

External evaluation of the National Allergy Research Centre

The evaluation concerns the period of Oct 2001 to Oct 2011 (10 years)

An overall evaluation of the concept and organisation of the Centre in relation to fulfilling the aims and performing the tasks

The main objectives of the National Allergy Research Centre (called “the Centre” in the following) are to determine the causes of cutaneous allergy to chemicals, establish limits for exposure to contact allergens which are safe for the majority of allergic individuals, and in general to determine methods for the prevention of eczema by various methods. These objectives now include (i) assessment of irritation as a co-factor for contact sensitisation and (ii) development of approaches for prevention of allergic contact dermatitis, including hand eczema. Such appreciation of the multi-factorial nature of contact dermatitis, which also includes genetic factors, is central to activities for primary and secondary prevention of this important and common group of diseases.

Structure

The Centre was established in collaboration between the Department of Dermatology, and the Department of Lung and Respiratory Medicine at Gentofte Hospital, Copenhagen University, and the Department of Dermatology at Odense University Hospital; and it is situated at Gentofte Hospital.

A very close working relationship exists with the clinical department of dermatology at Gentofte Hospital, of which the Centre is formally a part, although funding is separate. This relationship ensures that patients with skin diseases caused by exposure to substances present in cosmetic / personal care products, the household and the working environment provide a valid, up-to-date basis of research for the Centre. Conversely, this permits the best scientific evidence and research to be translated directly into patient care.

The Centre is efficiently organised, such that the structure consists of the director and researchers (PhD students and post-doctoral investigators) with a minimum of administrative support (secretary, IT specialist). This is only possible because the Centre is embedded in the general administration and support structure of a large teaching hospital (Gentofte).

A steering committee (consisting of clinicians, representatives from the National Environmental Protection Agency and National Board of Health) meets quarterly and agrees the yearly plan of work.

Scope of Research

Patient availability allows recruitment to complex dose-elicitation studies even to relatively rare allergens and the provision of biological samples for determination of genetic and biochemical profiles. Dose-elicitation studies, which offer a clinically relevant means of assessing an individual's threshold of elicitation to important allergens, known to cause significant disease in the population, are critical for risk assessment and management by authorities nationally and internationally.

Systematic / structured research (in interlinked projects), filling knowledge gaps pertinent to primary or secondary prevention of contact allergy, is a particular characteristic of the Centre.

Comprehensive epidemiological studies (e.g., questionnaire-based), with or without intervention, have become an important tool effectively performed by the Centre. Moreover, several contributions to exposure analysis in terms of methodology and its application have provided important evidence on a number of important triggers of contact allergy, including

- nickel: validation of dimethylglyoxime test;
- cobalt: development of a spot test;
- chromium: measurement in leather
- co-operation on the quantitative analysis of fragrance and other allergens in consumer products.

The Centre has no analytic laboratory of its own.

Qualitative research has hitherto focused on the effectiveness of self-management of patients with chronic hand eczema following specialist nurse support.

The Centre is a hub for activities related to cutaneous allergy nationwide. This is primarily achieved by the inclusion not only of hospital departments, but also of clinic-based data from dermatologists in private practice. Representation for the whole of Denmark is achieved by the geographical distribution of participating hospital departments and dermatologists in private practice throughout the country, see below. Moreover, the overall quality is high as specific education is provided to contributing clinicians (see below).

A central database, which includes data generated by the clinical department of dermatology at Gentofte, and from the geographically representative clinics throughout Denmark, allows monitoring of the prevalence of contact allergy, which is critical for the identification of emerging allergens, evaluation of efficacy of strategies for reducing exposure to allergens, and for comparison with other European countries.

On a European level, the Centre is integrated into extensive scientific networks furthering primary prevention of contact allergy by identifying new and emerging risks, or persisting problems. In this context, the variations of exposures and disease profiles nationally and within Europe can be evaluated and scientifically exploited.

The value of the surveillance systems in relation to monitoring contact allergy and improving quality of the medical services

The Centre has established a unique database collecting information on patients with suspected contact allergies throughout Denmark.

The surveillance system

Only a part of diagnostic patch testing is undertaken within the hospital setting in Denmark. Nevertheless, it is estimated that the database now captures data on approximately 20-25% of the patients investigated by inclusion of patients seen by private dermatologists throughout the country and by 3 major hospital departments. This coverage is considered remarkable, compared with other surveillance systems.

Currently, data of some 33 000 patients have been collected; aggregated results are published annually on the Centre website, in addition to scientific publications regarding trends and subgroup analyses. For long-term analyses, a database of patients investigated at the Gentofte Hospital, reaching back to 1980, is available in addition. This database is integrated into the European Surveillance System on Contact Allergy (ESSCA) since 2002; this allows the prevalence of contact allergy to specific allergens in Denmark to be compared to other regions in Europe.

Assurance of the quality of the surveillance data collected from centres outside Gentofte Hospital is by training in patch test readings and assessment of relevance for the clinicians (dermatologists and nurses) by the senior and experienced clinical members of staff.

Exposure surveillance in terms of nickel and cobalt release from consumer items has been used to evaluate the impact that regulatory measures have had on consumer safety, the need for improved provision and the need for additional provisions, respectively.

The use of surveillance results

The value for society of surveillance based on these databases lies in the identification of time trends in contact allergy, and specifically affected subgroups (health reporting), which impact costs to healthcare, ability to work and quality of life. These data provide an evidence-based starting point for preventive intervention by national and European regulatory measures to protect the citizen (consumers and workers).

The surveillance system being patient-based provides the data necessary to protect the population. Thus, the effectiveness of intervention targeted at the population (general or specific groups, including children) can be monitored based on this patient data.

The continual evaluation of patch test results also allows for the constant adaptation of the baseline series used for diagnostic patch test investigations, which is the foremost diagnostic screening tool for contact allergy. The elimination and inclusion of vanishing and emerging allergens, respectively, improves the diagnostic effectiveness of the test. This provides a valuable feed-back to the providers of data, but also to dermatologists performing patch testing in the whole of Denmark.

Quantity and quality of the knowledge building including scientific production in relation to the aims of the Centre and resources allocated

The data from the surveillance is published annually on the Centre's website, in addition to scientific reports.

The database provides a means of determining whether there is any regional or temporal variation in contact allergy within Denmark. This allows strategies to be developed for reducing putative causal exposures. Beyond Denmark, the Centre provides scientific evidence required by risk managers to reduce and eliminate exposure to problematic allergens. Much of this is directed to DG SANCO (Consumer Safety and Health Protection) of the European Commission. Examples of the use include demonstration of trends in nickel allergy, hair dye allergy (p-phenylenediamine), methyl dibromo glutaronitrile and fragrance chemicals. Such data has been instrumental in affecting Europe-wide regulatory activities.

Beyond the use of clinical data, population-based epidemiological studies have been performed and participated in, respectively:

- Questionnaire-based cohort studies have been used to measure the impact that hand dermatitis has on the ability of hairdressers to work and effects on quality of life.
- Patch test results, demographic and clinical characteristics and biological samples have been collected and analysed in the context of the Glostrup Allergy study (3rd repetition), providing unique insights into the role of the latter factors in contact sensitisation, and, moreover, a point of reference for sensitisation prevalences observed clinically.

Development of protocols and guidelines, respectively, for latex allergy and classification and management of hand eczema in co-operation with the Danish Contact Dermatitis Group. Information on skin care / protection to patients. More than 30 new patient information sheets have been produced and are available on the Centre's web site.

Eight standards have been developed for investigation of patients eg., investigation of hand eczema.

In the period 2001-2011, 22 researchers have been/are working at the Centre. This has resulted in 14 finished PhD theses, and 8 on-going PhD projects. Two of these PhD studies were undertaken at the Department of Dermatology, Odense University Hospital. In addition to the above, the Centre has been involved in a further 4 PhD studies, which were primarily performed elsewhere.

In total, 229 scientific papers have been published by the Centre in the period 2001 to July 2011, with a further 16 accepted for publication. The resulting average impact factor is 3.7 for the 117 original peer-review articles published in the period 2006-2010 in the English language and also for those in which first authorship is from a Centre member. This impact factor is to be considered high in the field of dermatology, allergy and occupational and environmental medicine.

Lectures at various scientific meetings, organisation of sessions at such meetings, and presentation to and involvement in governmental and risk assessment/management activities ensures that the quality data from the Centre's activities influences scientific thought and the protection of the citizen.

The relevance and impact of the results of the investigations performed in relation to: regulations and potential preventive effects concerning use of chemicals with sensitizing potential as well as the usability for the health care system, the patients and the public

Examples of the impact of scientific results of the Centre on regulation include those directed at certain problematic substances, and more general considerations.

Specific problematic substances

Nickel: This is the commonest contact allergen and the Centre has demonstrated a 50% reduction in allergy in young females, probably due to the Nickel Regulation. However, data from the Centre showed that important sources of nickel exposure were not affected by the Directive. An example is the presence in mobile (cell) phones, which are now included. The CEN standard for controlling compliance with the Directive (EN 1811) was recently revised and the permitted excess nickel release was reduced. Studies from the Centre contributed to this improvement. The value of reduction in nickel allergy over 20 years has been estimated (COWI consult) 9.7 billion Dkr to the Danish economy.

Methyldibromo glutaronitrile: Data collected by the Centre showed a marked rise of contact allergy to this preservative. Studies showed thresholds for the elicitation of allergic reactions in sensitised individuals, the cumulative effects of repeated exposures in relation to elicitation reactions and the influence of surfactants. The epidemiological data and response studies provided the scientific rationale used by the Scientific Committee on Consumer Products at DG Sanco, European Commission for the removal of the preservative from cosmetic products in Europe.

p-Phenylenediamine (PPD): This chemical, a main constituent of hair dyes and also a marker for hair dye allergy to related compounds, is representative of a group of chemicals used in permanent hair dyes and which may cause severe allergic reactions in consumers and be responsible for occupational disease in hairdressers. Data from the Centre has shown the extent and severity of allergy to this chemical and thresholds for elicitation. This information is currently being used to influence measures to control consumer exposures to this group of chemicals within Europe.

Fragrances: The development of 'fragrance mix II', which is now present in the European baseline series for routine diagnostic patch testing, by the Centre and collaborators has significantly improved the diagnostic usefulness of the screening patch test for fragrance contact allergy. Particular work on the fragrance chemical hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) has demonstrated the importance of this substance as an allergen, the relevance of anatomical sites of exposure and thresholds for elicitation responses. This important scientific work was incorporated within the Opinion of the European Commission's scientific advisory committee when it considered the safety of the substance and recommended a dramatic reduction in exposure limits. Similar work on (chloro-) atranol in *Evernia prunastri* has been used for similar purposes. The allergenic role of oxidation products of fragrance chemicals is presently being discussed at the European level.

Alerts have been raised based on the Centre results regarding the emergence of the preservative methylisothiazolinone as an important allergen for the consumer and occupationally. The Danish authorities have requested a review by the European Commission.

General aspects

Dose-elicitation studies have had particularly high impact as they cannot be performed outside the clinical setting, are difficult to perform and require skill to undertake. These studies, performed on a range of chemical types, show clear dose response effects that are influencing strategies to protect the consumer from the elicitation of allergic reactions (secondary prevention) and, by extension, even the prevention of induction of contact allergy (primary prevention).

The Centre uses patient-centred research, which has the effect of being able to directly affect patient care. A typical example is that of methyl dibromo glutaronitrile where the epidemiology showed a problem and experiments on patients demonstrated dose-response phenomena; the result was the elimination of the preservative from cosmetic products. Epidemiology now shows a dramatic reduction of contact allergy to this preservative in Europe; relevant contact allergy has been 'eliminated'. This is an elegant demonstration of evidence-based prevention: from epidemiology to laboratory to epidemiology.

Research from the Centre and from other groups has indicated that filaggrin mutations may affect an individual's susceptibility to contact allergy. All patients with

hand eczema seen at Gentofte Hospital are being offered to have their filaggrin status established.

The ability of the Centre to disseminate information to consumers, patients, health care professionals, authorities, industry and society in general

The competence of the Centre in being able to influence consumer protection by providing high worth scientific information to regulatory authorities has been well demonstrated above.

Involvement of Centre members in risk assessment and risk management activities at national and European level ensures that data generated by the Centre can directly influence discussions affecting the primary and secondary prevention of contact allergy. Dialogue with and seminars for national authorities, stakeholders and EU institutions also affect this.

The numerous, high quality research papers and reviews in the peer-reviewed scientific literature causes the dissemination of such material to the wider scientific community and industry (see above).

Educational programmes for clinicians and the development of guidelines improves quality of care for the patient in Denmark.

Educational programmes for hairdressing apprentices have been shown to reduce the incidence of hand eczema significantly and will now be implemented nationwide.

Increased awareness of the public regarding risks linked to e.g., hair dyes, fragrance products and nickel is provided by patient information material disseminated via the website or other media (films, leaflets, booklets), press releases, and contributing to patient self-help groups. The Centre website provides a focus.

A hotline, primarily intended for advice of hairdressers in relation to occupational dermatitis in the context of a project (Research Centre for Hairdressers and Beauticians) being run in parallel at the Centre, is used also by consumers and health care professionals and occupational hygienists from government.

Some consumers have difficulty in understanding the information provided on ingredient labels and which is intended to help them avoid substances to which they are allergic. The Centre provides instructions on reading ingredient labelling for these consumers.

The value of the educational programme of the Centre for young researchers

The Centre offers structured PhD programmes with classes in relevant science subjects, statistical methods and the scientific approaches to research. Recruitment is via advertisements for specific projects. Successful applicants are allocated to projects according to their background. Supervision is from Centre senior staff and relevant external experts, when necessary.

Part of the programme can be spent at other institutions, as appropriate. As an example, one student spent several months at the European Commission gaining experience in risk assessment. Collaboration with external facilities is encouraged to provide the resources and expertise to facilitate studies.

The particular value for PhD students at the Centre is the close integration of research work with clinical work (patch test readings, patient assessment, and clinical epidemiology).

The quality of the programme is illustrated by the high number of completed studies and the volume of scientific publications.

Following a successful PhD programme, clinicians return to clinical practice and use their experience as an integral and essential component of their practice of medicine for the benefit of patients and career progression.

Non-clinicians often continue research at the Centre as post-doctoral researchers for a period before moving to other academic institutions. Some find jobs at other institutions or with industry. Also some clinicians continue with post-doctoral studies at the Centre, often in parallel with further dermatological training. Those who continue at the Centre after PhD completion have to apply for funding to support their jobs. This may require about 20% of their working time.

If possible, benchmarking to other similar international Centres concerning productivity and impact

The concept of the Centre is unique worldwide. Parts of the scope of work are undertaken at other institutions internationally, but nowhere is there the large-scale, systematic and broad integration of activities and focus on clinically relevant allergy prevention.

In Germany, the Information Network of Departments of Dermatology (IVDK) collects data from patch tested patients. It is a multicentre project with large collection of routine patch test data, but only occasional in-depth research.

In Sweden, the Occupational and Environmental Dermatology Unit in Lund University in close collaboration with the clinical department in Malmö is able to undertake chemical analytic procedures relevant to the identification of allergens, but does not have the resources for the clinical studies, or data collection of the type undertaken at the Centre.

The Unit of Occupational and Environmental Dermatology at Karolinska Institutet in Stockholm works in close collaboration with the outpatient unit at Karolinska University Hospital. The tasks include research, risk assessment, dissemination of information, and examination of occupational dermatology patients. Methods for assessment of skin exposure to chemicals are developed and used. It does not have the resources for the clinical studies, or data collection of the type undertaken at the Centre.

The Centre for Allergy Research at Karolinska Institutet in Stockholm is a research network founded in 1999, with the aim to support and develop allergy research. Asthma is the main focus, atopic eczema has been addressed to minor extent, but not skin allergy to chemicals (contact allergy). Dissemination of information as undertaken at the Centre is not performed.

An evaluation of the sources of financing. Are all possible sources of financing being exploited? Is it possible to finance the centre fully or partially in a different way e.g. by partnerships with industry?

One of the internationally highly acknowledged characteristics of the NAC research is its independence from commercial interests. This must be maintained.

Since 2001, the Centre has received an annual grant of 5 million Dkr from state funds. As there has been no increase in the value of the grant over 10 years, in real terms there has been a grant reduction. Between 2005-2009, the grant was awarded jointly by the National Board of Health and the National Environmental Protection Agency. Since 2010 it has been from the National Environmental Protection Agency alone.

- From 2002-2004 additional external funding amounted to 425 000 – 1.7 million Dkr and from 2005-2010 between 2.0 – 3.5 million Dkr.

Separately, the research group working on the health of hairdressers has received funding of 2.0 – 2.5 million Dkr per annum from the hairdressers' trade union and research foundations. For the extension of this type of occupationally relevant work, funding by such bodies seems highly desirable.

There is continued effort to obtain funding elsewhere with at least 2 major and up to 15 minor applications each year. These applications have significant impact on working time, and, therefore, research time.

There are continued energetic efforts to put contact allergy on the EU agenda (DG Research, DG Sanco) and for it to be properly funded on this level.

Added value is obtained from:

- Unpaid manpower of senior clinicians and researchers, working as research leaders.
- Networking with other institutions shares or eliminates costs of large scale epidemiological studies and chemical analyses.

An overall assessment of the activities and the impact of the Centre in relation to prevention of allergy to chemical substances. The evaluation should take into account the resources allocated

The Centre has been instrumental in the collection of epidemiological data, exposure assessments and dose-response determinations that have been central and critical for the identification, reduction and elimination of contact allergy to problematic allergenic substances from the Danish and European markets. The interplay between epidemiological evidence and investigation of affected individuals resulting in strategies for the primary and secondary prevention of contact allergy and dermatitis is a unique facet of the Centre. As such, it must be seen as a Centre of Excellence, not only within Denmark but also in the European arena. It is an exceptional facility that continues to produce measurable benefit to society in terms of disease reduction and improvements to quality of life and ability for individuals to pursue their desired work.

Education of clinicians and patients benefits investigation and management of allergic contact dermatitis. Comprehensive information via various media and directed to clinicians, patients and risk managers encourages best practices for protection and prevention.

All of the above has been achieved by rather small grants from state resources in relation to the quality of the work that continues to be undertaken and its impact on disease prevention and quality of life. This is a remarkable achievement!

Conclusion and recommendations regarding the value of continuation of the work

The work of the Centre has been demonstrated to be of high importance for the reduction of contact allergy in Denmark and Europe. No other facility undertakes the patient-focused integrated research approach that has been shown to be so effective. It is critical for society (in Denmark and in Europe) that this important work continues. Independence from industry is seen as being essential for credibility.

Hitherto, much of the work of the Centre has been focused on the consumer; this should continue. However, additional investigation of work-related exposures is suggested; this will benefit disease prevention and management options. It is recommended that consideration of the global exposure of the citizen to allergens and irritants be given. A mandate to broaden the scope of the activities of the Centre will be required for this.

Funding from national state/public resources should continue and, preferably to a higher amount in view of the enormous importance and cost benefits of the work.

A short summary

The main objectives of the National Allergy Research Centre are to determine the causes of cutaneous allergy to chemicals, establish limits for exposure to contact allergens which are safe for the majority of allergic individuals, and in general to determine methods for the prevention of eczema by various methods. Such appreciation of the multi-factorial nature of contact dermatitis, which also includes genetic factors, is central to activities for prevention of this important and common group of diseases.

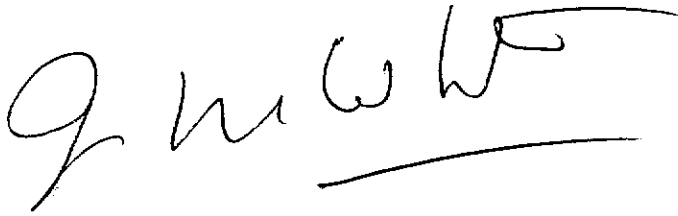
The unique organisational structure of the Centre and patient-focussed activity has permitted complex dose-elicitation studies to be undertaken with structured research (in interlinked projects), comprehensive epidemiological studies and exposure analysis providing important evidence on triggers of contact allergy. Monitoring of allergens is provided by a database and extensive scientific networks.

Education of clinicians, with consequent improvements to healthcare, has been established by the development of protocols and guidelines. Much information is available to the consumer via the Centre's published materials and web pages.

Successful training of researchers is illustrated by the large number of completed and ongoing PhD studies and the volume of peer-reviewed publications produced in the last 10 years.

The above has been achieved with relatively little direct funding. Funding from national state/public resources should continue and, preferably to a higher amount in view of the enormous importance and cost benefits of the work. Independence from funding from industry is considered important.

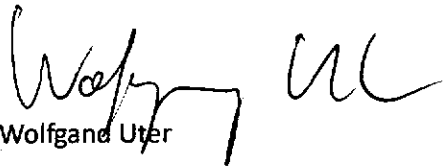
Much of the work of the Centre has been focused on the consumer; this should continue. However, additional investigation of work-related exposures is suggested and consideration of the global exposure of the citizen to allergens and irritants be given. A mandate to broaden the scope of the activities of the Centre will be required for this.

A handwritten signature in black ink, appearing to read 'Ian R. White', with a horizontal line underneath.

Ian R. White

A handwritten signature in black ink, appearing to read 'Carola Lidén'.

Carola Lidén

A handwritten signature in black ink, appearing to read 'Wolfgang Uter'.

Wolfgang Uter

Date: 20/9/14