University departments of dermatology. Most of the results produced by the Centre are clinical investigations, which are operational and may be directly implemented in clinical practice.

Examples are recommendations of use of alcohol based disinfection instead of hand washing, new diagnostic tests, and development of a scale for assessment of severity of hand eczema, guidelines for classification, diagnosis and treatment of hand eczema.

The surveillance system provides a running overview of the disease and alerts for emerging problems, information which is relevant for decision makers.

A PhD-study showed that the prognosis of hand eczema depended on the lag time before seeking medical attention and seeing a dermatologist. Such information is important in decision making regarding the organisation of the healthcare sector.

The programme on quality of care in contact allergy/contact dermatitis provides standards for investigation and information of patients, which are applied both to hospital departments and private practice. The performance of each clinic/department in relation to each standard of quality of care is measured every 6 months and is published at the end of the year. It is documented that the programme improves the quality of care and it is now made available to all dermatologists in Denmark.

The National Board of Health has used the expertise of the National Allergy Research Centre in building a new homepage concerning Asthma and Allergy in School and information pamphlets.

Disease patterns

Contact allergy/allergic contact dermatitis are systemic and potentially chronic diseases. It is important to see such environmental diseases in a context with other diseases. The research so far indicates that exposure to reactive chemicals (contact allergens) can lead to a complex interference with the human body and with unpredictable consequences for general health. These investigations are ongoing but this type of knowledge is important to health care providers, when diagnosing, treating and informing about diseases as well as for regulators taking preventive actions.

3.3.2 The patients

Improved secondary and tertiary prevention is of high relevance to those who have the disease. Many of the studies performed by the Centre aims at secondary/tertiary prevention (see above). Also any regulatory actions taken (see 3.1) will be of benefit to patients with the disease.

The understanding of the drivers of disease, causative exposures and specific allergens and how to avoid them improves the information which can be given to the patient and the change of cure increases.

The empowerment programme, which is currently being developed in a PhD study, will provide individualised and systematic information to the patients concerning prevention/treatment of disease.

3.3.3 The public

Contact allergy, contact dermatitis and hand eczema are frequent in the general population. Therefore the results provided by the Centre are of relevance to the public (see 3.1. and 3.2).

The causative exposures are a part of most peoples every day life, so it is of interest to the public to know more about these and a benefit to be able to take evidence-based precaution, if relevant.

4. Dissemination of results

4.1 General dissemination

4.1.1. Homepages

4.1.1.1 www.videncenterforallergi.dk

The primary homepage is www.videncenterforallergi.dk with an English version containing the core information.

The target groups of the homepage are patients with contact allergy, consumers, and occupational groups at risk, health care professionals, authorities and industry.

At the homepage all new research results are presented in summary. All the PhD-theses are available. Basis information to the citizens/consumer about contact allergy is provided as well as information about prevention (advice to the sensitized individual) and legislation. The patient information folders made by The National Allergy Research Centre are made available here.

Short films are available about patch testing, nickel and perfume allergy for those who are not strong readers.

The results from the National surveillance system are published. This information is used by industry, regulatory bodies, scientists and citizens.

A new sub-section of the home page is targeting persons with occupational skin problems.

A service is available to the clinician; a special part of the home-page has been developed to provide the clinician with up-dated information on testing patients and the standard operating procedures developed by the Danish Contact Dermatitis Group, the guideline for diagnosis and treatment of hand eczema etc.



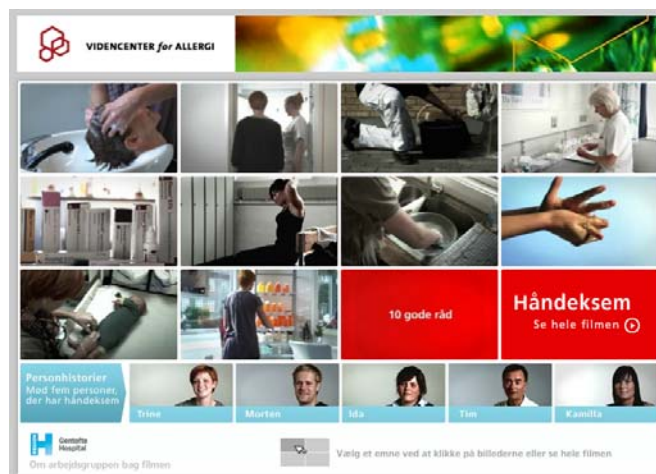
The new design of www.videncenterforallergi.dk

In 2010 videncenterforallergi.dk and allergyresearchcentre.com had in total 127.092 visitors, which represented an increase of 27 pct. compared to 2009, where 99.601 looked by the homepage. A visit is one or more pages shown.

In Januar 2011 www.videncenterforallergi.dk got a new design (see above).

4.1.1.2 www.handeksem.dk

At least 10 % of adult Danes suffer from hand eczema. An information site with a film about different aspects of hand eczema, prevention and treatment was produced and opened 1.april 2010. In 2010 it had about 5.000 visitors.



www.handeksem.dk

The film is also provided to the patients with hand eczema on a DVD, if they do not have computer access. In 2011 a film about atopic dermatitis will be produced.

4.1.1.3 www.kosmetikindhold.dk

This site contains information about ingredient labelling of cosmetics. The purpose is to educate the citizen/patient/consumer in the use of ingredient labelling. This site has been open since 2008.



www.kosmetikindhold.dk

4.1.2 Newsletters

Newletters concerning hot topics and new research results are produced 3-4 times á year. They are distributed to the subscribers (free). In case of information of special importance for dermatologists the newsletter is sent directly to all members of The Danish Dermatological Society.

4.1.3 Press

The National Allergy Research Centre is quoted around 100 times a year in the written press. In addition radio- and television-interviews are given.

4.1.4 Hot-lines

Citizens, patients, doctors and industry phones the National Allergy Research Centre. No specific statistic is made. The Research Centre for Hairdressers has a hotline, where about 250 hairdressers ask for advice each year.

4.2 *Dissimination of results to different target groups*

4.2.1 Consumers/citizens

Consumers and citizens are reached via the homepage, the newsletter, media and tefon hotlines. In addition The National allergy Research Centre provides the professional basis for campaigns run by Authorities eg. Astma Allergy in School by The National Board of Health and the campaign 'Skin Allergy – a partner for life' run twice by the National Environmental Protection Agency in 2007/2011. This campaign targets teen-agers and their use of hair dyes, perfumes and temporary tattoos. In 2011 The National Allergy Research Centre accompanied the Minister of Environment, when she visited a school as part of the campaign. The National Allergy Research Centre also assists in preparing relevant information materials issued by authorities e.g. on carreere guidance if you have eczema and allergy.

In case the citizens do not define themselves as patients and they experience hand eczema, information is provided via the homepages.

4.2.2 Patients

Patients are reached via the healthcare system but also through general communication means as the home pages. The general homepage contains all the new patient informations leaflets, which has been prepared, but also short films about patch testing, nickel and perfume allergy, including the patient perspective (testimonials) and a lot of written information concerning specific allergies, new research etc.

A special folder has been made on how to read ingredient labels on cosmetics and also a homepage with animations illustrating the practical point, and a quiz is available in case you want to practice. This information is targeted those with allergies to ingredients of cosmetics.

A homepage with information regarding hand eczema has been launched. It provides information on causes, diagnostics, treatment and prevention. In addition five persons with hand eczema tells their stories. The film is available at the homepage, but also provided as a DVD to those who do not have internet access. The film was also launched with posters to be used in the waiting room of the dermatologists attracting the attention of the patient to prevention.

The hand eczema film was recently evaluated by hand eczema patients. Most answered (80%) that it was a good film with the information they needed, communicated in an easy way. In total 20% reported that they had changed habits because of the film.

In the first years The National Allergy Research Centre had a column in the magazine of the Asthma-Allergy Foundation to provide information about contact allergies. Now it is done ad hoc.

In a new on-going PhD- study new ways of communication with patients concerning their allergy/eczema is being tested.

4.2.3 Healthcare professionals

Healthcare professionals are reached via the homepage which contains a sub-section with information to health care professionals. They are targeted by guidelines e.g. on hand eczema, sent out via the scientific society, standard operating procedures and the quality of care programme, which all dermatologists in Denmark are now offered to join.

Information to general practitioners is provided via papers in their own journal 'Månedskrift for lægegerning' about allergy to cosmetic ingredients, occupational eczema, hand eczema etc.

Educational seminars are offered every second year to personnel (mainly nurses) working in dermatology clinics.

The National Allergy Research Centre participated in a work shop in 2010 hosted by the National Board of Health concerning the need of health professionals of information regarding chemicals.

Scientific presentations are made at the meetings of The Danish Dermatological Society and eight small open seminars (1 hour duration) are made a year with presentation of topics of current relevance.

More than 150 teaching sessions have been made by staff of the National Allergy Research Centre, in most cases these target healthcare professional or health care professionals under education.

Scientific communications are made by the 245 peer-reviewed scientific papers and by more than 300 scientific presentations.

4.2.4 Authorities

Communication to national authorities is made by direct contact either personal or by letter.

The National Board of Health and The National Environmental Protection Agency are in the steering group and in this way they follow the work closely. In case of results of relevance to other Agencies meetings are established and the results discussed eg. contact has been made to the Board of Occupational Health concerning hand eczema in hairdressers.

In addition joint seminars are held every 2. year between the staffs of the National Allergy Research Centre, The National Board of Health, and the National Environmental Protection Agency. At these half-day seminars employees from all three organisations present their work and strategies for prevention of contact allergy and related diseases.

In case issues are of relevance for the European Commission letters are sent directly from the National Allergy Research Centre or via the relevant national authorities.

The staff of the National Allergy Research Centre is also represented in many expert groups, which facilitates communications e.g.:

- Professor Jeanne Duus Johansen is now chair of The Danish Cosmetic Council under the National Environmental Protection Agency; formerly it was Professor Torkil Menné.
- Professor Jeanne Duus Johansen has been ad hoc member of different Scientific Committee on Cosmetic Products/Consumer Safety advisory to the European Commission and formerly Professor Klaus Andersen was a permanent member.
- Professor Jeanne Duus Johansen and Professor Torkil Menné participate in the expert group on skin allergies under the European Commission.
- Dr. Suresh Rastogi has participated on behalf of The National Allergy Research Centre in The Expert group under Cen bt/wg 132 concerning establishment of methods for analysis of perfume allergens in cosmetics.
- Professor Jeanne Duus Johansen has participated in the WHO global work shop on Occupational Diseases and in several WHO/OECD-work shops on risk assessment and potency evaluation of contact allergens.

4.2.5 Interest organisations

The National Allergy Research Centre has close contact to non-governmental interest organisations (NGO) such as The Danish consumer council and patients' organisation The Asthma-Allergy Foundation. Regular meetings are held with the Asthma-allergy Foundation, who also has participated in the working group producing the hand eczema film. These two organisations are also invited to the small seminars held 8 times á year in The National Allergy Research Centre.

Once á year an information meeting is held for cosmetic industry in Denmark concerning news about contact allergy. It is held by their interest organisation The Danish Soap, Perfume and Toiletries Organisation (SPT) and The National Allergy Research Centre informs about their work every time.

The National Allergy Research Centre has close contact with different union e.g. the hairdressers union, Danish Metal Workers, Danish Painters and the corresponding employer unions. The unions and employers take active part in steering groups for projects, which are run by The National Allergy Research Centre.

4.0 Educational programme

The National Allergy Research Centre educates researchers for positions in the Healthcare system, Boards, Ministries and Industry. 22 PhD-students have been partly or fully associated to the Centre. Each PhD-student has his/hers own educational programme with a plan for courses at the University (200 hours each). In addition each has a work plan for their research activities.

Every two weeks the young researchers meet and basal subjects in allergy is being discussed from a prepared text (paper or book chapter). Further open seminars are held in the afternoon. At these seminars

senior researchers give lectures at subjects the PhD- students have been involved in choosing. In this forum the young researchers also give lectures and have the possibility to practice. The PhD students are encouraged to visit our research groups outside Denmark as part of their education eg. one student have been to visit to the Research Facilities of Unilever, UK, another has been three months at the Commission for training in risk assessment and regulatory affairs and one has visited the Department of Dermatology, San Francisco, University of California.

5.0 Awards

National Allergy Research Centre received together with the department of Dermato-allergology and The Copenhagen Studies on Asthma in Childhood the prize "Global Excellence – in health".

"Global Excellence – in health" is a prize given by the Region of Copenhagen to organisations of excellence within their field of health. The prize is given after application and evaluation by an international expert panel. The prize was given to The National Allergy Research Centre and partners for their leading role in treatment and research in allergic diseases.

6.0 Partners, collaborators and interfaces

National Allergy Research Centre has a broad network of national and international collaborators. Collaboration is made with more than 20 University department and research institutions within different specialties such as epidemiology, chemistry, immunology, genetics, microbiology, pharmacy etc. and a similar number of international high profiled institutions (lists can be provided).

Appendix I: Phd studies/students

Ongoing PhDs

Name of PhD student	Academic title	PhD thesis	Comments
Annette Mollerup	MSc Health, RN	Chronic hand eczema - self-management and prognosis	External funding from TrygFoundation
Ida Elisabeth Viller Tuxen	MD	PPD/hair dyes and effects on the immune system	
Josefine Bandier	MD	Irritant exposure on the skin - the role of the filaggrin system	
Katrine Ross-Hansen	MSc, Molecular biologist	Nickel allergy and fillagrin mutations.	
Maria Vølund Heisterberg	MD	Fragrance allergy, causes and impact on quality of life	
Susan Hovmand Lysdal	MSc, Public Health	Occupational hand eczema among hairdressers.	External funding from the Foundation for occupational health
Ulrik Fischer Friis	MSc, Engineering	Occupational hand eczema, systematic exposure assessment	External funding from the Foundation for occupational health

Completed PhDs

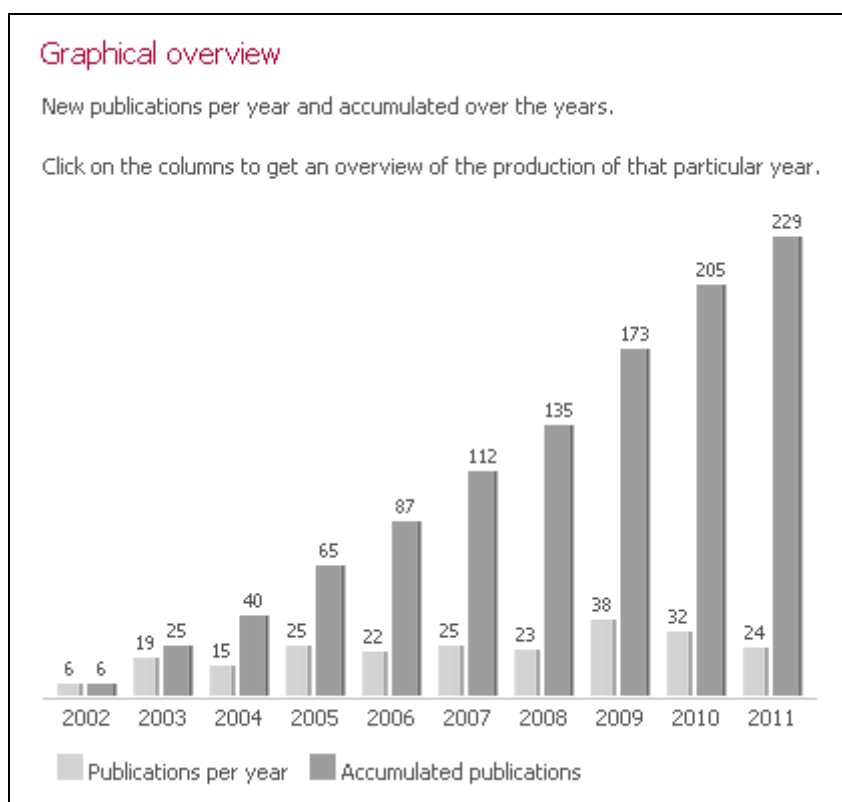
Name of PhD fellow	Academic title	PhD thesis	Comments
Anne Bregnhøj	MD	Prevention of occupational hand eczema among Danish hairdressing apprentices	External funding from the Foundation for Occupational Health
Michael Dyrgaard Lundov	MSc, Human Biology	Methylisothiazolinone: Contact Allergy and Antimicrobial Efficacy	Now senior researcher
Jakob Torp Madsen	MD	Microvesicle Formulations and Contact Allergy - Experimental Studies in In-Vitro, Mice and Man	Done at Odense University Hospital
Jacob Pontoppidan Thyssen	MD	The Prevalence and Risk Factors of Contact Allergy in the Adult General Population	Now senior researcher
Marianne Hald	MD	Hand eczema - severity and medical attendance in relation to prognosis	
Berit Christina Carlsen	MD	Patients with Multiple Contact Allergies: Population Characteristics and Clinical Presentation	Now senior researcher
Louise Arup Fischer	MD	Dose-response	

		relationships in contact allergy and studies on single and repeated exposures– perspectives for prevention	
Kåre Engkilde	MSc, Engineering	Allergic Contact Dermatitis and Autoimmune Diseases - Epidemiological and Experimental studies	Now senior researcher
Anne Lerbæk Sørensen	MD	Epidemiological and clinical studies on hand eczema in a population-based twin sample	
Heidi Søsted	MSc, Pharmaceutical Sciences	Allergic Contact Dermatitis to Hair Dye Ingredients	Now senior researcher
Malene Barré Pedersen	MSc, Human Biology	Chromium Allergy - Clinical and Cellular Studies	
Jesper Elberling	MD	Ocular and Respiratory Symptoms Elicited by Perfume and Fragrance Products	
Line Kynemund Pedersen	MD	Combined effects of allergens and irritants	
Charlotte Devantier Jensen	MSc, Human Biology	Contact allergy to the preservative methyl dibromoglutaronitrile	Odense University Hospital

Joint PhD projects (primarily at other institutions)

Name of PhD fellow	Academic title	PhD thesis	Comments
Nannie Bangsgaard	MD	Association between Contact allergy and Psoriasis	In cooperation with dept. of Dermato-Allergology, Gentofte Hospital
Liselotte Brydesholt Halkjær	MD	Predictors and Risk factors for Atopic Dermatitis in early Infancy	In cooperation with COPSAC
Rikke Skøt Cvetkovski	MD	Occupational Hand Eczema - a survey and identification of prognostic risk factors	In cooperation with The National Board of Occupational Health
Siri Heydorn	MD	Fragrance allergy and dermatitis on the hands	EU - FP5-project

Appendix 2: Publications



Overview of types of publications (2001-2011) (10 years)

	Original articles	Reviews	Case reports	Letters to the editor	Editorials
Printed publications	195	30	-	2	2
- English	192	26	-	2	2
- Other languages	3	4	-	0	0
Accepted for publication	13	1	-	2	0

Impact factor 2006-2010 (5 years)

	Number of articles	Total impact factor	Average impact factor
Peer-reviewed articles, all languages	140	492	3,5
Peer-reviewed original articles in English	117	439	3,7
Peer-reviewed original articles in English with first authorship	107	399	3,7
Peer-reviewed editorials, letters to the editor and reviews in English	18	53	2,9

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