(Contract SANCO/2008/C7/015)

REPORT

The collection and evaluation of data on incidence and severity of skin and respiratory allergy related to exposure of chemicals from non-food sources.

Flemish Institute for Technological Research (VITO)
Drs. Karolien Bloemen
Drs. Sandra Verstraelen
Prof. Dr. Greet Schoeters

Catholic University Leuven (KUL)
Dr. Barbara Legiest
Prof. Dr. Ben Nemery

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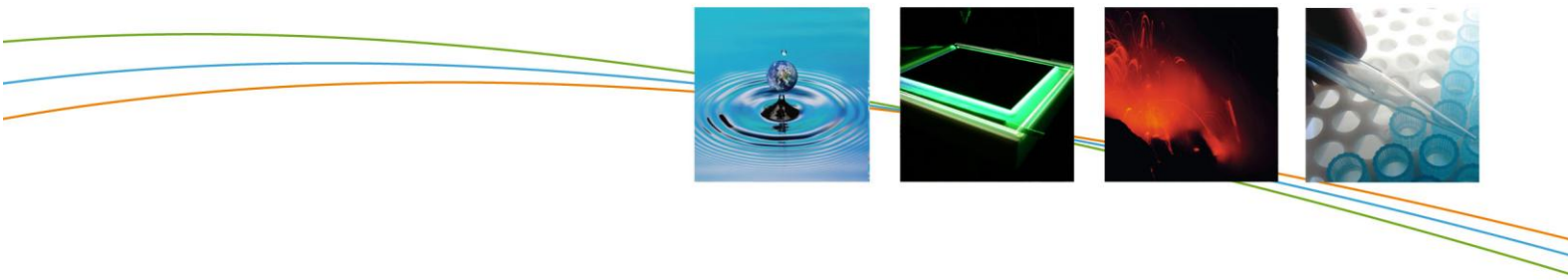

VITO NV
Boeretang 200 – 2400 MOL – BELGIUM
Tel. + 32 14 33 55 11 – Fax + 32 14 33 55 99
vito@vito.be – www.vito.be

VAT BE-0244.195.916 RPR (Turnhout)
Bank 435-4508191-02 KBC (Brussel)
BE32 4354 5081 9102 (IBAN) KREDBEBB (BIC)

DISTRIBUTION LIST

Dr. Takis Daskaleros
European Commission
Health & Consumer Protection Directorate-General
Directorate C – Public Health and Risk Assessment
Unit C – Risk Assessment

Prof. Dr. Greet Schoeters
VITO NV

Prof. Dr. Ben Nemery
KUL

EXECUTIVE SUMMARY

The objective of this work is to set the knowlegde basis for a systematic approach to the issue of allergies by collecting and evaluating incidence data in relation to information on chemical exposures and providing a first assessment of the issue.

In the first task, respiratory and skin sensitizers were selected based on European reports and reviews. Literature search included peer-reviewed European publications identified from PubMed, ScienceDirect and Google Scolar, relevant books, and reports from the years 1960-2008. Literature search for skin sensitizers was done for 252 chemicals. Human data were found and collected for 76 of these chemicals (Annex I). About 900 references were checked. Literature search for respiratory sensitizers was done for 152 chemicals. Most of them are discussed categorized in chemical classes. Additionally, relevant surveillance schemes were studied. Furthermore, 44 organizations were contacted for available epidemiological data or reports concerning incidence data or cases of human exposure to specific chemicals, related to respiratory allergy (asthma) or allergic contact dermatitis. Half of them responded, of which 13 were able to share information. Seven of those were contacted again, because they mentioned to have access to a patient database. Unfortunately, these valuable data could not be included in this report since they are not freely available. The compound information collected by this project is presented electronically in an Excel file (available in the electronical Annex V). This database was used to facilitate further evaluation of the data in a weight-of-evidence approach and by meta analysis. The file including the skin and respiratory sensitizers contains respectively 2715 and 341 records.

An initial literature search was performed on general trends in incidence of asthma and allergic contact dermatitis in Europe. These general trends are reported in chapter 4.

A weight-of-evidence approach was used to evaluate the strength of knowledge for a chemical to be a sensitiser for skin or airways. Information on number of cases, diagnostic methods, and clarity of the data were obtained from original publications and a quality score for the information was inserted in our database. In a second step, information on individual chemicals (skin sensitizers) or chemical classes (respiratory sensitizers) was collected. R phrases, LLNA data, availability of human data, and scores of the individual publications are taken into account. A higher score means that there is more evidence that the compounds or chemical classes are skin or respiratory sensitizers (Annex I).

Prevalence data were checked for completeness. A meta analysis was used to describe and evaluate regional differences, time trends, and the effect of regulatory actions (Annex VI). Data gaps are discussed.

The most frequent skin sensitizers in the general population are nickel sulfate, fragrances, and cobalt chloride. In occupational groups, especially hairdressers and dentists suffer from allergic contact dermatitis. Isocyanates are the most important respiratory sensitizers.

It is difficult to evaluate the severity of skin allergies based on the data available. Data on potency is especially obtained from local lymph node assay (LLNA) data. Further mechanistic research (both *in vivo* and/or *in vitro*) is required for hazard assessment. More information on exposure to mixtures is needed. Some chemicals are reported to be both skin and respiratory sensitizers, however, the respective mechanisms are largely unknown. More efforts are needed for risk assessment: specific data for establishing dose-response relations and for identifying risk factors are lacking.

Regulatory actions (restricted use/banning) have been shown effective (e.g. nickel sulfate and MCI/MI). New chemicals should be tested before introduction on the market. Exposure and exposure response should be monitored in the population. Preventive actions, appropriate training, education, and correct information are important to increase the awareness of the general population. Data obtained from LLNA, R phrases, and human data are not always in agreement. Correct labelling of products is however important.

Various European countries report data of allergic contact dermatitis, especially in Germany and the UK. It would be valuable to coordinate these efforts through a European network. Further actions to harmonize collection of European data on surveillance are needed. Comparison of human data is often difficult due to different protocols and differences in patch test interpretation. Potential causal factors are not well recorded. Various surveillance schemes for occupational asthma were described in the report. Harmonization of these various systems may be valuable. In addition, harmonization of the definitions and classification of asthma diagnosis and job description and of the measurement metrics, used in the reporting, should be enhanced

Time trends are reported, for individual compounds if data are available (Annex VI). However, care must be taken to compare data from different centers. Increasing time trends were found for para-phenylenediamine (PPD), isoeugenol, hydroquinone, and imidazolidinylurea. Decreasing time trends were observed for colophony, formaldehyde, MCI/MI, and tetramethyl thiuram disulfide. Time trends should be monitored, preferably in various centers across Europe. This will allow to take targeted actions. Additionally, the standard patch test series needs to be adapted regularly to the actual set of allergens. For respiratory sensitizers, less information for each chemical is available, which makes evaluation of time trends difficult.

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CHAPTER 1 SCOPE OF THE CONTRACT

This initiative follows a number of reports in the public domain and indications from scientific experts that show that the incidence of respiratory and skin allergies is increasing in the European Union (EU). The objective of the work is to set the knowledge basis for a systematic approach to the issue of allergies caused by exposure of humans to chemical substances by collecting and evaluating incidence data and providing a first assessment of this.

The results of the study will be used to identify methodological issues that will need to be addressed by the European Commission Scientific Committees. It will also help to orientate possible policy discussions in this area.

TASK 1 Search, collect, and report in a concise manner available (un)published epidemiological evidence on the incidence of respiratory (asthma) and skin (contact dermatitis) allergy in the EU that is related to exposure of humans to chemical substances. To the extent possible, exposure to chemicals from all possible non-food sources (consumer products, environment, occupational setting, leisure, sports, and professional activities) should be considered. Evidence should be reported in such a way that would allow both the evaluation for a particular exposure/use situation and comparisons.

The contractor should make use of all available information sources, not limited to web pages. For example:

- Scientific journals and reports
- Published epidemiological studies from hospitals
- National allergy/asthma centres
- Poison centre information and published reports
- International organisations (e.g. WHO and FAO) activity reports

Information from third countries may be used in a complementary and comparative manner in relation to the data/information gathered at the EU-level, but may not be used as a surrogate for missing EU data. Evidently all information used should be properly referenced in the study report.

TASK 2 Critically evaluate the evidence in order to:

- Establish cause and effects relationships between particular exposure situations to chemicals and clinically manifested skin and/or respiratory allergies;
- Where appropriate, comment on the severity of the clinical picture;
- If possible, categorise chemicals and exposure situations in terms of severity in the context of incidence (frequency) and morbidity (severity);
- If possible, include a critical evaluation of the possible effect (mitigating or potentiating or no effect) of human behaviour (voluntary versus involuntary activities, knowledge of the risk for allergy via product/activity risk communications activities (labelling, explanations, sign posting, etc), use patterns or particular products and services on the incidence and disease pattern of skin and/or respiratory allergies in the EU.

TASK 3 Identify data gaps and recommend additional data gathering and research activities (epidemiology, primary research, risk assessment (hazard and/or exposure) methodology development, surveillance, and possibly other) that should be undertaken in the EU in order to address them.

This should include among others information on the need to further study particular products, product uses, or exposure situations/scenarios, identify the skin/respiratory sensitization potential of chemicals in experiments, develop and validate new or optimise existing risk assessment methodologies for skin/respiratory sensitizers, conduct epidemiological studies, etc.

CHAPTER 2 TERMS AND DEFINITIONS

Incidence is a measurement of the number of new individuals who contract a disease during a particular period of time. Incidence conveys information about the risk of contracting the disease.

Prevalence is a measurement of all individuals affected by the disease within a particular period of time. Prevalence indicates how widespread the disease is. Incidence and prevalence are often mixed up. Incidence data are rather scarce, while prevalence data are more available. Therefore, we will also use available prevalence data in this project.

Potency is related to the amount of chemical which is able to induce an allergic response of a given severity. This is often confused with relative prevalence. E.g. nickel is a common cause of allergic contact dermatitis (ACD) (prevalence). However, the evidence is that nickel is only a relatively weak allergen (potency).

A **Sensitizer** is an agent that is able to cause an allergic response in susceptible individuals. The consequence of this is that following subsequent exposure via the skin the characteristic adverse health effects of ACD or atopic dermatitis may be provoked. After inhalation exposure, adverse health effects include asthma (and related respiratory symptoms such as rhinitis) or extrinsic allergic alveolitis [1].

The local lymph node assay (**LLNA**) is a mechanistically based assay carried out in mice. The test is accepted for regulatory purposes (Organisation for Economic Co-operation and Development; OECD). It monitors the induced proliferative response of auricular lymphocytes in the draining lymph nodes during sensitization. The proliferative response is common to both skin and respiratory sensitizers, although the resultant T cell populations differ.

Allergic contact dermatitis is the clinical expression of contact allergy. Among the key steps required for a chemical to induce sensitization via skin contact are gaining access to the viable epidermis, protein binding, metabolic activation (if required), internalization and processing by Langerhans cells (LC), transport of antigen by LC to draining lymph nodes, and presentation to and recognition by T lymphocytes [1]. This induction process to sensitization makes that the subject is now allergic. Contrary to other allergic diseases, e.g. asthma or hay-fever, ACD is cell-mediated (type IV allergy) and not mediated by circulating antibodies (type I allergy) [2]. Contact allergy is demonstrated through **patch testing**: amounts of standardized and/or suspected allergens are applied with an adhesive on the skin of the back for 48 hours. A positive test shows up as a miniature eczema during the following few days [2]. These test are carried out to see if an individual is sensitized to a specific agent, and not to determine whether the agent can cause sensitization [1]. In this report, the general patch-tested population, which are those people with ACD complaints that see a dermatologist to perform patch tests, is often discussed.

Asthma is a complex clinical disease characterized by airway obstruction, airway inflammation, and airway hyperresponsiveness (AHR) to a variety of stimuli. Inhaled allergens are taken up and processed by antigen presenting cells (APC). The processed

allergen is presented to allergen-specific T and B cells. Activation of T helper (Th) cells by APC leads to the production of cytokines that regulate the isotype switch of B cells in their production of immunoglobulin (Ig)E. Once synthesized, IgE binds to the high-affinity IgE receptors that are present especially on mast cells. After re-exposure, allergens cross-link to mast cell-bound specific IgE, resulting in degranulation of mast cells and the early-phase asthmatic reaction (EAR), which is characterized by constriction of airway smooth muscle (ASM) cells, vascular leakage, mucus production, enhanced AHR, and recruitment of inflammatory cells. This EAR is followed by the late-phase asthmatic reaction, which is characterized by excessive inflammation of the airways, resulting in structural changes, including airway wall thickening, subepithelial fibrosis, goblet cell hyperplasia, myofibroblast hyperplasia, ASM cell hyperplasia and hypertrophy, and epithelial hypertrophy. This is collectively known as airway remodeling [4, 5].

Occupational asthma (OA) can be defined as asthma that is caused specifically by exposure to an agent present at work. The important notion in this definition is the phrase "caused specifically". This implies that when asthma is not really caused, but only aggravated by work, this should not be considered as OA. Certainly, pre-existing asthma does not automatically exclude the possibility of OA. There are different categories of OA depending on pathogenesis. The first category, which has also been studied most extensively, includes OA that is caused by allergic sensitisation to a specific agent present in the workplace also called OA with latency. The second category includes asthma that is not due to allergic sensitisation to a specific agent, but to exposure to irritants, such as chlorine, sulphur dioxide or acid fumes, hence the term irritant-induced asthma. Mostly this asthma develops after a single inhalation incident; the condition is commonly called reactive airways dysfunction syndrome (RADS). However, irritant-induced asthma may also be caused by repeated exposures to high levels of inhaled irritants. In such cases there is generally a period during which the worker does not yet have prominent respiratory symptoms. A possible third category of OA is the asthma-like syndrome, which occurs in workers who are exposed to high levels of organic (vegetable) dusts, generally in agro-industry. Irritant-induced asthma and the asthma-like syndrome will not be covered further in this project. The causes of immunologically mediated OA are commonly divided into agents with high-molecular weight (HMW) and agents with low-molecular weight (LMW; < 1500 Da). In this project only respiratory diseases due to the LMW agents will be highlighted.

CHAPTER 3 TASK 1: COLLECTION AND REPORTING OF THE DATA

Various publications state that the prevalence of respiratory and skin allergy is increasing in the EU [6-8]. Exposure to specific chemicals, such as in consumer products, environmental and occupational settings, leisure, and sports may contribute to the increased prevalence of allergy. The objective of this work is to collect and evaluate European incidence and prevalence data, and to provide a first assessment of the relative contribution of exposure to chemicals as a risk factor to the increasing prevalence of allergy.

3.1 Selection of the chemicals based on literature reports

Skin sensitizers
Information on response to skin sensitizers is widely available mainly from patients, from workers, but also from the general population. Skin sensitizing chemicals to be further considered were selected based on the Technical Report No 77 of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), which lists both positive and negative test chemicals for skin and respiratory sensitization [9], and on publications concerning *in vivo* (e.g. LLNA) and *in vitro* test systems for skin sensitization [10-12]. For all these chemicals, a literature search was performed and data from a variety of sources were considered: consumer experience and comments, preferably followed up by professionals (e.g. diagnostic patch tests); diagnostic clinical studies (e.g. patch tests and repeated open application tests); records of workers' experience, and exposure studies including medical surveillance; case reports in the general scientific and medical literature; epidemiological studies. Also issues from 2008 of the journal Contact Dermatitis were checked for relevant articles on chemical sensitization.

Respiratory sensitizers
In a first step, well known respiratory sensitizers were selected from the Technical Report No 77 of ECETOC [9], from *in vitro* studies, *in vivo* studies, and human data. Human data on respiratory reactions were obtained from a variety of sources: records of workers' experience, case reports in the general scientific and medical literature, accidents, exposure studies, epidemiological studies, and results of medical surveillance schemes. The diagnosis of asthma is based on lung function measurements, bronchial provocation tests, skin prick tests, and measurements of specific IgE serum levels. Most publications in the open literature about the epidemiology of asthma are based on information of occupational respiratory diseases. These data can be considered as the most important source. The interest for OA is needed because the fraction of adult-onset asthma that is attributable to work exposure is estimated on approximately 9-15% [13-15]. Hence, the initial list has been extended based on a previous literature overview described in the book "Asthma in the workplace" [16].

3.2 Data collection via internet search and literature reports

The literature search for further information of the selected chemicals included peer-reviewed European publications identified from PubMed, ScienceDirect, and Google Scholar searches, as well as relevant books, all published between 1960 until December 2008. Search terms included the name of the compound (all synonyms used) combined with either of the following terms: allergy, (allergic contact) dermatitis, incidence, sensitization, patch test, and asthma. The PubMed "related articles" function was used to search for other relevant articles not retrieved in initial keyword searches and for additional relevant chemicals. Other searches were done using names of authors of relevant articles.

In the literature search, we focused on human, European data. Only LMW chemical compounds were taken into account. Furthermore, we focused on chemicals that cause the allergy, not those who trigger the symptoms. For ACD, especially chemicals present in consumer products were taken into account. Most publications found in the literature about the epidemiology of asthma are based on information of occupational respiratory diseases. These data can be considered as the most important source. Exposure to chemicals via food or pharmaceutical products (if they are not also present in consumer products) is excluded from this study.

3.3 Results of literature study

Skin sensitization
Literature search for skin sensitizers was done for 252 chemicals. For 76 of those, human data were identified and collected (Annex I). For another 176 chemicals, LLNA were available, but no human data were found during the above mentioned literature search. These potential human sensitizers are listed in Annex II. The lack of positive findings in humans does not necessarily overrule positive and good quality animal data [1].

Respiratory sensitization
Literature search for respiratory sensitizers was performed for 152 chemicals. Most of them are discussed categorized in chemical classes, which are listed in Annex I. Additionally, relevant surveillance schemes were studied, which contain relevant information on the most important respiratory sensitizers.

3.4 Further steps taken by contacting EU organizations

In a first step, Prof. Goossens (KUL) was contacted because of her responsibility for a patient database of contact dermatitis in Belgium. This database includes more than 10000 individuals since 1990. For all chemicals, time trends can be studied in this database, as mentioned for the individual chemicals further in this report.
Unfortunately, it was not possible to include these valuable data in this project, due to the extra cost for access to the database.

Additionally, 43 organizations (listed in table 1) were contacted by e-mail (contact addresses mentioned on their website). The letter and questionnaire used, are added in Annex III. Twenty-two organizations answered, of which 13 were able to share information. Five of those were contacted again, because they mentioned to have access to a patient database (Indicated in bold in table 1, UK: Sword, Epiderm, Opra, and Thor-GP; Germany: IVDK, ESSCA; Poland: ESSCA and Voivodship Centers of Occupational Diseases across Poland; The Netherlands: Hospital patient database and ESSCA; Spain: Patient database at University Department of Dermatology). They were

asked for more information about the database itself, and eventual costs involved to receive those data. The letter used is added in Annex IV. An overview of the number of chemicals and patients included in these databases, as well as the years for which the information is included, is summarized in table 2. Most of these databases include information on age, gender, and atopy status of the individuals. Also source of exposure, duration of symptoms (time since the first symptoms), and location of the symptoms are often available. Time since the first exposure, temporal pattern of the symptoms (continuously or only directly after exposure), and latency (time between the last exposure and the beginning of the subsequent symptoms), are not always present in the database. Additionally, other databases may exist across Europe, that we are not aware of.
However, because of the high costs involved to receive these data, it was not possible to include this valuable information in this report.

Table 1: List of the contacted organizations.

Organisation	Website*	Contact*	Answer Received[$]
EAACI	http://www.eaaci.net	executive.office@eaaci.org r.gerthvanwijk@erasmusmc.nl gianna.moscato@fsm.it	No data (other contact)
EAACI Asthma Section	http://www.eaaci.net/site/content.php?l1=91&sel=92	s.johnston@imperial.ac.uk	
EAACI Dermatology Section	http://www.eaaci.net/site/content.php?l1=91&sel=93	torsten.zuberbier@charite.de	No data
Austrian Society for allergology and immunology	http://www.oegai.org/html	rudolf.valenta@meduniwien.ac.at	
Belgian Society for Allergy and Clinical Immunology	http://www.belsaci.org	omichel@ulb.ac.be	No data
Astma en Allergiekoepel vzw	http://www.astma-en-allergiekoepel.be	info@astma-en-allergiekoepel.be	
British Society for Allergy and Clinical Immunology	http://www.bsaci.org	fiona@bsaci.org p.cullinan@imperial.ac.uk **raymond.agius@manchester.ac.uk**	X
Cyprus Society for Allergology and Immunology		liveris@spidernet.com.cy	
Czech Society of Allergology and Clinical Immunology	http://www.csaki.cz	vit.petru@homolka.cz	X
Danish Society for Allergology	http://www.danskallergi.dk/default.asp?id=3	all-unit@rh.dk	No data
Estonian Society for Immunology and Allergology	http://biomedicum.ut.ee/eias	kaja.julge@kliinikum.ee	No data
Finnish Society of Allergology and Immunology		elina.toskala-hannikainen@ttl.fi	
French Society of Allergology and Clinical Immunology		Frederic.DEBLAY@chru-strasbourg.fr	
German Society for Allergology and Clinical Immunology		dgaki@T-Online.de	
Hellenic Society of Allergology and Clinical Immunology		kontoufk@otenet.gr	

Organisation	Website*	Contact*	Answer Received[$]
Lithuanian Society of Allergology and Clinical Immunology		emuzyte@yahoo.com	
Dutch Society of Allergology		grooth@rdgg.nl	No data (other contact)
Dermatology Society in the Netherlands		c.bruijnzeel@umcutrecht.nl t.rustemeijer@azvu.nl	
Polish Society of Allergology		pkuna@sunlib.p.lodz.pl **cpalczyn@imp.lodz.pl**	X X
Portuguese Society of Allergology and Clinical Immunology		spaic@sapo.pt	
Romanian Society of Allergology and Clinical Immunology		diana_dumitrascu@yahoo.com	No data
Slovakian Society of Allergology and Clinical Immunology		peter@bonusccs.sk	
Slovene Association of Allergology and Immunology		mitja.kosnik@klinika-golnik.si	X
Spanish Society of Allergology and Clinical Immunology		secretaria_seaic@leti.com	
Swedish Association for Allergology		monica.arvidsson@lungall.gu.se	
Turkish Society of Allergy and Clinical Immunology		okalayci@hacettepe.edu.tr	
ESCD	http://www.escd.org	**22505aga@comb.es**	X
Arbeitsgruppe Allergologie der Österreichischen Gesellschaft für Dermatologie und Venerologie (ÖGDV)	http://www.allergologie.at	stefan.woehrl@meduniwien.ac.at	X
Groupe d'études et de recherches en dermato - allergologie	http://www.gerda-assoc.com	mvigan@chu-besancon.fr	X
Deutsche Kontaktallergie-Gruppe e.V. (DKG)	http://www.ivdk.gwdg.de/dkg	jgeier@gwdg.de	
European Dermato-Epidemiology network (EDEN)	http://orgs.dermis.net	**p.j.coenraads@med.umcg.nl**	X
British Epidermo-Epidemiology Society (BEES)	http://www.bees.org.uk	margaret.whittingham@nottingham.ac.uk	
European network of patient organizations (EFA)	http://www.efanet.org	susanna.palkonen@efanet.org	No data
The Global Initiative for Asthma (GINA) - GINA Assembly	http://www.ginasthma.com	guy.joos@ugent.be	

Organisation	Website*	Contact*	Answer Received[$]
The UCB institute of allergy	http://www.theucbinstituteofallergy.com	ioawebcontact@ucb-group.com	No data
WAO: World Allergy Organization	http:// www.worldallergy.org	info@worldallergy.org	X
World Health Organization, section Europe	http://www.euro.who.int	postmaster@euro.who.int	
ESSCA: European Surveillance System of Contact Allergies	http://www.ivdk.gwdg.de/essca	**Wolfgang.uter@rzmail.uni-erlangen.de**	X
IVDK: Information network of departments of dermatology	http://www.ivdk.gwdg.de/ivdk/eng/index.html	aschnuc@gwdg.de **Wolfgang.uter@rzmail.uni-erlangen.de**	X
Astmafonds Nederland	http://www.astmafonds.nl	info@astmafonds.nl	
Astma-organisatie UK	http://www.asthma.org.uk	info@asthma.org.uk	No data
European Lung Foundation	http://www.european-lung-foundation.org	pippa.powell@ersj.org.uk	No data
ISAAC	http://isaac.auckland.ac.nz/contact.php	p.ellwood@auckland.ac.nz	

** Letters were send to the contact address mentioned on the website.*
Answers received[$]: X=positive response, and data provided. If no data was available from this source, it is mentioned in this column. Also if other contact details are given, this is mentioned; and these contacts are added in the list. Empty fields: we did not receive an answer from this contact person.
***Bold**: Contacted a second time for more information about available databases*

Table 2: European databases

Patient databases	Country	# Chemicals	#Patients	Respiratory / Skin	Years	Costs involved to receive data
KULeuven, hospital database	Belgium	About 1000	+ 11000 patients	Skin	Since 1990	25000 Euro
ESSCA	11 European countries	About 35, including European baseline patch test series	About 40000 patients	Skin	2002-2006	5000-20000 Euro
IVDK	Mostly Germany, but also Graz (AT), Basel, Bern and Zurich (CH)	About 35, including European baseline patch test series	160000 patients	Skin	Since 1989	
Database from hospital	Spain	+1000	More than 2000 subjects	Skin	2004-2009	?
National Register of Occupational Diseases + Data collected during participation in ESSCA	Poland	30-50	6000 (30% positive) 200 (20-30% positive)	Skin Respiratory	Last 20 yrs	25 Euro / positive patient
University Medical Centre Groningen	The Netherlands	About 200	8000-10000 patients	Skin	?	1000 Euro ??
Sword, Epiderm, Opra, and Thor-GP	UK	? *	? *	? *	? *	? *

** We didn't receive their answer.*

3.5 Database structure to report the collected information

For each selected sensitizing chemical, relevant data from literature were collected and brought together in a Microsoft Office Excel template. This database can be questionned, for example to view all data related to one chemical class. The data can also be sorted, to have an overview in for example time trends. Following information is included in the database.

**** Name chemical compound***
The name used is derived from PubChem [17].

**** CAS number***
The CAS number is derived from the Hazardous Substances Data Bank (HSDB) at Toxnet [18].

**** Classification***
The classification, if available, is derived from PubChem [17].

**** R label***
The use of risk phrases (R phrases) is a system of hazard codes and phrases for labelling dangerous chemicals and compounds. R phrases are defined in annex III of the Council Directive of 27 June 1967 on the approximation of laws, regulations, and administrative provisions relating to the classification, packaging and labelling of dangerous substances (EU Directive 67/548/EEC): 'Nature of special risks attributed to dangerous substances and preparations'. The list was consolidated and republished in Directive 2001/59/EC, where translations into other EU languages may be found [19]. Of interest in this project are the R phrases R42 and R43: "May cause sensitization by inhalation / skin contact", respectively. But also the phrases R37 and R38 (Irritating to respiratory system / skin) are included in this report. R phrases mentioned in this report were taken from the European chemical Substances Information System (ESIS) or the BIG database (databank van het Brandweer-informatiecentrum voor Gevaarlijke Stoffen) version 17.0 in July 2009.

The guidance given in the EU classification and labelling system (Directive 67/548/EEC) regarding respiratory sensitization is rudimentary. It states that substances (and preparations) should be classified in the category of "danger sensitizing" and assigns the symbol "Xn", with the indication of "danger harmful" and the risk phrase R42 (may cause sensitization by inhalation), if at least one of the following criteria apply: if evidence shows that the substance or preparation can induce specific respiratory hypersensitivity; if there are positive results from appropriate animal tests (e.g. mouse IgE test and pulmonary responses in guinea pigs), and if the substance is an isocyanate, unless there is evidence that the substance does not cause respiratory hypersensitivity (annex to Directive 96/54/EC) [20].

The following human evidence is sufficient to classify a substance or preparation with R43: positive data from appropriate patch testing, normally in more than 1 dermatological clinic; positive data from experimental studies in humans; or epidemiological studies showing ACD caused by the substance or preparation.
When there is supportive evidence, the following is sufficient to classify a substance with R43: isolated episodes of ACD; or epidemiological studies where chance, bias, or confounders have not been ruled out fully with reasonable confidence. Supporting evidence may include data from animal tests performed according to existing guidelines, with a result that does not meet the criteria given in the section on animal studies, but is sufficiently close to the limit to be considered significant; data from non-standard methods; or appropriate structure-activity relationships (SAR). In the case of animal data, positive results from appropriate animal tests are needed [21].

The new regulation on classification, labelling and packaging ("CLP Regulation") contributes to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). This regulation aims that the same hazards will be described and labelled in the same way all around the world. Substance classification and labelling must be consistent with the new rules on 1 December 2010. The R phrases R42 and R43 will be replaced respectively by Respiratory sensitization Hazard Category 1: H334, and Skin sensitization Hazard Category 1: H317 [22].

**** Source***
If mentioned, the source of the exposure is added to the template. It is also stated whether the exposure was occupational or not.

**** Country***
The country in which the study is performed. For chemicals with few available European information, also non-European data may be added to the template.

**** Year***
Year of publication of the report or, if mentioned, year that the study took place.

**** Nr individuals***
The total number of individuals tested/described in the article/report.

**** Nr cases***
The number of individuals positive for ACD or asthma.

**** Individual characteristics***
Gender and age of the cases are given, as well as reported atopy and their smoking habits.

**** Duration of symptoms***
Time since the first symptoms were experienced.

**** Temporal pattern of symptoms***
Continuously or only directly after contact.

**** Time of exposure***
Total time since the first exposure.

**** Latency***
Time between the last exposure and the beginning of the symptoms. For part of the respiratory sensitizers, the time between the first exposure and the onset of symptoms is given (indicated in *italic*).

**** Test used for diagnosis***
For ACD, reported tests are PATCH test, repeated open application test (ROAT), and questionnaire. When other tests were performed, these are also mentioned.
For respiratory sensitization, tests reported are questionnaire, radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA), Ig measurement, skin prick test, spirometry, (non-)specific provocation challenge, cell count, and nasal test.

**** Symptoms***
For ACD, the place of the dermatitis is mentioned (and locally or systemic).
For respiratory sensitization, reported symptoms are wheeze, dyspnoe, cough, and chest tightness.

**** Related activity (only for respiratory sensitization)***
Nocturnal, by exercise, daily activity, or work-related.

**** Associated symptoms (only for respiratory sensitization)***
Nasal, skin, and/or systemic.

**** Medication (only for respiratory sensitization)***
Reliever or controller.

Additional information concerning for example time trends or selection criteria of the population, are indicated in the remarks. All references are stated only in this electronic Excel file (legend of the electronic file in Annex V). Additionally, it is indicated whether we had access to the full text of the reports, or whether we only found the abstracts.

3.6 Data collected in this database

Skin sensitization
The human data of the 76 skin sensitizers, which were tested in the LLNA, are listed in the electronic template (Annex V). When the literature reports also mention additional human data caused by skin sensitizers, which were not tested in the LLNA, they were also added to the template. The latter chemicals were not used for further analysis in this project. In total, the electronic skin sensitization template contains 2715 Excel records.

Respiratory sensitization
For respiratory sensitizers, literature data is rather scarce. The template contains 152 different respiratory sensitizers, of which 88 were reported in European publications. The other data are obtained mainly from USA and Canada. These literature reports are included in the template because of the power of the study, the expertise of the research group, or the similarity of occupational circumstances in US and EU. The electronic respiratory sensitization template contains 341 Excel records (Annex V).

CHAPTER 4 TASK 2: CRITICAL EVALUATION OF THE DATA

4.1 Initial literature search – analysis of general prevalence/incidence trends

Allergic contact dermatitis
Several reports on trends in skin sensitization have been published. The main conclusions are described here.

The European Surveillance System on Contact Allergies (ESSCA) started in 2001 as a project funded by an EU grant. It was aimed to detect trends in skin sensitization in an international patch-tested population. In their results from 2004, published in 2008, no time trends have been discussed [23].

The German Information Network of Departments of Dermatology (IVDK) is an epidemiological surveillance system which continuously monitors skin allergy [24]. This group has a long publication list on specific chemicals related to contact dermatitis. These reports are mentioned in the literature review of the individual chemicals.

In Sweden, prevalence of positive patch tests for various chemicals was compared between 1992 and 2000. Significant time trends in sensitization rates, both up and down depending on the chemical, were observed [25]. The rate of positive reactions to the fragrance mix in a large UK patch-test population is relatively constant, in contrast with a Danish study comparing the periods 1979 – 1983 and 1988 – 1992, when there was an increase in the rate of positive reactions from 4.7 to 6.3% [26]. However, in Denmark, the frequency of contact allergy to fragrances has decreased in recent years (since 1999), but is still high and remains a problem for consumers [27].

Asthma
For many countries, there are not many data on temporal changes in the prevalence of asthma before 1990. After 1990, estimates of temporal trends in the prevalence are conflicting [28]. Trends in the prevalence of symptoms suggestive of asthma show greater variation than trends in the prevalence of diagnosed asthma. The variability may in part be explained by the differences in definitions of asthma symptoms and the changes in diagnostic labelling of (occupational) asthma. The prevalence of both the symptoms and diagnoses are dependent on the awareness of the studied population and the skills of the physician.

The prevalence of allergic asthma has increased decades earlier in Western Europe compared to Eastern Europe [29]. The International Study of Asthma and Allergies in Childhood (ISAAC) is a worldwide study on the prevalence and risk factors associated to asthma and allergic diseases that started in 1991 (period: 1992 – 1998, mostly 1994 – 1995) [30]. Phase III of the study included repeating the original cross-sectional study after at least 5 years (period: 1999 – 2004, mostly 2002 – 2003), to assess time trends in the prevalence of asthma and asthma symptoms. The global burden of asthma

continues to rise (the percentage of children reported to have asthma increased significantly), but the regional differences in prevalence become smaller. Particularly for the 13 – 14 year age group, it was concluded that asthma symptom prevalence decreased in English speaking countries over the world and in Western Europe, and increased in regions where prevalence was previously low [31, 32]. In Europe, the prevalence of asthma symptoms is increasing in most countries in the age group 6 – 7 year. In the 13 – 14 year age group, the prevalence increases in most countries from Northern and Eastern Europe [33-35], but only in half of the countries of Western Europe [32, 36-38]. The overall prevalence of asthma increases across Europe in both age groups [31].

The European Community Respiratory Health Survey (ECRHS II) study aims to provide basic information on the prevalence and distribution of asthma in Europe [39, 40]. The first ECRHS study was performed from 1991 – 1993, and was followed by ECRHS II in the period 1998 – 2003. There is good overall agreement with regard to international prevalence patterns between the ISAAC study (children) and the ECRHS study findings (adults) [41]. In Spain, for example, increased prevalence rates of asthma diagnosis and treatment were detected [42].

The Czech society of allergology and clinical immunology send us their data on prevalence of allergy in children and adolescents. The official data from the National Institute of Public Health in Prague is presented in table 3.

Table 3 Prevalence of allergy in children and adolescents in Prague

	1996	2001	2006
Allergy	16.9 %	24.7 %	31.8 %
Allergic rhinitis	5.7 %	13.7 %	16.1 %
Bronchial asthma	3.3 %	6.7 %	8.2 %

N = 7075; age: 5, 9, 13, 17 year; 1996 only 5, 9, 13 year

In Austria, prevalence data of asthma are collected at military health examinations of national service recruits. These are reported for the period 1986 – 2005 for 18 year olds. The prevalence for bronchial asthma was 0.76% in 1986 and rose almost 4-fold over the years to 2.73% in 2003. Since 2003, the military health examination records show a decrease in the prevalence of asthma (2.31% in 2005) [43].

After increasing dramatically, the prevalence of adult asthma has not increased in Italy in the period 1991 – 2000 [44].

Occupational asthma

About 9-15% of adult-onset asthma is considered attributable to occupational exposure [13, 15, 45]. The prevalence of OA caused by sensitization to LMW substances is estimated at around 40% of all cases of OA by some authors. The agents most frequently implicated in the disease in industrialized countries have generally been diisocyanates, which cause asthma in 5-10% of workers [46]. In recent years, lowering the permissible concentration from 20 ppb to 5 ppb may have reduced cases [47]. Other substances, such as glutaraldehyde, cleaning products, and persulfates are emerging as disease-causing agents in workers involved in the health care, cleaning, and hairdressing industries [48-50].

International comparisons on the incidence of OA suggest a wide variation between industrialized and developing countries, with a rising incidence in industrialized countries. Very high incidence rates are reported by Scandinavian countries (7-18/100000), with Finland reporting the highest incidence. Western Europe and the USA having intermediate rates (2.4-4.3/100000) [51].

4.2 Weight-of-evidence approach

A weight-of-evidence approach was used for evaluation of the relationship between cause and effects. This was done separately for each chemical, which was listed as a potential sensitizer. For each selected chemical, the chemical compound name with corresponding CAS number, the number of reported cases, and information on severity of disease (duration of symptoms, time of exposure, and latency) were collected in the electronic Excel template (Annex V; TASK 1).

Weight-of-evidence is a common term, however, its definition is unclear. Therefore, it is important to define all criteria used [52]. In TASK 1, the criteria and work plan for data collection were already mentioned. Here, the criteria for evaluation of the reports and chemicals are described. The weight-of-evidence approach results in a scoring system, ranking the strength of evidence of the ability of chemicals to cause skin and respiratory allergy. This system allows to categorize chemicals in terms of evidence for its sensitizing capacity in the context of skin or respiratory allergy.

Sometimes, results from worldwide studies or studies outside Europe are mentioned in the reports, but these are not used in the scoring system, nor shown in the graphs or maps.

Evaluation of an individual publication / report

Number of cases reported = more than one:	score +1
Method used for diagnosis*:	
Questionnaire	score +1
Immunologic tests: more than one	score +1
Pulmonary test: more than one	score +1
Data on duration of symptoms, time of exposure, and latency:	score +1

**Only for respiratory sensitizers*
Every publication / report has a maximum score of 2 (skin allergy) or 3 (respiratory allergy)

Evaluation of a compound

R-phrases R42 or R43:	score +1
LLNA test data are positive:	score +1
Human data available, reported by at least 2 groups or 10 cases*:	score +1
At least one publication with score 2 or 3:	score +1

**Only for respiratory sensitizers*
The higher the score, the more evidence that the compound is sensitizing for skin or airways and may cause ACD or asthma.

The weight-of-evidence scores for each chemical compound are listed in Annex I.

4.3 Meta analysis

Meta analysis was performed when enough data were available to discuss time trends and/or regional differences. For each chemical sensitizer, a chemical report was created containing a summary of the available data concerning source of exposure, gender, age, information on latency, EU regional differences, and time trends. All data on

sensitizing chemicals, as well as all original references, are provided electronically in the Excel template (Annex V). For the chemicals for which enough information was available, a complete chemical report is added in Annex VI. Those chemicals for which only one or few reports were found, are summarized in an overview table (Annex VI).

Little is known on contact allergy from population-based studies, since most data were derived from patient populations (so-called general patch test population). Both types of studies have been included in this report.

The origin of the collected data for skin and respiratory sensitization is not completely analogue. For that reason, the meta analysis is performed separately. First, meta analysis for skin sensitizers is reported, followed by the analysis of respiratory sensitizers.

4.3.1 Skin sensitizers

→ ***Cause and effect relationships***

Most reported chemicals
Nickel sulfate is the most common allergen. Taken all studies (all years!) performed in a general patch test population together, we calculated an average European prevalence of 14.5%. The ESSCA reported a prevalence of 20% for the year 2004, with the highest prevalence in Italy (32.2%) and the lowest in Denmark (9.7%) [23]. The worldwide incidence was reported around 19% in 2002 [53]. Nickel allergy was observed significantly more frequently among young women, explained especially by early ear piercing.

In the general population, the most mentioned cause of ACD in published literature are fragrances. Fragrances are present in almost all household products, soaps, shampoos, and cosmetics. Commercial perfumes may contain hundreds of individual fragrance chemicals, but the most common are included in the standard fragrance patch series [26]. Prevalence values are around 10% in the general patch test population (see chemical report). In the general population, it has been estimated that 2 – 4% suffers from ACD to fragrances contained in the fragrance mix [54]. According to Buckley *et al.* (2000), it is the second common cause, only nickel causes more cases of dermatitis [26]. The sale of cosmetics, and thus, exposure to perfumes has increased during the past decades, which leads to an increasing prevalence of sensitization to the fragrance mix components [55].

Table 4 Top 6 of most frequent skin sensitizers in the general population based on meta-analysis of collected data (Annex V)

1. Nickel sulfate
2. Fragrances
3. Cobalt chloride
4. PPD
5. Colophony
6. Potassium dichromate

Additionally, the chemicals that are mentioned most as a causing agent of ACD, are those included in the European standard patch test series. Of course, these are most studied in epidemiological studies, and therefore also most reported. Although these

chemicals are included in this standard series because allergic responses to them are common, also other compounds may be potential sensitizers. In the European patch test series, 20 individual chemicals and chemical mixes are included, as shown in the following table 5.

Table 5: Overview European patch test series

Discussed in this report (Annex VI)	Not discussed, but information in electronic file
Potassium dichromate	Thiuram mix
para-Phenylenediamine (PPD)	Neomycin sulfate (antibiotic)
Cobalt chloride	Benzocaine (local anaesthetic)
Nickel sulfate	Clioquinol (Chinoform & Vioform) (antibacterieel)
Colophony	Parabens mix
Methyldibromo glutaronitrile	N-Isopropyl-N-phenyl-4-phenylenediamine
Formaldehyde	Mercapto mix
Fragrance mix (cinnamic alcohol, cinnamic aldehyde, hydroxycitronellal, amylcinnamaldehyde, geraniol, eugenol, isoeugenol, oakmoss absolute)	Epoxy resin
	Tixocortol pivalate (topical corticosteroid)
	4-tert-Butylphenol formaldehyde resin
MCI/MI (Kathon CG)	Mercaptobenzothiazole
	Sesquiterpene lactone mix (alantolactone, dehydroxosus lactone, costunolide) (plant dermatitis)
	Quaternium-15
	Primin (plant)
	Budesonide (topical corticosteroid)
	Lanolin alcohol
	Myroxylon pereirae resin (balsam of Peru)

Most reported exposures

In case of ACD to para-phenylenediamine (PPD), the cause of sensitization is often found in temporary henna tattoos, which are often placed during holiday vacations [56] [57, 58]. The dye in the henna often contains a very high concentration of PPD. Symptoms and complaints are sometimes observed when the tattoo is repainted after fainting. However, complaints can also start years later, when the person starts using for example hair dye. Because they are already sensitized earlier caused by the high concentrations, they react also faster to the lower concentrations in the hair dyes. Exposure to hair dyes and shoes is mentioned often as a cause. Less frequent causes mentioned in the literature are for example sunscreens, lip balm, wet suites, and diving material.

In occupational settings, more reports concern hairdressers. Although most of them are aware of the risks due to sensitization initiatives in that sector, they are still the most mentioned and studied occupational group suffering from contact dermatitis. The most common causes of hairdressers' skin allergies are PPD and its derivatives in hair dyes, and ammonium persulfate in bleaching agents [59]. For PPD, the prevalence among hairdressers decreased significantly (see chemical report), while in the general population, an increasing trend is observed for this compound.

Other common occupational settings in which workers are affected by occupational contact dermatitis, are dentists (acrylates), healthcare workers and nurses, and construction workers. Also exposure to glue is often mentioned as a cause of contact dermatitis in occupational settings.

Table 6 Top 5 of most reported occupations affected by skin sensitization, based on meta-analysis of collected data (Annex V)

1. Hairdressers
2. Dentists / dental personnel
3. Nurses / healthcare workers
4. Metalworkers
5. Construction workers

Attention should be paid to the possibility of active sensitization during the diagnostic patch tests and ROAT tests. During these tests, patients are exposed to various chemicals, and care must be taken that the used concentrations are safe. Sensitization rarely occurs during patch tests, but the risk depends on the test concentration of the allergen. Various reports already studied this problem. Active sensitization is characterized by a negative reaction at the conventional time of reading of the patch test (day 2 – 4), followed by a late patch test reaction at day 10 – 20, and then a positive patch test reaction when re-tested already observed after 2 or 3 days [60, 61]. For various compounds, it was concluded that the concentrations used in the patch tests can cause active sensitization, e.g. fragrance mix I and PPD [60, 62], however, for other chemicals this is not enough studied at the moment. One study suggested that compounds for which active sensitization occurs, should not be included in the standard patch series, because of the risk [62].

→ ***Severity of clinical picture***

Generally, human skin sensitization tests only evaluate hazards. Based on the data collected here, conclusions for dose-response, potency, and severity of the allergic reactions can not be drawn. If available, information on potency is based on LLNA data.

For skin allergies, it is difficult to evaluate severity of symptoms, since there is few gradation. Individuals mostly experience eczema, redness of the skin, or itchy skin, but this is often an individual characteristic. The patch tests, which are usually performed to identify the allergen during diagnosis, don't really reflect severity. Interpretation of these results is not always uniform, and very subjective. Especially the difference between an irritant or sensitization reaction is not always clear. Various studies only report a positive reaction for the patch test, without further details on the reaction (e.g. scorings using +?; +; ++ or +++ reactions), while other groups are more careful in their interpretation. Additionally, both false-negative and false-positive patch test results occur [63].

In this report, individual chemicals have been examined. Cross-reactions were not discussed. The presence of irritants in a product can enhance for example penetration of the allergen through the skin. Additionally, one chemical can mimic the reaction of another chemical compound.

In the Human Repeat Insult Patch Test (HRIPT), a dose-response study may be conducted to determine whether a response elicitation threshold can be established. These data could also be used to assess potency. It is important to emphasize that a HRIPT, or any other type of human skin sensitization test, is performed to confirm safety under exaggerated conditions of product exposure. It is not conducted to identify skin sensitization hazards [64]. Provided that the risk of inducing skin sensitization in volunteers is judged to be minimal (based on assessment of pre-clinical sensitization data), human testing may be conducted. However, these tests are not always accepted for ethical reasons [1]. The test is still used in several countries as a confirmatory test

in the safety evaluation of skin sensitizers. This is despite the criticism it receives from an ethical perspective and regarding the scientific validity of such testing [3]. Additionally, frequency of exposure, and the amount of exposure or use, should be taken into consideration. The data collected in this project, contain little or no information based on these human tests. However, *in vivo* mouse tests (LLNA) allow to assess dose-response and potency of chemicals. Also *in vitro* research is performed to asses the sensitizing capacity of the chemicals, and also in these tests, more efforts are being made to assess sensitizing potency of the chemicals. This kind of information may be very important in risk assessment and may help to understand what drives the vigor of a sensitization reaction. Results of the LLNA are included in the weight-of-evidence approach (Annex I).

→ ***Categorization***

Some compounds can be grouped in chemical classes, e.g. aldehydes, amines, etc. The categorization in classes was based on available information in the PubChem database [17]. However, chemical classification is not available for all chemicals in this database. Also other databases and possibilities, such as Quantitative (Q)SAR (DEREK software), were checked, but none of them gave complete information. The classification was used to evaluate incidence and severity per chemical class if possible. This was applied especially for respiratory sensitizers, where few information for the individual compounds is available.

For skin sensitizers, the chemical compounds were discussed individually in the chemical reports. However, respective prehaptens (not sensitizing on its own; is converted into a hapten in contact with air) and prohaptens (not sensitizing on its own; is enzymatically converted into a hapten) are discussed together with the haptens, which have the sensitizing capacities.

Some chemicals were found to be both skin and respiratory sensitizers. Human data for both was found for chloramine T, cobalt chloride, colophonium, ethylenediamine, formaldehyde, glutaraldehyde, nickel sulfate, and phthalic anhydride. Based on the available information, it is not known whether one exposure can lead to both skin and respiratory sensitization, whether both allergies occur in the same individuals, or whether these are two completely independent disorders.

In the weight-of-evidence approach, it became clear that the data obtained by LLNA and the formulated R phrases, are not always uniform. Some chemicals were reported to be non-sensitizers in the LLNA, while a R phrase was reported (e.g. coumarin and 2-hydroxypropyl methacrylate). For both these chemicals, publications were found that report sensitization to these chemicals in humans. On the other hand, some chemicals which were categorized as extreme sensitizers in the LLNA, had no R43 phrase (e.g. 1-chloro-2,4-dinitrobenzene).

Of the 76 skin sensitizers discussed in this report, 28 obtained the maximum score of 3: they were classified as sensitizers in the LLNA, obtained a R43 phrase, and valuable reports on human data were found. 23 chemicals obtained a score of 2, and 23 chemicals a score of 1. For the latter two groups, no R43 phrase was assigned or no human patch test data of good quality were found.

→ ***Effect of human behavior***

Exposures change over time either due to fashion trends, technological developments, or as a result of official regulations [55]. Once the diagnosis of ACD has been

confirmed, products containing the allergens can be avoided. Some examples of the effects of official regulations are described here.

The regulation concerning nickel exposure via costume jewelry in Germany was already reflected in the IVDK data shortly after implementation in terms of a significant decrease in nickel sensitization in the subgroup of young women. In 1992, the German Ministry of Health declared labelling mandatory ('contains nickel') in products which remained in prolonged contact with the skin and released more than 0.5 mg/cm²/week. In 1994, the EU prohibited trading in such products (EU Nickel Directive 94/27/EEC) [65, 66]. Also in Sweden and Denmark (regulation in Denmark since 1991 [55]), this decreasing trend was observed after the implementation of regulations on nickel exposure [25, 67].

After the European restriction of MCI/MI used in cosmetics, the new preservative methyldibromo glutaronitrile (MDBGN) was introduced in the 1980s for use in industrial and cosmetic products [68]. Soon after introduction to the market, the first case of contact allergy caused by this compound was reported. Based on the advice from the Scientific Committee on Non-Food Products, a change to the Cosmetic Directive was made in 2005, banning its use in leave-on products, and limiting its use to rinse-of products (2003/83/EC) [69, 70]. In 2007, this decision was revised to include a legal prohibition on the use of MDBGN also in rinse-off products, as no safe use level could be established [71, 72]. A decreasing prevalence has been seen after this regulatory intervention.

A change in regulation does not always lead to a decreased prevalence of sensitization for the chemical compound. Although labelling for isoeugenol is required if the compound is present in certain concentrations (since 1998, 10 times lower concentrations are allowed in products [73]), an increasing trend in ACD was observed for this compound [74]. The authors of this report suspected that this increasing trend may be due to allergen substitution with compounds chemically related to isoeugenol, or which hydrolyze to isoeugenol itself [74]. Therefore, research is needed for all new chemicals introduced in consumer products.

Concerning occupational contact dermatitis, job change to other rooms without exposition to the chemical sensitizer, often leads to complete clearing of the complaints. This was for example observed in a perfume factory [75]. Also other personal protection measures have been proposed and realized successfully, such as the use of disposable nitrile gloves [75].

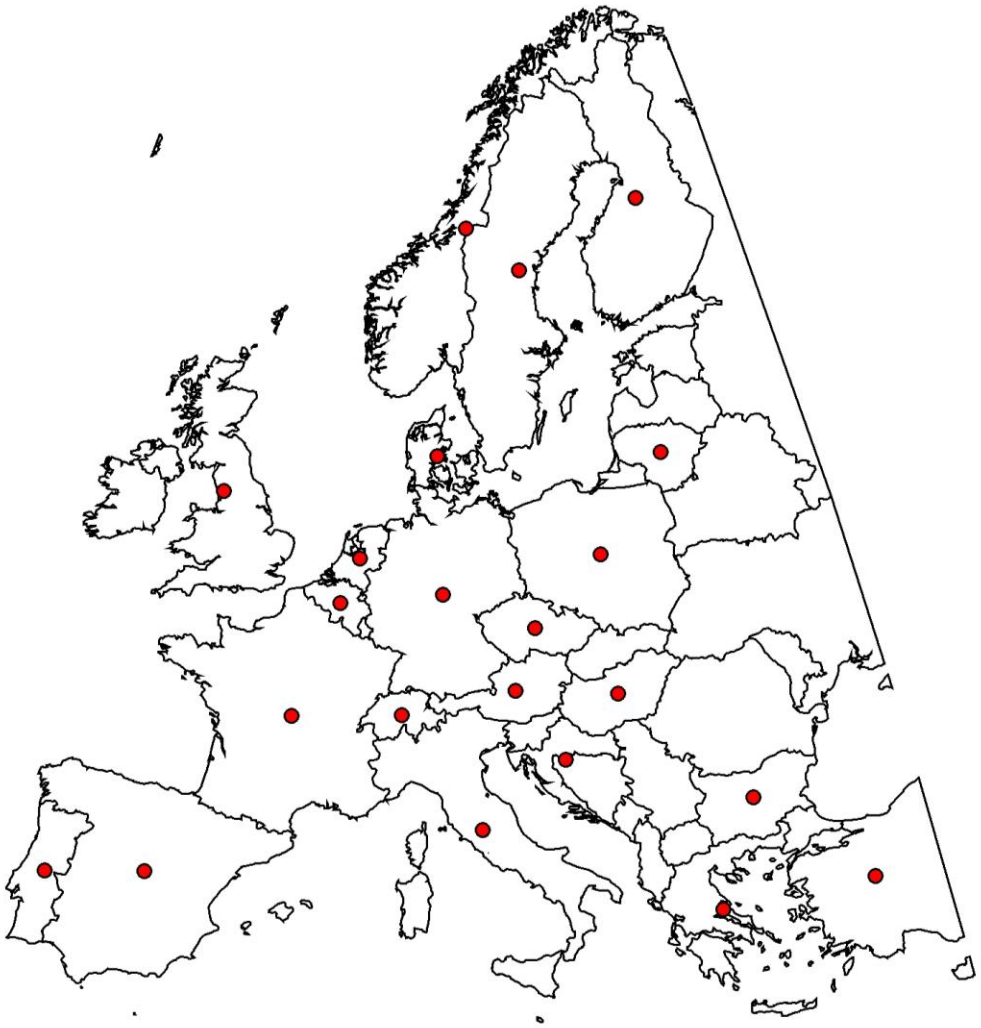
→ ***European regions***

Only a few studies were found that compare prevalence data for ACD between various European regions or countries. In 2005, the prevalence of skin allergy to fragrance mix I and II from 5 patch test centers were compared to each other [76]. Somewhat higher prevalence rates were reported in Belgium and Sweden, compared to Germany and the UK. In Denmark, 2 centers were included: data in one center (Odense) were comparable to Belgium and Sweden, while data in the other center (Copenhagen) were comparable to Germany and the UK. The same authors published in 2002 highest concentrations for the fragrance mix in Belgium, followed by Sweden, Germany, UK, and the 2 Danish centers had the lowest percentage of positive patch tests [77]. In 2000, variation from country to country in the frequency of allergic reactions to individual fragrance mix constituents has been reported [26]. Also for nickel sulfate, large international variations were observed [78]. For R-(+)-limonene, highest prevalence values were in 2003 reported in Spain (6.5%), followed by Sweden (3.9%), Belgium (3.8%), and Portugal (0.4%) [79]. In 2006, prevalence was higher in Denmark (4.3%), followed by Belgium (3.7%), UK (2.3%), Sweden (1.6%), and Germany

(0.4%) [80]. Especially in Sweden, prevalence has decreased in this time period. This variation may reflect differences in exposure, the frequency of use of one or more popular products containing a potential sensitizer, and/or the concentration and purity of the allergens used for patch testing.

In the chemical reports, for each chemical is stated in which European countries data were reported. Some countries report very valuable data for various chemicals. For example Germany and the UK have large databases containing a lot of patient data on contact dermatitis. Also a database including 11 European countries has been reported for the years 2002 – 2006. On the following map is shown for which 22 European countries data on contact dermatitis were found in literature for the various chemicals.

Figure 1:Overview of countries for which human data concerning ACD was found.



Red dots indicate for which European countries data concerning ACD were found. Each dot is positioned in the centre of the country. The dot for Croatia is near the border of this country, caused by the shape of it. In the chemical reports in Annex VI, the cases are indicated at the same places as the red dots in this fig. 1. In the reports for each chemical, 3 types of studies are included in the maps: the number of case reports for each country, studies in the general patch test population (here called epidemiological studies), and studies performed in a selected group (mostly occupational exposure).

Care must be taken when reports from different European countries are compared. For example the study design is not always exactly the same. Most manuscripts report data from patch test centers, and give prevalence values for the so-called 'general patch test population': people with symptoms or complaints, who want to find out for which chemicals they experience allergic dermal reaction. Other reports concern only patients with complaints on certain body parts, such as their hands. The age of the individuals may differ between the various reports: some reports include for example only schoolchildren. When studies are compared, the MOAHLFA index (male; occupational; atopic dermatitis; hand; leg; face; age above 40) should be compared. Based on the data available, there are not enough data to include all these different parameters and to report on specific differences between regions. This might be possible for example when data from existing databases could be used, because these include far more individuals. Therefore, in the individual chemical reports, regional differences have only been described when this was mentioned in published reports. Only than, we can be certain that the interpretation of the data, characteristics of the population, and the inclusion or exclusion criteria of the described population, are comparable. Also in the ESSCA network report [23], which offers the advantage of continuous surveillance of contact sensitization in Europe, it is stated that before comparing results between centers and countries, the issue of possible methodological variation should be addressed. Other variables that need to be considered include patch test interpretation, patient demographics, referral patterns and selection bias, and local expertise [71].

→ ***Time trends***

When enough data were available for a chemical compound, these are combined and prevalence values are plotted in a graph, to study trends during time (shown in the individual chemical reports in Annex VI). To discuss time trends, only studies concerning the general patch test population are included. Especially for the compounds included in the European patch test series, enough data are available to study time trends. But also for other compounds, data are shown in a graph.

Data are given as precise as possible: when tests are reported for various years, but only one result is discussed for the whole time period, the median year is taken for that time period (e.g. 1996 – 1998 is indicated as 1997). When results are given for all years separately, these are all added separately in the graph. However, not all manuscripts report during which period the tests are performed they describe. When no year is given, the year of publication is taken and shown in the graph. This might give not a completely correct image, but will come close to the correct view.

The use of different test concentrations often complicates comparison of results between different countries or different time periods. The concentration used is not always mentioned in publications. When lower concentrations are used in certain studies, some less sensitive cases will be missed. Also some reactions to the patch test can be misinterpreted as low level sensitivity or irritancy. The vehicle used, and occlusion time (time between patch test and reading of results) can further influence the patch test results and interpretation. Both false-negative and false-positive patch test results are possible, e.g. for glyoxal [81].

Both increasing and decreasing trends have been observed. For the skin sensitizers abietic acid/colophony, formaldehyde, MCI/MI, and tetramethylthiuram disulfde, decreasing trends have been observed throughout Europe. Increasing trends were found for PPD, isoeugenol, hydroquinone, and imidazolidinylurea (the latter not in all countries). A stable prevalence was observed for cobalt chloride. More details can be found in the individual files.

Studies concerning specific populations, such as occupational groups, can of course not be compared to the general patch test population. For some chemicals, enough data are available for specific groups to examine time trends. For example for PPD, 9 studies reported on contact dermatitis in hairdressers. When these data were taken together, a clear decreasing trend was observed in this group (see chemical report of PPD in Annex VI). In occupational settings, the "healthy worker effect", which would be a problem if workers with allergies left the profession, has to be taken into account in the interpretation of the results. However, this information is not always available.

Only a few reports discuss trends between age groups. In most studies, the age range is reported, including often a broad range of ages. Therefore, trends in age groups were not discussed further in this report. Cases are reported in all age groups. When individual data would be available (e.g. from European databases), it would be possible to include this information in the analysis, and to draw some conclusions.

It is difficult to compare prevalence values between both sexes in this report, because most reports mention only the percentage of males and females. However, various publications indicate that especially for allergens present in cosmetic products, more women experience allergic reactions, probably because they use these products more often.

4.3.2 Respiratory sensitizers - surveillance schemes

Surveillance data provide a source of information on potential risk occupations. However, surveillance schemes reporting occupational diseases stratified by occupation, industrial sectors, and causative agents over several years are scarce [51].

It is more appropriate to discuss groups of LMW agents causing OA instead of individual chemicals. Table 7 summarizes the percentages of OA caused by groups of agents, as reported in the various surveillance schemes. Additionally, table 8 gives an overview of the same data ordered by occupation. When occupationally exposed groups are discussed together, not only LMW sensitizing chemicals are taken into account. These groups are exposed to a mixture of LMW and HMW agents.

Table 7 Percentages of OA caused by groups of agents

Reference	Country	Acronym	Time period	Total number OA	Isocyanates	Hairdressers chemicals	Cleaning agents	Wood dust	Metals	Un-Known
[82]	Finland	FROD	1989-1995	2602	4,8	1,4	0,4	2,7	0,5 (cobalt, nickel)	2,3
[83]	Sweden	SRROD	1990-1992	1010						
[84]	France	ONAP	1996-1999	2178	14,1	5,8		3,7	0,8	
[85]	Italy (Piedmont)	PRIOR	1996-1997		2			2		
[86]	Belgium	-	2000-2002	260*	17,3	4,2		3,1	3,9	11,5
[50]	Spain (Catalonia)	-	2002	174	15,5	12,1	8,6	8,0		2,3
[87, 88]	UK (Midlands)	SHIELD	1991-2005	1461	21			4		23
			2006	57	16		10,5			
			2007	36	36		18	6	2 (chrome)	
			2008	36	28		6	6	6 (chrome)	
[89]	UK	SWORD	1989-1991	1528	22	1	1	4	6	8
			1992-1994	2857	15	<1	1	4	7	9
			1995-1997	3002	14	<1	1	6	5	7
			2002-2004		17			3	5 (chrome)	
[90-92]	UK	THOR	1999-2005	1698						

		THOR: SWORD +OPRA	2005-2007	358+106	13+3	0	0	0	1+0	8+13
		IIDB	2002-2004		21			11		
			2005-2007		17			9		
[51, 93]	Germany	-	1986-1990	8144*		3,6	0,8	1,7		10,6
			1991-1995	9069*		4,6	1,6	3,2		12,7
			1996-2000	7164*	other disease code	2,9	1,2	3		6
			2001-2005	4310*		4,6	1,1	2,9		1,1

**Only cases of occupational obstructive airway diseases due to allergens, including rhinitis; a distinction is made with cases of irritant-induced asthma*

Table 8 Percentages/occupational annual rates of asthma in occupational groups

Reference	Country	Acronym	Time period	Total number OA	Welders	Healthcare workers	Hair-dressers	Painters	Cleaners	Wood workers
[82]	Finland	FROD	1989-1995	2602					R:3	
[83]	Sweden	SRROD	1990-1992	Men:587	R:647			R:599 (spray painters)		R:455
				Women:423		R:52	R:129		R:133	R:494
[84]	France	ONAP	1996-1999	2178*	1,6%	10,4% R:41	6,8% R:308	8,1% R:326 (car painters)	3,6% R:55	5,1% R:218
[85]	Italy (Piedmont)	PRIOR	1996-1997				21%			
[86]	Belgium	-	2000-2002	260*		8,5%	4,9%	6%	5,7%	
[50]	Spain (Catalonia)	-	2002	174						
[87, 88]	UK (Midlands)	SHIELD	1991-2005	1461	9%	9%	1%	5% (car body shop)	4%	2%
			2006	57						
			2007	36						
			2008	36		9%	1%			2%
[89]	UK	SWORD	1989-1991	1528	R:158	R:17	R:81		R:9	R:45
			1992-1994	2857	R:265	R:52	R:17		R:9	R:110
			1995-1997	3002	R:266	R:74	R:32		R:28	R:171
[90-92]	UK	THOR	1999-2005	1698						
		THOR: SWORD+OPRA	2005-2007	358+106						

[51, 93]	Germany	-	1986-1990	8144*						
			1991-1995	9069*						
			1996-2000	7164*						
			2001-2005	4310*						

**Only cases of occupational obstructive airway diseases due to allergens, including rhinitis; a distinction is made with cases of irritant-induced asthma*
R: Occupational annual rate = number of new cases per million workers/year, by occupation

→ ***Cause and effect relations***

Most reported agents and occupations
In 1-23% of cases with OA, the causative agent is not identified. Several reasons are possible: 1) the association between a compound and asthma is not made by the patient or the physician; 2) the tests to indicate the specific agent are not yet developed; and 3) the specific test can not be used by the treating physician, since only specialised centres are qualified to perform certain testes [86].

Germany (since 1970)
For this surveillance scheme, a specific disease code (BK number) is used for isocyanate-induced respiratory disease. As a consequence, not all these patients are asthmatic. Therefore, it is not possible to compare incidences between countries. It is also not possible to compare incidences induced by LMW agents. Nevertheless, it represents a large group (510 cases/year). The other important LMW agents causing asthma are chemicals used by hairdressers (e.g. persulfates), wood dust, and cleaning agents.

Belgium (2000-2002)
In Belgium, isocyanates are clearly the most important causing agent. Persulfates, metals, and wood dust are responsible for respectively 4.2%, 3,9%, and 3,1%. Divers synthetic resins are not listed in table 7, although they induce 6.2% of OA. The occupations most associated with LMW-induced asthma are health workers (8,5%), painters (6%), cleaners (5,7%), and hairdressers (4,9%).

UK - SHIELD (1991-2005)
SHIELD is the Midland Thoracic Society's Surveillance Scheme of OA. Welders and health workers have a high risk to develop OA (9%). Attention is needed for the high incidence in car body painters (5%).

UK – SHIELD (2005-2008)
Isocyanates, which were the most common causing agents in previous years, stay most important. Metal working fluids is in this region a frequently reported cause, due to several outbreaks (up to 44%). Biocides, cleaning agents, wood dust, and welding fumes are also listed among the top of most reported agents.
UK - SWORD (since 1988)
SWORD is the Surveillance of Work-related Occupational and Respiratory Disease. Isocyanates are the most common agents inducing OA over time. Colophony and other soldering products, cutting oils, and paints belong also to the top of causative agents.

UK - THOR (since 2002)
THOR represents the Health and Occupation Reporting Network. The latter includes data from SWORD and OPRA, which is Occupational Physicians Reporting Activity. The results are similar to the results of SWORD. For the period 2002-2005, many cases induced by cutting oil and coolants are reported (5%). There is not enough background information to deepen this out.

France - ONAP (1996-1999)
ONAP represents the 'Observatoire National des Asthmes Professionnels'. The main suspected causal agents of OA are isocyanates (14,1%), persulfate salts (5,8%), and wood dust (3,7%). Aldehydes cause also a high percentage of OA (5,9%) and resins and glues are also worth mentioning (1,5%). Valuable information is obtained when the annual occupational rate is calculated. Car painters, hairdressers, and wood workers are occupations with a striking high risk of OA with incidence rates of 326/million, 308/million, and 218/million, respectively.

Spain, Catalonia (2002)
The most frequent agents causing OA are isocyanates (15,5%), persulfates (2,1%), cleaning agents (8,6%), and wood dust (8,0%). Resins and glues (4,6%) and colophony (4,0%) are also important for the development of OA.

Sweden - SRROD (1990-1992)
SRROD is the Swedish Register of Reported Occupational Diseases. In this study, a distinction is made between genders. Male welders (647/million), spray painters (599/million), and woodworkers (455/million) have the highest reporting rates when focusing on occupations with exposure to LMW agents. Female woodworkers represent an annual rate of 494/million. Other important occupations with possible exposure to LMW agents are chemical process workers (952/million) and plastic production workers (565/million).

→ ***Human susceptibility***

Age
Analysis of cases reported in Sweden and UK has shown an increase in the incidence rate of OA with age, but the latter is not confirmed in other countries. This may be related to socio-economic reasons. Older workers want to keep their jobs, despite their medical complaints, and seek medical care at a later age. On the other hand, young subjects change jobs more easily when symptoms develop. A second explanation is that the cumulative occupational exposure to asthmatic agents increases with age and hence the risk of developing asthma [94].

Gender
In all the databases, a higher incidence of OA in men has been reported. This can partly be explained by different distributions of occupations and exposures between both genders. However, for wood dust there are indications that women are more susceptible with regard to development of bronchitis, coughing, and possibly asthma. Study results report that women, but not men, have an accelerated decline in lung function in a cohort exposed to relatively low concentrations of wood dust [95, 96]. There are also hypothesis that OA is probably more underdiagnosed in women [87]

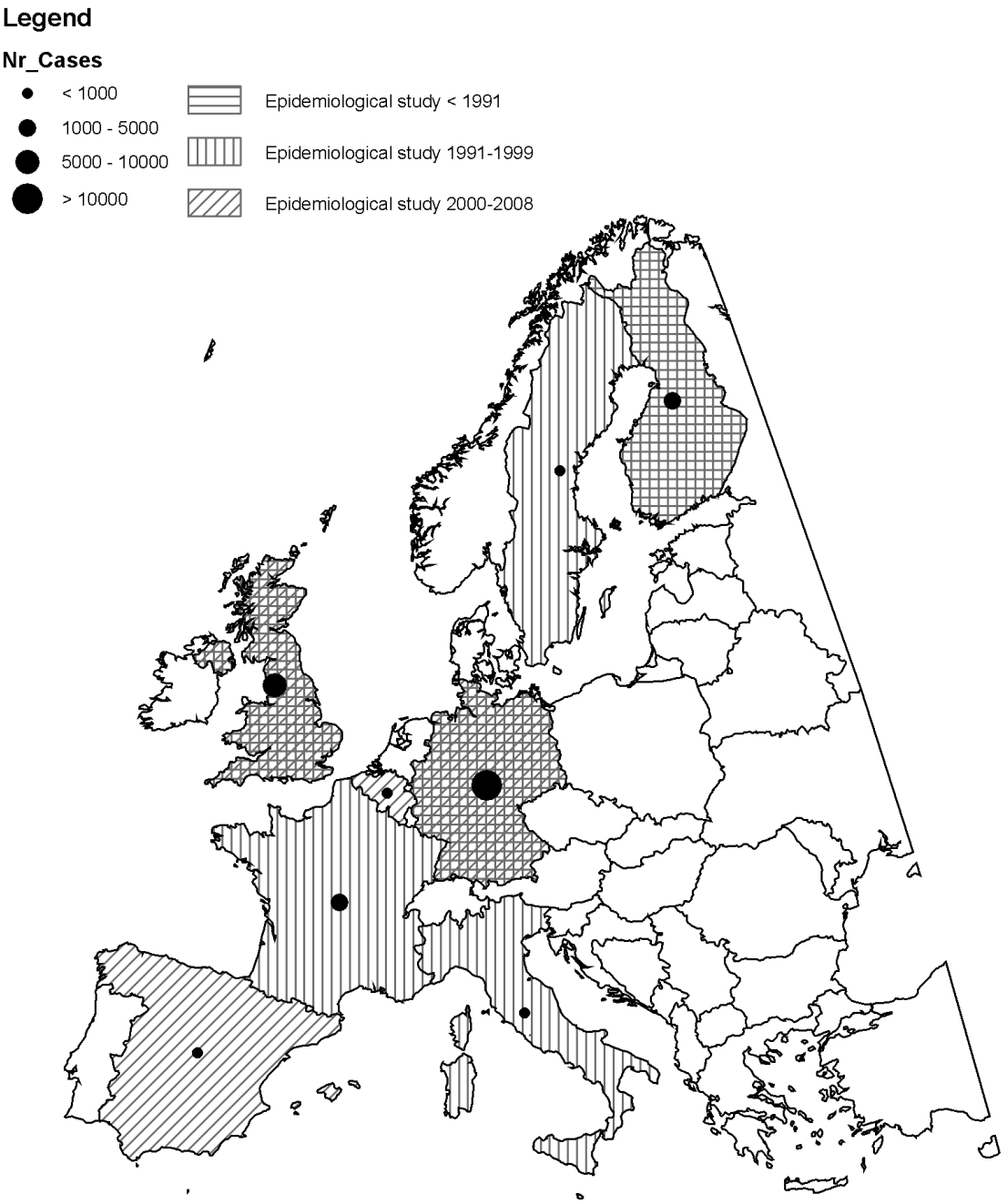
→ ***European regions***

The international comparison of OA incidence in ECRHS II shows very wide differences in Europe. A range in annual incidence has been reported from 24 (Italy, 1997) to 18 (Finland, 1995, female) per million workers. Further analysis by geographical region showed that OA is present in all regions, with the highest risk in Southern European countries. The comparison of OA-inducing agents from different countries is difficult due to different industrial structures, legislation, and data collection. Also the code of industry is different.

Considerable regional differences in incidences also occur within a country. This is a reflection of different levels of identification and reporting [84, 86], but it is also due to different industries [87].

A decline in exposure can be explained by preventive measures on all precaution levels. We have to be alert on the possible shift of dirty jobs to other less developed countries in Europe (or outside Europe) [97].

Figure 2 Overview of surveillance schemes in European countries



→ ***Time trends***

Germany

Although trends in occupational disease may be influenced by several factors, the data indicate a steady reduction of occupational respiratory diseases in Germany after 1996. The latter is mainly based on the decrease of disease incidence due to silica and allergic- and irritant-induced asthma. Since 1998, the distribution among causative recognized LMW agents has not changed [93]. Few cases are due to LMW agents, permitting no evaluation of time trends. Diseases caused by isocyanates show no clear trend for the numbers or rates of suspected and recognized cases.

UK - SHIELD

The SHIELD registration system gives a detailed overview of agents and occupations related to asthma, year after year. However, the investigated region with specific high industry is small; 91% of the reports are of one hospital, and an average of 40 employers is reported. Outbreaks will have a great impact on the incidence figures (for example metalworking fluid in 2004). It is difficult to compare notification for each year properly, nevertheless there is a slow decline of OA over the period 1980-2008.The higher incidence of metalworking fluid is correlated with a higher proportion of workers in these settings. Nevertheless, handling of metal working fluid is an emerging problem in the West Midlands, due to several outbreaks. The falling incidence of OA from glutaraldehyde is an encouraging example showing that control measures are feasible to reduce the amount of new cases [88]. Also the isocyanate industry was the focus of a health and safety campaign which results in reduced reports [87].

UK - SWORD (1989-1997)
The change in reporting and organization doubled the estimates, but has little impact on distribution of cases by occupation or agent, which remained almost unchanged. An apparent fall since 1992 was obvious in the proportion of cases attributed to isocyanates. This decline is also seen in the number of awards of disablement benefit (IIDB) for isocyanate-induced asthma between 1992 and 1997. Despite this decline, isocyanates remain the most often reported cause of OA. Furthermore, a decline in OA among hairdressers is also noted.

UK - SWORD (1999-2005)
The average annual change in OA was -1,9%, but the pattern was erratic. The relative high rate in 2004 was partly due to a large outbreak in one workplace for several months (see SHIELD). However, if only the reports of the core participants was taken into account, there was almost no change in time (-0,4%). Trends for LMW-induced OA are not analyzed in the publications and without more background information it is not possible to evaluate these in this project.

UK - OPRA (1996-2005)
There was a downward trend for OA comparable with SWORD: the change over ten years was -8,1%.

UK - IIDB
The decrease of OA from 1993-2007 is undeniable. Isocyanates as responsible agents for OA are decreased in percentage.

4.3.3 Respiratory sensitizers - literature

→ ***Cause and effect relationships***

The exposure-response relation remains unfortunately poorly defined for LMW agents. During synthesizing and producing a specific compound, the circumstances of exposure are controlled. Exposure of the end user is more complex and less controlled. It is necessary to pay attention for possible uncontrolled exposure at the workplace while maintaining or even cleaning and also at home using a compound containing product. Below, two good examples are mentioned. The effect of isocyanates, but also the complexity of exposure, is illustrated by the different incidences of OA in different jobs. Contribution of isocyanates to OA for spray painters is 41%; in the primary industry, however, the contribution is 5-6% [98]. Secondly, among woodworkers there are different tasks resulting in different degrees of exposure. This implies also a difference in exposure conditions at the workplace. In the Netherlands, the wood dust exposures in the joineries were usually below limits, but in the furniture factory the present limit was

regularly exceeded [99]. Ventilation in the manufacture is possible. Many workers perform carpentry at home, where general and personal protection is not possible or not used.

Occupational asthma due to isocyanates and wood dust, and probably other LMW agents, can occur at very low levels of exposure below current regulatory limits [100]. Indicating safe exposure levels is difficult when the exposure-response relation is not clearly defined. Nevertheless, the question is raised if the levels encountered in common environmental exposures are sufficient for increasing the risk of asthma and allergies. Diisocyanates are a well-studied cause of OA, but its use in consumer products in the general population can be overlooked [101].

Despite reductions in workplace respiratory exposures, isocyanate asthma continues to occur. The hypothesis that skin may be an important site of exposure becomes more important [102]. The concern for this skin exposure pathway is confimed by case reports and cross-sectional studies reporting asthma with minimal airborne levels [103, 104]. This hypothesis is also supported by animal experiments. Several different animal models have used isocyanate skin exposure to induce sensitization, followed by inhalation challenge to induce asthma like responses [105]. Recently, there are studies using new developed qualitative and quantitative methodologies to document the skin exposure of isocyanates [106]. Further research is needed to define the risk of skin exposure. There is, however, sufficient evidence to justify greater emphasis on the potential risk of isocyanate skin exposure and the importance of preventing such exposures at work and during consumer use [100]. The information is focused on isocyanates, but extrapolation to other LMW agents can be appropriate.

→ ***Severity of clinical picture***

The clinical presentation of respiratory effects due to LMW chemicals resembles that of allergic asthma. A small proportion of the exposed population becomes asthmatic with a latency period between the exposure and asthmatic manifestation. Once the patient is sensitized, there is only a low level needed to provoke symptoms.

Epidemiologic aspects of occupational rhinitis are less established than those of OA. Many of the causative agents of OA are also capable of inducing occupational rhinitis, however, rhinitis seemed to be less common after LMW exposure than HMW exposure. Patients with OA frequently report symptoms of rhinitis. Rhinitis may start before asthma [107] and has been established as an independent risk factor for asthma. The predictive value, however, of symptoms of rhinitis in regard to development of OA has not often been investigated. Karjalainen and colleagues (2003) found a clearly elevated risk of asthma among patients with occupational rhinitis compared with patients with other occupational diseases [108]. Woodworkers, hairdressers, and cleaners with occupational rhinitis had a relative risk of 7; 2,4, and 2,5, respectively. Wood dust, persulfates, formaldehyde, phtalic acid anhydrides, and acrylates are mentioned as most common LMW agents. The rate of asthma was especially high during the year following the notification of occupational rhinitis, yet still there was an increased incidence of OA even after several years. This risk must be taken into account for the prevention, identification, and management of OA.

→ ***Categorization***

The first challenge in causal inference is the identification of the specific agent [109]. Many products and their emissions linked to asthma are complex mixtures of chemicals, particles, and biohazards, which make it difficult to ascribe causibility [110]. Some mixtures and situations can be unravelled.

The metalworking fluids have many sensitizing ingredients, such as formaldehyde, ethanolamines, and colophony. Resins are used in paints, varnishes, reinforced plastics, surface coatings, adhesives, and powder paints.

Metalworkers are not only exposed to metal dusts and fumes. Often it is a complex mixture containing also epoxy resins, hardeners, and metalworking fluids and their components.

One of the problems is that in the wood processing sectors not only an exposure of wood dust occurs. While handling the wood there are many other chemical agents that become free. Some of these are known as sensitizing agents: formaldehyde, isocyanates, and epoxy resins.

→ ***Effect of human behavior***

Smoking has been associated with increased rates of sensitization among workers exposed to platinum salts and certain acid anhydrides, but not to diisocyanates or plicatic acid [111]. In the analyzed reports, there is no evidence found of an association between smoking and LMW agent-induced asthma.

CHAPTER 5 TASK 3: IDENTIFICATION OF DATA GAPS AND RECOMMENDATIONS FOR FURTHER DATA GATHERING AND RESEARCH ACTIVITIES.

Based on the data collected, the meta analysis performed, and the general discussion of the findings, we have noticed some data gaps which are discussed below. This might help the European Commission Scientific Committees to guide further data gathering and prioritize research activities in the field of allergy. Recommendations are formulated below, and include mechanistic and toxicological issues, surveillance, awareness, and organizational aspects.

5.1 Skin sensitizers

5.1.1 Human data collection

Most studies report prevalence data. Incidence data on contact dermatitis are rare.

→ ***Comparability of human data***

Comparison of patch test results between various centres are hampered due to differences in interpretation of the clinical diagnosis:

- The distinction between doubtful (erythematous) reactions and '+' reactions, or between irritant and allergic reactions, is not always clear, and evaluation scores may differ between centers. There is a need for harmonization and European guidelines for interpretation of patch test results. Organization of training programs would be very helpful.

- Sensitization by contact allergens depends on the mode of exposure to the allergen. Concentration of the allergen, duration of exposure and individual conditions such as integrity of the epidermal barrier or pre-existing dermatitis are important [61]. It is necessary to record data of relevant allergic reactions accurately along with patch testing details, such as concentrations and vehicles.

- In various centers, a notable number of cases with, for example, fragrance contact allergy are probably not diagnosed due to the fact that they are only tested for the standard fragrance mix [63]. However, some cases may only be identified using specific commercial products and the individual chemical compounds present in these products. It is technically simple to test this and it carries little risk of serious side-effects, but it is not sufficiently used in practice. Maybe this technique should be recommended to use for all patients, to ensure a correct diagnosis.

- To get more insight in life style factors and/or occupational exposures that lead to sensitization, a standardized questionnaire or checklist would be very helpful. This would help to document exposure information in a harmonized way allowing further categorization of exposure sources.

→ ***Access to human data***

Most information obtained for this project was derived from literature search on public scientific webpages, such as PubMed and ScienceDirect. Additionally, various international organizations have been contacted, from which we learned that various patient databases exist in Europe. However, access to these databases is limited and information from each individual center can only be obtained at a high cost. To derive an overview of complete European data, suggestions are made in 5.4.

5.1.2 Hazard, potency of chemicals and safety assessment

→ ***Hazard***

Further mechanistic research is needed, since not all biological steps of the process of sensitization are completely understood at the moment.

For various chemical compounds, it is difficult to establish whether it is an allergen or an irritant, or both. This needs further hazard assessment and testing. LLNA is an animal test which has been validated and which is able to discriminate sensitizing chemicals. However animal tests cannot be used after 2013 for testing cosmetic ingredients. *In vitro* tests using dendritic cells or dendritic-like cell lines are currently being developed, such as for example VITOSENS® [112, 113], which allow distinction between skin sensitizers and non-sensitizers. In addition, *in vitro* tests for respiratory sensitization that can distinguish between respiratory sensitizers and respiratory non-sensitizers (including skin sensitizers and irritants) are currently under development [114]. Irritants are classified by this test in the non-sensitizer group. However, further research is still needed to improve these test systems, and to validate them.

→ ***Potency***

In order to reduce risks for allergy from cosmetics to a minimum, it is essential that toxicologists develop not only tools to classify chemicals as sensitizers but also to evaluate their potency. Classifying sensitizers according to their potency is still problematic. Only the LLNA has the potential to score chemicals according to their sensitizing potency. *In vitro* tests for potency scoring are under development. In addition manufacturers should continue to limit the use of known sensitizers in formulations and final products, find suitable alternatives, and correctly label their products [115].

→ ***Mixtures***

Combined exposure to different allergens and combined exposure to allergens along with irritants may lower the threshold for elicitation, and most probably also for the induction of contact allergy [61]. Such combinations may be very common in everyday exposures to consumer and occupational products, and perhaps the regulation of permitted concentrations for allergens should take this observation into account.

However, to learn about these mixtures, future research will be needed to understand the mechanisms. At this moment, information on this issue is lacking.

→ ***Susceptibility***

The most relevant risk factors for sensitization to common contact allergens are still not known, although disturbances of the skin barrier function, for example by physical or chemical damage, as well as genetic background or immunological imbalances, have been discussed. Also here, more research is needed, such as analysis for known genetic polymorphisms [116]. Recent technologies such as epigenetics or next-generation sequencing technologies could be used to search for unknown genetic markers related to the risk of developing ACD for individual chemicals.

Improved knowledge of the mechanisms of contact allergy is a condition to enable the best management and treatment of this common disease [117].

→ ***Risk assessment***

We lack specific exposure data for establishing dose-response relationships and for identifying risk factors. Information on morbidity (and individual-related risk factors) should be linked to exposure (and product-related risk factors. Exposure should be better documented using e.g. standardized questionnaires. So far, risk assessment-based on human data was possible only in very limited settings (topical drugs and fragrances) [116, 118].

5.1.3 Time trends

Periodical analysis of known sensitizers allows to identify trends, both downward (e.g. after interventions) or upward (prompting further investigation or direct intervention) [118]. Based on limited available information, for example two known skin sensitizers, lauryl gallate and imidazolidinylurea show increasing trends over time. Regular analysis of clinical surveillance data on incidence of contact allergies should allow to recognize increasing or persistent problems. Therefore, trends should be monitored annually, preferably in various European centers or in a central European database (as described in more detail in 5.4). Focus must not only be on standard patch test series, but also on less frequent allergens. Downward trends may reflect the success of prevention programs (as described above). By focusing on increasing trends of sensitization, whether generally or in well defined subgroups (for example selected occupational exposures or in specific countries or regions), targeted action can be taken. Within relatively short time periods, significant changes in the incidence rates of sensitization for specific chemicals (used in cosmetics) have been observed, obviously due to varying exposures to cosmetic ingredients [68]. Chemicals showing increasing trends require further follow up.

Also 'new' allergens continually emerge and sensitization trends for these new chemicals have to be followed at the population level. Therefore, the patch test standard series of skin sensitizers needs to be continuously adapted.

5.1.4 Spatial trends in Europe

Only a few studies are available that compare prevalence and/or incidence data in various countries (with harmonized protocols). Further studies in various European

countries should be performed, as there might be regional differences in sensitization rates.

Although a lot of patch test data are available across Europe, comparison is not always that simple, as stated above (test concentrations, interpretation of patch test results, selection criteria, year, …). Therefore, efforts should be made to harmonize the surveillance of contact allergies in European regions. This can be achieved by coordinated patch testing in various regions (as described further below). Another possibility is to formulate standardized questionnaires, to examine the general population across Europe.

By contacting various European organizations and projects, information was received about the presence of various patient databases across Europe. These databases contain valuable information on a large amount of chemical sensitizers and a large amount of individuals allergic to them. These databases are often an initiative of hospitals or research centres, and the exact information gathered, may vary. Instead of all these individual databases in various formats, it might be valuable to coordinate the structure of patient databases at a European level or to harmonize the information on exposure and on clinical diagnosis that is available in various countries. It would make data gathering, analysis, and interpretation a lot easier. It would offer a more reliable overview of incidence and prevalence.

Coordination could be realized through a European network for collecting patch-test data. An example is ESSCA, a data center which started in 1996, and which was established in 2001 with funding from the EU [23]. After 2004 however, no further funding was received [118]. Such a European network has several advantages: for example, continuous surveillance on a European level of various contact allergens, especially those in the standard or other series, collective expertise and communication to other research groups and regulatory authorities [78]. In 2008, 11 countries were included in this network, and ESSCA published that it welcomes the addition of new members [23]. The participation of not just one, but several centres per country will average out special characteristics of one department and offer a more representative view on the country's pattern of contact sensitization morbidity. European funding to sustain and expand a coordinating data centre would be a good step in the harmonized collection of European data concerning ACD. Alternatively, a new database could be initiated, but then all efforts already made for ESSCA, have to be performed again.

Information collected in such a harmonized database may be widely disseminated to EU authorities, (patient) organisations, or industries. Additionally, increasing trends and incidence rates related to new allergens should be observed closely, and communicated as fast as possible, to start preventive actions.

In such a European network, the issue of possible methodological variation should be addressed. Effort is needed to obtain further standardization of methods (for example exactly the same patch test material and concentration or exposure time before reading).

5.1.5 Awareness rising

When 'new' allergens emerge or when increasing trends for certain sensitizing compounds are observed, individuals or subgroups at exposure risk for a specific contact allergen need to be identified and preventive actions should be taken. For known occupational sensitizers, such as PPD in hair dyes, prevention should already start at the beginning of the training of hairdressers, to make them aware of the potential risks involved.

New substances are introduced to the market all the time and these need to be scrutinized, as predictive pre-marketing animal testing may sometimes fail to identify contact allergy risk [118].

Sensitization to PPD, which is present in high concentration in temporary henna tattoos, seems to be an unknown risk in the general population. Although PPD concentrations in for example hair dyes are limited, individuals still can experience allergic reactions to these low concentrations when they were already sensitized. This risk caused by earlier exposure to black henna tattoos, is already mentioned on the packaging of hair dyes. However, two additional, preventive actions can be taken here:

- Ameliorate the awareness of parents for the potential risk of sensitization of their children when temporary tattoos are applied;
- Improve regulations and inspections for PPD concentrations in these tattoos. However, this last actions might be complicated due to the fact that these tattoos are often placed during holiday vacations and often by street artists.

More information and advice on the development of skin care policies should be disseminated to management and those with responsibility for health and safety [119]. Individual workers could be further encouraged to make effective use of appropriate skin care provision, such as barrier creams, and the use of protective measures, such as gloves and overalls [119].

5.1.6 Regulatory measures

The most important task is primary prevention. Daily use of products and their individual chemicals should be safe. It will be up to regulators to minimize the risk through effective legislation if required.

→ *Classification and labelling*

For regulatory classification and/or labelling purposes, the correct classification into sensitizing chemicals is wanted. Further research is needed to develop or improve classification models. As can be seen in the weight-of-evidence approach used in this report, not for all chemicals for which human cases were found, R42/R43 labels were assigned. For skin sensitizers, human data were available for various compounds, but only for 76 chemicals these were discussed in the chemical reports. Of those 76 chemicals, only 45 received the R43 label.

Some chemical compounds can lead to both skin and respiratory allergy. However, whether these are 2 completely different mechanisms, or whether these reactions are basically the same, is unknown at this moment. Also whether exposure via skin can lead to or induce respiratory sensitization, is unknown. Also here, further mechanistic research is needed to distinguish between respiratory or skin allergenic properties of a compound. Also a better documentation of human exposures and symptoms will give valuable information.

In 2003, the lack of hazard labelling for household products has been reported [120], followed in 2005 by the lack of hazard labelling for fragrance ingredient in cosmetics [121]. Only ‘fragrance’ or ‘perfume’ must be declared on the container of household and cosmetic products [122]. At this moment, individual chemical compounds are mentioned on these products, but they are still followed by the general term ‘fragrance’ or ‘perfume’. Care must be taken that all known allergens present in the product are correctly mentioned. This is important information for ACD patients, to avoid their allergens selectively. The only alternative for them is to choose for unscented products. Additionally, this information is needed to document the clinical relevance (in terms of

fragrance intolerance) of sensitization to individual fragrance allergens (by positive patch tests) in individual cases.

→ ***Restricted use/banning***

European regulations about the maximum concentration of chemicals in user products do have their effect. Some examples shown earlier such as regulations for nickel sulfate and MDBGN indicate that regulation may stop increasing trends in allergy prevalence already one year after implementation of the regulation. Extended knowledge (e.g. hazard characterization, dose-response) of compounds for which increasing prevalence trends are reported, is needed for future regulations. Future legislation on restriction of allergens should address the problem of allergen substitution in order to protect the consumer. The newly introduced chemicals should also be tested and allergic reactions must be monitored (for example MCI/MI was substituted with MDBGN, which showed also to be an allergen).

5.2 Respiratory sensitizers

5.2.1 Data Gaps

→ ***Surveillance schemes***

Data collection
The question of diagnostic accuracy is a potential source of error. The precision of the reported data remains questionable because the dependency on the definition of OA, job classifications, physician's motivation and recognition. Especially long term surveillance schemes are characterized by practically uniformity and rapidity rather than accuracy and completeness [90]. The time trends are less susceptible to errors than the absolute numbers of diseases in individual years [93].

ECHRS II
One of the aims of ECHRS II was to estimate the relative and attributable risks of new-onset asthma to occupations and work-related exposures. It is a large prospective population-based study in 13 industrialized countries, with 10 European countries. Despite the large setup, the analysis of specific occupations and exposures are based on small numbers and do not allow precise assessment of more specific and uncommon agents and occupations.

Self-reporting system
All workers' own reports and claims of OA may be registered and classified. With a self-reporting system, the diagnosis of asthma has not been validated or confirmed. Self-reported asthma is in general a definition with high specificity but low sensitivity. Such a system is sensitive to misclassification: aggravation of pre-existing disease may be reported as OA, irritant-induced asthma is difficult to distinguish, and asthma-like symptoms can be seen as asthma. These bias results in a higher amount of reported cases compared with other reporting systems.

Voluntary reporting systems / Sentinel programs
Reasons of Underreporting:

- Employees with asthmatic symptoms consult not always a doctor. Many patients are reluctant to report occupational risk factors for fear of losing their job [123].
- The diagnosis is made by specialized physicians, so qualified to make the right diagnosis but the attribution to a causal agent is not always correct. Chest physicians are not always aware of the link between the specific agent and asthma and they have no access or knowledge of the workplace circumstances.
- The system gives little relevant information on new causal agents, probably there is a tendency to attribute OA to well known agents [84]. It is also more difficult to objectively diagnose the causal relation for a new substance to OA.
- An occupational cause is hence not always considered but even if correctly diagnosed not always reported.
- Mostly occupational and chest physicians are asked to participate, the cases treated by the general doctor are therefore not taken into account [86].

The information of a voluntary system is complementary to the medico-legal scheme. For example in SWORD: 40% higher number reported cases compared to disability benefit scheme but the distribution is comparable with the figures of the assurances. Also Vandenplas *et al.* (2005) has notified a doubling of cases for the voluntary system [86]. In Spain there are also arguments to find the voluntary surveillance system more efficient than the medico-legal compulsory system [50].

Medico-legal system / Disablement Benefit scheme
In most countries, this system is undoubtly underreporting the new diagnosed OA. Supplement to the reasons of no reporting or no diagnosing mentioned under the chapter "Voluntary reporting schemes", these factors may account for underreporting:

- The self employed workers are not covered by this system;
- Individuals may be unaware of the possibility of disablement benefit for their diseases.;
- The asthmatic employees find the compensation insufficient and prefer to stay at work despite the symptoms;
- This system picks up fewer cases when the link of the substances or the occupational setting with the development of asthma is not well established.

Compulsory register systems
The Finish Registry of Occupational Diseases (FROD) is maintained by the Finnish Institute of Occupational Health. Reporting of all known or suspected occupational diseases to provincial labor protection authorities is compulsory for Finnish physicians. Additionally, notifications of every new case reported to the insurance companies as an occupational disease are gathered. This system gives a good evidence of the diagnosis and the causal link.

According to German law, it is mandatory for all physicians to report to the responsible accident insurance agency all patients with injuries and diseases possibly related to work. Also additionally, employers and employees can report. The three federal accident insurance agencies have to recognize and confirm these suspected cases by examination of an experienced medical expert. The self employed workers are not covered by this system what is the reason why some risk trades are not well represented (for example hairdressers). This system gives valuable statistics of already recognized cases, but does not identify new health problems.

Time trends
Consistency of diagnostic criteria across time is an important criterion for valid estimation of temporal trends of any disease. There is evidence that non-response of the physicians in a voluntary reporting system increases with membership (e.g. SWORD: The new members reported 31% more cases in their first months compared to later activity). This can be compromised by increased ability to recognize disease by awareness of epidemiological evidence or government policy or compensation. These compromises are typical and evitable for long term surveillance systems [90].

The relative percentages of causative agents allow to see the evolution in handling of these agents. When compounds are more frequently used more workers will be exposed so the relevance for society will be slightly changed. For the health and safety management the annual rate per million workers in this occupation gives a good view, however, this data is not often mentioned.

Time trends of asthma due to LMW agents have to be drawn and analyzed with a critical view. The development of lung disease to such a LMW agent is rather sporadic and uncommon; so many years and several settings with possible risk of exposure are necessary to have enough data. Mostly conclusive answers can not be given.

→ ***Literature of respiratory sensitizers***

Data collection
The small number of studies in the different chemical reports did not allow filtering the potential publication bias. There is a possibility that manuscripts with positive findings were more published than with negative findings.

The frequency of publishing about respiratory diseases due to a specific agent can not always be associated with the incidence of lung diseases or with the potency of the sensitizing agent. A bigger amount of studies published, concerning the development of asthma due to a LMW agent, does not mean directly a bigger incidence of asthma due to this compound. When in the scientific and political world a consensus has been found about the risks and limitations needed, the publications focusing on the incidence and prevalence may decrease. When there is a research or medical centre with a specific expertise, more publications will be found about this particularly pathology in that region of Europe where the research group is situated. However, a higher incidence in this region can not be concluded. Some countries invest more in a regular reporting system, resulting in a valuable database. The information gathered in this way can be used to estimate the incidence and incidence rate for the examined population. Caution is needed to extrapolate for the whole population of this country, let alone for European citizens in general.

Exposure
Inhalation exposure can be measured by environmental measurements, assessments directly from the breathing zones, or by analysis of urinary biomarkers where there is also undefined duration of the exposure. These measurements are not always or not adequately performed. Often is there also an undefined duration of the exposure.

Many studies indicate only a job description. This can be valuable to deepen the occupational health and safety management for a specific industrial sector and to judge the need for further research. However more information is needed to evaluate the relation between a compound and asthma, let alone to find out the contribution to the higher incidence of asthma.

There is a large variation within the plant and between plants with similar manufacturing processes. Therefore, comparison between the studies based on a specific occupational setting or activity is not always correct and valuable.

In the recent years, there are a few interesting examples of studies where the cumulative dust exposure index is used as quantitative measurement of exposure [95, 96, 124, 125]. This cumulative dust exposure index is a personal measurement which brings the duration into account. More detailed information is necessary to investigate the exposure-effect relation more in depth. In turn this evidence enables the development of preventive strategies with propositions of acceptable limits of exposure.

Diagnosis
When comparisons are made between prevalence surveys, the definition of OA becomes an important issue. Different definitions can obviously lead to substantial ascertainment bias [126]. This is the result of absence of consensus of the diagnosis of OA.

Using clinical history as only diagnostic tool create a possibility of overreporting: it is sensitive but not specific. In large epidemiological studies, the use of questionnaires, interrogating only clinical manifestations, are often chosen. This facilitates research of a large work and general population over an extended region. The line between asthma and irritant-induced asthma is not always easy to draw. Because the exposure is not always clear, the distinction between new-developed asthma and aggravated asthma is neither without difficulties [86].

The diagnostic pulmonary tests for asthma in general can also be used for LMW respiratory allergy. Bronchial hyperresponsiveness (BHR) is considered as hallmark of asthma because of the high association between BHR and symptoms; lung function measurements is considered more as marker of inflammation. This can be important for

prevention: the decline in forced experitory volume is maybe a clear and for prevention a measurable important parametric [125].
The specific provocation test is considered as ideal diagnostic test. Practically it is not always used because the expensive and time-consuming procedure and the possible health risk. Only specialised centres can perform this test. The disadvantage is the artificial exposure and it is not sufficiently sensitive.
Serial pulmonary experiatory flow rate indicates an association between the tested agent and the response, but indicates no causality, nevertheless gives it the diagnosis of OA.

A remarkable effort was made by the ECRHS II; harmonized investigation methods and definitions were used to asses the variation in the incidence of asthma in 22 countries with 140000 participants.

Methods to measure the specificity and therefore to ascertain the diagnosis of specifically LMW asthma are still needed to improve. A large amount of patients with LMW-induced asthma have no detectable specific IgE antibodies. There has been already much debate as to whether this is due to a non-IgE mechanisms or whether it is the result of using inappropriate conjugates [127]. In the listed reports IgE mediated astma has been described for chloramine T, diazonium salt, nickel, chrome, cobalt, platinum, reactive dyes, and acid anhydrides.

Additional to the diagnostic pitfalls, some patients are not included in the studies because of the "healthy workers effect":

- Many employees may choose to leave the job because of respiratory complaints before the diagnosis of OA is made;
- Workers with airway hyperresponsiveness, a cardinal finding in asthma, appear to choose jobs that minimize dust exposures;
- A study found out that the atopy was less common among spray painters in the highest range of exposure, compared with less exposed painters [98].

This "healthy workers effect" is considered the most important bias in prevalence estimates in cross sectional surveys, particularly in individual workplaces [126]. Because of these selection factors, cross-sectional prevalence studies are likely to underestimate the risk of asthma related to occupational exposures compared with more resource-intensive longitudinal study designs.

5.2.2 Recommendations

→ ***Reporting systems***

Prevalence studies, such as case reports and cross-sectional studies, will remain useful for the study of workforces exposed to a newly recognised agent. Cohort studies and longitudinal case control studies give the opportunity to investigate the exposure-response relationship more deeply. Comparisons between studies or between regions are currently difficult and too often biased. Harmonization of the definitions and classifications of asthma diagnosis and job description and of the measurement metrics, used in the reporting, should be enhanced.

The surveillance schemes, even a big scale system, cope with a lack of reporting and lack of resources.

Technical and organisational changes can be helpful to improve the accuracy and to help keep data up to date. Programs that work through the internet can make it self-

funding and can enhance the accessibility and collection of these data, as reported in the SHIELD report in 2008 [88].

→ ***Research needs***

The pathological mechanism is still unclear for LMW agents. This understanding is necessary to indicate the tools for diagnosis, prevention, and therapy.

Occupational asthma has the potential to be preventable. Many of the novel respiratory sensitizers causing asthma are LMW chemicals. Unfortunately no successful method to screen for respiratory sensitizers among new chemicals currently exists [128]. Research investments are needed to eliminate the current lack of suitable *in vitro* or *in vivo* methods for the large-scale identification of respiratory sensitizers [114]. QSARs link a chemical structure with a biological endpoint mathematically. Due to the current uncertainties regarding molecular mechanisms for LMW respiratory sensitizers, QSARs are here appropriate. These statical methods can be the starting point for an efficient screening protocol [129].

More quantitative exposure measurements of LMW agents are necessary to investigate the dose-response relation. This evidence enables the development of preventive strategies with propositions of acceptable limits of exposure.

Study of reliable immunologic markers of LMW asthma may indentify individuals at risk. Only for platinum salt-induced asthma there is general consensus that skin prick testing is a useful technique for surveillance and early detection [130].

→ ***Prevention***

The likely population burden of asthma attributable to occupational exposures is estimated on 15%. These figures underscore the need for further actions to reduce the occupational exposure likely to lead to work-related asthma, on both the individual and population level [94].

Some points need more attention to ameliorate primary prevention in the health and safety policy:

- Evidence is growing for the importance of repeated moderate exposures to sensitizing agents in the development of asthma [131]. Studies describe that low concentrations of isocyanates (as low as 1 ppb) can induce functional and inflammatory pulmonary changes [132];
- Inhalation accidents, in both occupational and environmental scenarios, contribute substantially to new-onset asthma. This suggests that workers having such accidents should be monitored closely, as reported in the SHIELD report (2006) [88];
- Proportional, the small businesses are linked to a higher risk of occupational asthma [87]. The most important possible reason is the absence of an adequate policy of health and safety in the companies with only a few employees;
- Studies confirm isocyanate skin exposure in the workplace and support the concept that such exposure may lead to sensitization and asthma after airway challenge. Integrated animal and human research is needed to better understand the role of dermal exposure in human asthma induced by isocyanates and other LMW agents [100].

Some points need more attention to ameliorate the secondary prevention in the health and safety policy.

The importance of early detection and early withdrawal from exposure for the outcome of asthma is generally confirmed.

- The development of rhinitis prior to asthma can be used as alarm signal of asthma and required more frequent surveillance [133]. This association is described in some LMW asthma without being conclusive yet;
- Unfortunately there has often been a period of several years between the onset of symptoms of OA and diagnosis; possible reason is the lack of awareness of the association between the symptoms and the exposure. This is especially likely when the sensitizer is a LMW agent [134]. Workers education and physicians training can be useful;
- Health surveillance can detect OA at an earlier stage. The assessment of a preventive program for diisocyanates in Ontario showed an earlier diagnosis and a better outcome for isocyanate-induced OA compared with OA from other causes [128]. Removal from platinum exposure leads to regression of the symptoms and preventing progression to established and disabling disease [135].

It would be useful to also consider asthma resulting from exposure to irritants in the workplace as well as pre-existing asthma exacerbated by workplace environmental exposures. In some cases these types of asthma can have similar socio-economic impact as sensitizer-induced asthma. Taking into account all components of work-related excess of asthma should enhance prevention and management of asthma at workplace [82].

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ANNEX I CHEMICALS FOR WHICH HUMAN CASES WERE FOUND IN THE LITERATURE, INCLUDING WEIGHT-OF-EVIDENCE SCORE

Skin sensitizers

Compound	CAS	Publications#	R phrase	LLNA*	Score of publications^	Total Score **
1,2-Benzisothiazolin-3-one	2634-33-5	5 (5)	1 (R38/R43)	1 (Moderate)	2	3
1-Butanol	71-36-3	0 (1)	0 (R37/R38)	1 (None/Very weak)	1	1
1-Chloro-2,4-dinitrobenzene	97-00-7	1 (5)	0	1 (Extreme)	2	2
2,5-Diaminotoluene	95-70-5	10 (1)	1 (R43)	1 (Strong)	2	3
2-Hydroxyethyl acrylate	818-61-1	4 (4)	1 (R43)	1 (Moderate)	2	3
2-Hydroxypropyl methacrylate	923-26-2	2 (1)	1 (R43)	0 (None)	2	2
2-Mercaptobenzothiazole	149-30-4	19 (16)	1 (R43)	1 (Moderate)	2	3
3-Aminophenol	591-27-5	4 (0)	0	1 (Moderate)	1	1
3-Dimethylaminopropylamine	109-55-7	8 (6)	1 (R43)	1 (Moderate)	2	3
3-Phenylenediamine	108-45-2	0 (1)	1 (R43)	1 (Strong)	2	3
4-Nitrobenzyl bromide	100-11-8	0 (3)	No records	1 (Extreme)	1	1
6-Methylcoumarin	92-48-8	0 (5)	No records	1 (None/Very weak)	1	1
6-Methylcoumarin	92-48-8	0 (5)	No records	1 (None/Very weak)	1	1
Abietic acid/colophonium	514-10-3	41 (1)	No records	1 (Weak)	2	2
Alpha-amyl cinnamic aldehyde	122-40-7	9 (2)	1 (R43)	1 (Weak)	2	3
Aniline	62-53-3	1 (0)	1 (R43)	1 (Weak)	1	2
Balsam of Peru - Myroxylon pereirae	-	44 (0)	No records	0	2	1
Benzaldehyde	100-52-7	1 (0)	0	1 (None/Very weak)	1	1
Benzoyl peroxide	94-36-0	11 (22)	1 (R43)	1 (Strong)	2	3
Benzyl alcohol	100-51-6	7 (4)	0	1 (None/Very weak)	1	1
Benzyl cinnamate	103-41-3	2 (1)	1 (R43)	1 (Weak)	1	2
Benzyl salicylate	118-58-1	5 (0)	1 (R43)	1 (Moderate)	1	2
Bisphenol A - diglycidyl ether	1675-54-3	0 (4)	1 (R38/R43)	1 (Moderate)	2	3
Camphorquinone	465-29-2	0 (1)	No records	1 (Weak)	1	1
CD-3	25646-71-	0 (4)	1 (R43)	1 (Strong)	1	2

	3					
Chloramine T	127-65-1	0 (1)	1 (R42)	1 (Strong)	1	2
Cinnamic alcohol/aldehyde	104-54-1	14 (31)	1 (R43)	1 (Weak)	1	2
Citral	5392-40-5	14 (6)	1 (R38/R43)	1 (Weak/Moderate)	2	3
Cobalt chloride	7646-79-9	33 (11)	1 (R42/R43)	1 (Strong)	2	3
Coumarin	91-64-5	6 (3)	1 (R43)	0 (None)	1	1
Diethyl maleate	141-05-9	1 (1)	0 (R37/R38)	1 (Moderate)	1	1
Diethylenetriamine	111-40-0	0 (8)	1 (R43)	1 (Moderate)	2	3
Dihydrocoumarin	119-84-6	1 (1)	0 (R38)	1 (Moderate)	1	1
Dimethylsulfoxide	67-68-5	0 (1)	0	1 (Weak)	1	1
Diphenylthiourea	102-08-9	6 (2)	0	1 (Weak)	1	1
Ethyl acrylate	140-88-5	3 (3)	1 (R37/R38/R43)	1 (Weak)	1	2
Ethyl vanillin	121-32-4	0 (1)	0	0 (None)	1	0
Ethylene glycol dimethylacrylate	97-90-5	10 (10)	1 (R37/R43)	1 (Weak)	2	3
Ethylenediamine	107-15-3	4 (14)	1 (R42/R43)	1 (Moderate)	1	2
Eugenol	97-53-0	16 (9)	1 (R38/R43)	1 (Weak)	1	2
Formaldehyde	50-00-0	40 (3)	1 (R43)	1 (Strong)	2	3
Fragrance mix	-	48 (1)	No records	0	2	1
Glutaraldehyde	111-30-8	6 (15)	1 (R42/R43)	1 (Strong)	2	3
Glycerol	56-81-5	1 (0)	0	1 (None/Very weak)	1	1
Glyoxal	107-22-2	4 (3)	1 (R38/R43)	1 (Moderate)	2	3
Hydroquinone	123-31-9	6 (9)	1 (R43)	1 (Strong)	1	2
Hydroxycitronellal	107-75-5	14 (4)	1 (R38/R43)	1 (Weak)	1	2
Imidazolidinylurea	39236-46-9	11 (9)	No records	1 (Weak)	2	2
Iodopropynyl butylcarbamate	55406-53-6	8 (2)	1 (R43)	1 (Strong)	2	3
Isoeugenol	97-54-1	16 (10)	1 (R38/R43)	1 (Moderate)	2	3
Isopropanol	67-63-0	1 (2)	0	0 (None)	1	0
Isopropyl myristate	110-27-0	4 (1)	0	1 (None/Very weak/Weak, False positive)	1	1
Lactic acid	50-21-5	0 (1)	0 (R38)	1 (None/Very weak)	1	1
Lanolin	8006-54-0	30 (0)	0	0	2	1
Lauryl gallate	1166-52-5	3 (0)	1 (R43)	1 (Strong)	2	3

Lilial	80-54-6	4 (3)	1 (R43)	1 (Weak)	2	3
Limonene	138-86-3	15 (4)	1 (R38/R43)	1 (None/Very weak)	1	2
Linalool	78-70-6	6 (5)	1 (R43)	1 (None/Very weak/ Weak)	2	3
Lyral	31906-04-4	13 (4)	1 (R43)	1 (Weak)	1	2
Maleic anhydride	108-31-6	0 (2)	1 (R42/R43)	1 (Strong)	1	2
MCI/MI	26172-55-4	44 (30)	No records	1 (Extreme)	2	2
Methyl 2-nonynoate	111-80-8	0 (1)	No records	1 (Moderate)	1	1
Methyl salicylate	119-36-8	0 (2)	0 (R38)	1 (None/Very weak)	1	1
Methyldibromo glutaronitrile	35691-65-7	49 (19)	1 (R43)	1 (Strong)	2	3
Metol	55-55-0	3 (1)	1 (R43)	1 (Strong)	1	2
n-Butyl glycidyl ether	2426-08-6	0 (3)	1 (R37/R43)	1 (Weak)	2	3
Nickel sulfate	7786-81-4	47 (13)	1 (R42/R43)	1 (Moderate)	2	3
Para-phenylenediamine	106-50-3	79 (16)	1 (R43)	1 (Strong)	2	3
Phenylacetaldehyde	122-78-1	1 (1)	1 (R38/R43)	1 (Moderate)	1	2
Potassium dichromate	7778-50-9	36 (17)	1 (R42/R43)	1 (Extreme)	2	3
Propyl gallate	121-79-9	5 (7)	1 (R43)	1 (Strong)	2	3
Propylene glycol	57-55-6	9 (2)	0	1 (None/Very weak)	2	2
Resorcinol	108-46-3	2 (2)	0 (R38)	1 (None/Moderate)	1	1
Sodium lauryl sulfate	151-21-3	1 (1)	0 (R38)	1 (Weak, false positive)	1	1
Tetramethylthiuram disulfide	137-26-8	18 (38)	1 (R38/R43)	1 (Moderate)	2	3
Vanillin	121-33-5	1 (2)	0	1 (None/Very weak)	2	2

** Potency classification as described by Gerberick et al., Natch et al., or in the hCLAT study*
 # Based on number of publications: full text publications (abstract publications)
^ Maximum score for quality of individual report/publication based on number of cases reported and available data on duration of symptoms, time of exposure and/or latency
*** Total weight-of-evidence score for each compound*
R phrase: '0' means no R42/R43 phrase available and 'no records' means that the chemical is not listed in the BIG or ESIS database. R37/38 are mentioned informatively.

Respiratory sensitizers

Classification	Compound	CAS	# Publications[#]	R phrase	LLNA*	Human data	Score of Publications^	Total score**
Acid anhydride	*Whole class*	-	13 (2)			1	1	
	Chlorendic anhydride	115-27-5	1	0 (R37/R38)	0	0	1	1
	Hexahydrophthalic acid anhydride	85-42-7	2(1)	1(R42/R43)	0	1	1	3
	Himic anhydride	826-62-0	(1)	1(R42/R43)	0	0	0	1
	Maleic anhydride	108-31-6	2(1)	1(R42/R43)	1 (strong)	1	1	4
	Methyltetrahydrophthalic acid anhydride	34090-76-1	3	1(R42/R43)	0	1	1	3
	Phthalic anhydride	85-44-9	5(2)	1 (R37/R38/R42/R43)	1 (strong)	1	1	4
	Pyromellitic dianhydride	89-05-4	2(1)	1(R42/R43)	0	1	1	3
	Tetrachlorophthalic anhydride	117-08-8	1	1(R42/R43)	0	0	1	2
Acrylate	*Whole class*		4(4)			1	1	
	Ethyl acrylate	140-88-5	1	1(R43/R37/R38)	0	0	1	2
	Ethyl methacrylate	97-63-2	1	1(R43/R37/R38)	0	0	1	2
	Ethylene glycol dimethacrylate	97-90-5	1(1)	1(R37/R43)	1 (weak)	1	1	4
	2 hydroyethyl methacrylate	868-77-9	1(1)	1(R43/R38)	0	1	1	3
	Glycidyl methacrylate	106-	1	1(R43/R38)	0	0	1	2

		91-2						
	hydroxypropyl methacrylate	27813-02-1	1(1)	0(R37/R38)	0	1	1	2
	methyl cyanoacrylates	137-05-3	1	0(R37/R38)	0	0	1	1
	Methyl methacrylate	80-62-6	3(2)	1(R37/R38/R43)	0	1	1	3
Amine	*Whole class*		16(1)			1	1	
Aliphatic amine				0	0	1	1	1 / 1
Aliphatic amine	Aminoethylethanolamine	111-41-1	2	1(R43)	0	0	1	2
Amine	EPO60		1	0	0	0	0	
Aliphatic amine	Ethylenediamine	107-15-3	1	1(R42/R43)	1 (moderate)	1	1	4
Amine	Hydroxylamine	7803-49-8	(1)	0	0	0	1	1
Amine	Isophorone diamine	2855-13-2	1	0	0	0	1	1
Heterocyclic amine	N-methyl-morpholine	109-02-4	1	0	0	1	1	2
Heterocyclic amine	N-methyl-piperazine	109-01-3	1	0	0	0	1	1
Heterocyclic amine	Piperazine	110-85-0	5	1(R42/R43)	0	1	1	3
Heterocyclic amine	Piperazine dihydrochloride	142-64-3	2	1(R37/R38/R42)	0	1	1	3
Aliphatic amine	Triethanolamine	102-71-6	1	0	0	0	1	1
Aliphatic amine	Triethylene tetramine	112-24-3	1	1(R43)	0	0	1	2
Amine	Trimethylhexanediamine		1	0	0	0	1	1
Biocides	*Whole class*		8					
	Chloramine T	127-65-1	2	1(R42)	1 (strong)	1	1	4
	Chlorhexidine	55-56-	1	1(R37/R38/R43)	0	0	1	2

		1						
	Glutaraldehyde	111-30-8	2	1(R42/R43)	1 (strong)	1	1	4
	Hexachlorophene	70-30-4	1	0	0	0	1	1
	Isothiazolinones		1	0	0	0	1	1
	Lauryl dimethyl benzyl ammonium chloride		1	0	0	0	0	0
Chemicals	*Whole group*		12(1)					
	Azobisformamide	123-77-3	2	1(R42 /R43)	0	1	1	3
	ECG ink		1	0	0	0	0	0
	Ethylene oxide	75-21-8	2	0(R37/R38)	0	1	1	2
	Iso-nonanyl oxybenzene sulfonate		1	0	0	0	1	1
	Metabisulphite		1	0	0	0	1	1
	Methyl blue		1	0	0	0	1	1
	Ninhydrin	485-47-2	1	0(R37/R38)	0	0	1	1
	Polyethylene	9002-88-4	1	0	0	0	0	0
	Polyfunctional aziridine	151-56-4	1	0	0	0	0	0
	Tetrazene		1	0		0	0	0
	Triglycidyl isocyanurate	2451-62-9	1	1 (R37/R38/R42/R43)	0	0	1	2
Colophony and fluxes	*Whole class*		5					
	Colophony		3	0	0	1	1	2
	Alkylarul polyether alcohol + 5% polypropylene glycol		1	0	0	0	1	1
	Zinc chloride and ammonium chloride flux 95%		1	0	0	0	1	1

Diazonium salt and reactive dyes	*Whole class*		14			1	1	
	Diazonium salt		2	0	0	1	1	2
	Drimaren brillant yellow K-3GL		2	0	0	0	1	1
	Lanasol yellow 4G		2	0	0	0	1	1
	Drimaren brilliant blue K-BL		3	0	0	0	1	1
	Monascus ruber		1	0	0	0	1	1
	Scarlet 32		1	0	0	0	1	1
	Cibachrome brilliant scarlet 3R		1	0	0	0	1	1
	Levafix brilliant yellow E-36		1	0	0	0	1	1
Formaldehyde and resin	*Whole class*		5(1)			1	1	
	Formaldehyde	50-00-00	4(1)	1(R43)	1 (strong)	1	1	4
	Urea formaldehyde	9011-05-6	1	1(R43)	0	0	1	2
Metals	*Whole class*		19(8)			1	1	
	Aluminium	91728-14-2	1	0	0	0	1	2
	Chromium	7440-47-3	7	0	0	1	1	2
	Cobalt	7440-48-4	2(3)	1(R42/43)	0	1	1	3
	Nickel	7440-02-0	5	1(R43	1 (moderate)	1	1	4
	Palladium	7440-05-3	1	0	0	0	1	1
	Platinum	7440-06-4	2	0	0	1	1	2
	Platinum salt: Ammonium tetrachloroplatinate	13820-41-2		1(R38/R42/R43)	0	1	1	3
	Platinum salt: Disodium hexachloroplatinate	16923-58-3	1	1(R42/R43)	0	1	1	3

	Platinum salt: Hexachloroplatinic acid	16941-12-1	1	1(R42/R43)	0	1	1	3
	Platinum salt: Potassium Tetrachloroplatinate II	10025-99-7	1	1(R38/R42/R43)	0	1	1	3
	Stainless steel		1	0	0	0	1	1
	Tungsten carbide	12070-12-1	1	0	0	0	1	1
	Zinc	7440-66-6	2	0	0	0	1	1
	Persulfate salts		6	0	0	1	1	2

** Potency classification as described by Gerberick et al., Natch et al., or in the hCLAT study*
 # Based on number of publications: full text publications (abstract publications)
^ Score of the publication, based on maximum score for quality of individual report/publication based on number of cases reported, diagnostic methods used, and available data on duration of symptoms, time of exposure and/or latency
*** Total weight-of-evidence score for each compound*
R phrase: '0' means no R42/R43 phrase available and 'no records' means that the chemical is not listed in the BIG or ESIS database. R37/38 are mentioned informatively.

ANNEX II LIST OF POTENTIAL HUMAN SKIN SENSITIZERS, FOR WHICH NO HUMAN DATA WERE FOUND IN THIS PROJECT

Compound	CAS	LLNA
1-(2,3,4,5-tetramethylphenyl)-3-(4-tertbutylphenyl) propane-1,3-dione	55846-68-9	None
1-(2,3,4,5-tetramethylphenyl)butane-1,3-dione	167998-73-4	Moderate
1-(2,5-dimethylphenyl)butane-1,3-dione	56290-55-2	Weak
1-(3,4,5-trimethoxyphenyl-4-dimethylpentane-1,3-dione	135099-98-8	None
1-(cyclopropylmethyl--4-methoxybenzene	16510-27-3	Weak
1-(p-methoxyphenyl)-1-penten)3-one	104-27-8	Moderate
1,1,3-trimethyl-3-phenylindane	3910-35-8	None/Very weak
12-bromo-1-dodecanol	3344-77-2	Moderate
12-bromododecanoid acid	73367-80-3	Weak
1-benzoylaceton	93-91-4	Extreme
1-bromobutane	109-65-9	None
1-bromodocosane	6938-66-5	Moderate
1-bromododecane	143-15-7	Weak
1-bromoeicosane	4276-49-7	Moderate
1-bromoheptadecane	3508-00-7	Moderate
1-bromohexadecane	112-82-3	Moderate
1-bromohexane	111-25-1	Weak
1-bromooxtadecane	112-89-0	Weak
1-bromopentadecane	629-72-1	Moderate
1-bromotetradecane	112-71-0	Moderate
1-bromotridecane	765-09-3	Weak
1-bromoundecane	693-67-4	Weak
1-chlorohexanedecane	4860-03-1	Moderate
1-chloromethylpyrene	1086-00-6	Extreme
1-chlorooctadecane	3386-33-2	Weak
1-chlorotetradecane	2425-54-9	Weak
1-iododododecane	4292-19-7	Weak
1-iodohexadecane	544-77-4	Weak
1-iodohexane	638-45-9	None
1-iodononane	4282-42-2	Weak
1-iodooctadecate	629-93-6	None
1-iodotetradecane	19218-94-1	Weak
1-methyl-3-nitro-1-nitrosoguanidine	70-25-7	Extreme
1-naphthol	90-15-3	Moderate
1-naphtol	?	Moderate
1-phenyl-1,2-propanedione	579-07-7	Moderate
1-phenyl-2-methylbutane-1,3-dione	6668-24-2	Weak
1-phenyloctane-1,3-dione	55846-68-1	Weak
1-spiro(4,5)dec-7-en-7-yl-4-penten-1-one	224031-70-3	Moderate
2-(4-amino-2-nitro-phenylamino)-ethanol	2871-01-41	Moderate
2,2,6,6,-tetramethyl-heptane-3,5-dione	1118-71-4	Weak
2,3-butanedione	625-34-3	Weak
2,3-dihydro-2,3,3-trimethyl-1H-Inden-1-one	54440-17-4	None/Very weak
2,4,6-trichloro-1,3,5-triazine	108-77-0	Extreme
2,4-dimethyl-3-cyclohexene-1-carboxaldehyde	?	Moderate

2,4-heptadienal	5910-85-0	Moderate
2-acetylcyclohenanone	874-23-7	None
2-amino-6-chloro-4-nitrophenol	6358-09-4	Moderate
2-aminophenol	95-55-6	Strong
2-bromotetradecanoid acid	10520-81-7	Moderate
2-bromotetradecanoid acid	10520-81-7	Moderate
2-methoxy-4-methyl-phenol	93-51-6	Moderate
2-methyl-2H-isothiazolin-3-one	?	Moderate
2-methyl-3-(4-(2-methylpropyl)phenyl)-propanal	6658-48-6	Moderate
2-methyl-5-hydroxyethylaminophenol	55302-96-0	Strong
2-methyl-butanoic acid-hexyl-ester	10032-15-2	None/Very weak
2-methylundecanal	110-41-8	Weak
2-nitro-p-phenylenediamine	5307-14-2	Strong
2-phenyl-propionic aldehyde	?	Moderate
3,5,5-trimethylhexanoyl chloride	36727-29-4	Moderate
3-bromomethyl-5,5-dimethyldiydro-2(3H)-furanone	154750-20-6	Moderate
3-ethoxy-1-(5,3,4,5-tetramethylphenyl-propane-1,3-dione	170928-69-5	Weak
3-methyl-(5Z)-5-cyclotetradecen-1-one	259854-71-2	Weak
3-methyleugenol	186743-26-0	Weak
3-methylisoeugenol	186743-29-3	Moderate
3-propylidenephrhalide	17369-59-4	Moderate
4,4,4-trifluro-1-penylbutane-1,3-dione	326-06-7	Weak
4-chloroaniline	106-47-8	Moderate
4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (oxazolone)	15646-46-5	Extreme
4-hydrobenzoic acid	99-96-7	None
4-hydroxybenzoic acid	99-96-7	None/Very weak
4-methoxyacetophenone	100-06-1	None/Very weak
5,5-dimethyl-3-methylene-dihydro-2(3H)-furanone	29043-97-8	Moderate
5,6,7-trimethyl-(2E)-2,5-octadien-4-one	357650-26-1	Moderate
5-methyl-2,3-hexanedione	13706-86-0	Weak
5-methyleugenol	186743-25-9	Weak
6-(1-methylpropyl)quinoline	65442-31-1	Weak
6-ethyl-3-methyl-6-octen-1-ol	26330-65-4	Weak
6-methoxy-2,6-dimehtyl octanal	-	None/Very weak
6-methyleugenol	186743-24-8	Weak
6-methylisoeugenol	13041-12-8	Moderate
7,12-dimethylbenanthracene	57-97-6	Extreme
7-bromotetradecane	74036-97-8	Weak
alpha-butyl cinnamic aldehyde	7492-44-6	Weak
Ambrettolide	63286-42-0	Weak
a-methyl cinnamic aldehyde	101-39-3	Moderate
a-methylphenylacetaldehyde	93-53-8	Moderate
benzenesulfonic acid	98-11-3	None
benzo(a)pyrene	50-32-8	Extreme
Benzocaine	94-09-7	None/Weak
Benzoquinone	106-51-4	Extreme
benzyl benzoate	120-51-4	Weak
benzyl bromide	100-39-0	Strong

benzylidene acetone	122-57-6	Moderate
beta-damascone	23726-91-2	Moderate
beta-propriolactone	57-57-8	Strong
bis-1,3-(2,5-dimethylphenyl)-propane-1,3-dione	-	None
C11 azlactone	176665-06-8	Weak
C15 azlactone	176665-09-1	Weak
C17 azlactone	176665-11-5	Weak
C19 azlactone	-	Weak
c4 azlactone	176664-99-6	Moderate
c6 azlactone	176665-02-4	Moderate
c9 azlactone	176665-04-6	Moderate
cis-6-nonenal	2277-19-2	Weak
cyclamen aldehyde	103-95-7	Weak
cyclopropanecarboxylic acid, 2-[1-(1,1-dimethylcyclohexyl)ethoxy]-2-methylpropyl ester	477218-42-1	Weak
diethyl acetaldehyde	97-96-1	Weak
diethyl sulfate	64-67-5	Moderate
Diethylphthalate	84-66-2	None/Very weak
Dihydroeugenol	2785-87-7	Moderate
dimethyl sulfate	77-78-1	Strong
dodecyl methane sulfonate	51323-71-8	Moderate
Estragole	140-67-0	Weak
ethyl benzoylacetate	94-02-0	None
ethylene brassylate	105-95-3	None/Very weak
Farnesal	502-67-0	Weak
fluorescein-5-isothiocyanate	3326-32-7	Strong
Furil	492-94-4	None
Galbanone	56973-85-4	Moderate
Hedione	24851-98-7	None/Very weak
Hexane	110-54-3	None
hexenol-2-trans	928-95-0	None/Very weak
imidazolidinyl urea	39236-46-9	Weak
isononanoyl chloride	57077-36-8	Moderate
isopropyl eugenol	51474-90-9	None
isopropyl isoeugenol	2953-00-7	Strong
Kanamycin	59-01-8; 8063-07-8	None
methyl 2-sulphophenyl octadecanoate	-	Moderate
methyl atrarate	4707-47-5	Weak
methyl dodecane sulfonate	2374-65-4	Strong
methyl hexadecene sulfonate	26452-48-2	Strong
methyl hexadecyl sulfonate	4230-15-3	None
methyl methanesulfonate	66-27-3	Moderate
MPT	3775-21-1	Moderate
n-ethyl-n-nitrosourea	759-73-9	Moderate
N-methyl-N-nitrosourea	684-93-5	Extreme
nonanoyl chloride	764-85-2	Moderate
octanoic acid	124-07-2	None
oleyl methane sulfonate	35709-09-2	Weak
oxalic acid	144-62-7	Weak
palmitoyl chloride	112-67-4	Moderate
pationic 138C	13557-75-0	Weak

Annex IIList of potential human skin sensitizers, for which no human data were found in this project

Pentachlorophenol	87-86-5	Weak
Perillaldehyde	2111-75-3	Moderate
phenyl ethyl alcohol	60-12-8	Very weak/None
p-methylhydrocinnamic aldehyde	5406-12-2	Weak
product 2040	525-76-8	Strong
Propylparaben	94-13-3	None/very weak
Pyridine	110-86-1	None/ Very Weak/Weak
QRM2113	620159-84-4	Weak
Saccharin	81-07-2	None
Safranal	116-26-7	Moderate
salicylic acid	69-72-7	None/Very weak
sodium 3,5,5-trimethylhexanoyloxy benzenesulfonate	94612-91-6	Moderate
streptomycin sulfate	3810-74-0	None
Sulfanilamide	63-74-1	None
sulfanilic acid	121-57-3	None
tartaric acid	87-69-4	Moderate
tetrachlorosalicylanilide	1154-59-2	Extreme
trans-2-decenal	3913-71-1	Moderate
trans-2-hexenal	6728-26-3	Moderate
trans-anethol	104-46-1	Moderate
trimellitic anhydride	552-30-7	Moderate
undec-10-enal	112-45-8	Moderate
vinyl pyridine	1337-81-1	Moderate
vinylidene dichloride	75-35-4	None

ANNEX III LETTER AND QUESTIONNAIRE SEND TO (INTER)NATIONAL ORGANIZATIONS, TOGETHER WITH THE LETTER PROVIDED BY DG SANCO

Dear Sir/Madam,

Under the authority of the European Commission – Health and Consumer Protection Directorate-General – public health and risk assessment, we are collecting and evaluating available European data on incidence and severity of skin (contact dermatitis) and respiratory allergies (asthma) related to exposure of chemicals from non-food and non-pharmaceutical sources.

We would like to ask whether you have available epidemiological data or reports concerning incidence data or cases of human exposure to specific chemicals, related to respiratory allergy (asthma) or allergic contact dermatitis. We would be very pleased when you could share this information with us.

May we ask you to fill in the short questionnaire (5 questions) attached to this letter, and send it back to the address mentioned below, electronic or by postal services. Would it be possible to send this back before the end of March? If you organization is not able to answer, can you please let us know?

Thank you very much for your cooperation.

Kind regards,

Prof. Dr. Greet Schoeters
Karolien Bloemen
Flemish Institute for Technological Research (VITO NV)
Environmental Risk and Health
Boeretang 200
2400 Mol
Belgium

Tel: +32 14 33 51 07
Fax: + 32 14 58 26 57
greet.schoeters@vito.be
karolien.bloemen@vito.be
www.vito.be

Questionnaire

In this questionnaire, "chemicals" are all chemical substances, except from those derived from food and pharmaceutical sources.

1. Do you have original information (numbers) on incidence of asthma and/or contact dermatitis caused by exposure to chemicals, specified by year and by chemical compound? We are especially searching for human data, clinical data, case reports, or statistical files.

☐ Yes
Please specify:
.....
Can you send us this information?
☐ Electronically
☐ By postal services
☐ Comments: .....

☐ No

2. Do you have reports or manuscripts available concerning incidence and/or severity of respiratory and/or skin allergies caused by chemicals?

☐ Yes
Please specify:
☐ You will send us this report
☐ Electronically
☐ By postal services
☐ Comments: .....

☐ No

3. Do you have access to a (patient) database from which we could get information concerning asthma or contact dermatitis caused by exposure to chemicals?

☐ Yes
Please specify:
- Can you give information by chemical compound? ☐ Yes ☐ No
- Can you provide data for each year separately? ☐ Yes ☐ No
- Can you provide specific data concerning gender, age, etc of the individuals? ☐ Yes ☐ No

☐ Yes, but data may not be used for this study

☐ No

4. Can you refer us to other sources where we can find additional data?
.....
.....
.....

5. Based on your experience, are there evident information data gaps on this topic? Do you have suggestions to fill these data gaps?
.....

……
……

Thank you for your answers. If necessary, could we contact you again for further information?

☐ Yes

☐ No

If you have any questions, don't hesitate to contact us.

Please send your answers to the following address.

Karolien Bloemen
Flemish Institute for Technological Research (VITO NV)
Environmental Risk and Health
Boeretang 200
2400 Mol
Belgium

Tel: +32 14 33 51 07
Fax: + 32 14 58 26 57
karolien.bloemen@vito.be
www.vito.be

ANNEX IV LETTER SEND TO (INTER)NATIONAL ORGANIZATIONS WHICH HAVE ACCESS TO A PATIENT DATABASE

Dear Sir/Madam,

Thank you very much for your answer on our previous email of February 20th. You mentioned in the questionnaire that you have access to a patient database. We are evaluating at this moment the possibility of using the valuable data that are available in the various databases in Europe. Therefore, we would like to ask you to answer the 6 short questions below in the column at the right.

A short description of the data we would like to collect:
For each chemical, we would like to know how many individuals experience allergic contact dermatitis / asthma (total amount of individuals with allergic reactions for this chemical / total amount of individuals tested for this chemical), and this for each year separate, for the last 20 years (since 1990), to evaluate trends.

Additionally, we would be very pleased if, for each chemical, specific information about exposure and individual characteristics would be available (averages or percentages for the whole group):

- source of exposure (e.g. deodorant, soap, …), and whether or not the exposure was occupational; *Yes / No*
- Time of exposure (since the first exposure); *Yes / No*
- Duration of symptoms (time since the first symptoms); *Yes / No*
- Temporal pattern of the symptoms: continuously or only directly after exposure; *Yes / No*
- Latency (time between the last exposure and the beginning of the subsequent symptoms); *Yes / No*
- Symptoms: local or systemic; and location; *Yes / No*
- Individual characteristics:
  - age *Yes / No*
  - gender *Yes / No*
  - smoker *Yes / No*
  - atopy *Yes / No*

Could you give us an idea about how many chemicals you can give us data?

……

Could you give us an idea how many individuals are included in your database?

……

It might be possible that we make a selection in the chemicals. Therefore, are there chemicals which are, according to your experience, important to include in this project (e.g. when incidence rates are increasing/decreasing obviously during the last years)?

……
……
……
……

Could you give us an idea of the potential costs/funding involved to receive the data mentioned?

……
……

Would it be possible to have these data available for us before the end of September 2009? *Yes / No*

The data will be collected in a report for the European Commission, who will become owner of them. We will not use the data for any other publication.

If you have any further questions, please don't hesitate to contact us.

Of course, if you have reports concerning this topic available in you organization, we would be very pleased if you could send them to us.

Thank you very much,
Kind regards,

Prof. Dr. Greet Schoeters
Karolien Bloemen
Flemish Institute for Technological Research (VITO NV)
Environmental Risk and Health
Boeretang 200
2400 Mol
Belgium

Tel: +32 14 33 51 07
Fax: + 32 14 58 26 57
greet.schoeters@vito.be
karolien.bloemen@vito.be
www.vito.be

ANNEX V LEGEND OF THE ELECTRONIC FILES

Electronic files are added with all raw data from the articles, including the information used for the scoring in the weight-of-evidence approach (Annex I) and the meta analysis (chemical reports, Annex VI), and all the individual references. The data included in these electronic files is discussed in title "3.5 Database structure to report the collected information" of this report.

An overview of the different files provided is given here:

Skin sensitizers

- Total skin (including all chemicals, also those not discussed further in this report)
- European patch test series, including the individual chemicals on various sheets
    - Balsam of Peru (mix)
    - Cobalt chloride
    - Colophony
    - Formaldehyde
    - Fragrance mix
    - Lanolin
    - MCI-MI
    - Methyldibromo glutaronitrile
    - Nickel sulfate
    - Para-phenylenediamine
    - Potassium dichromate
- Balsam of Peru, including the individual chemicals on various sheets
    - Benzyl alcohol
    - Benzyl cinnamate
    - Benzoyl peroxide
    - Benzyl salicylate
    - Vanillin
- Fragrance mix, including the individual chemicals on various sheets
    - Alpha-amyl cinnamic aldehyde
    - Cinnamic aldehyde + cinnamic alcohol
    - Citral
    - Coumarin
    - Eugenol
    - Hydroxycitronellal
    - Isoeugenol
    - Lyral
- Other chemicals
    - Includes all other chemicals listed in Annex I. Data from each chemical in a different sheet.

Respiratory sensitizers

- Total airways (including all chemicals)
- Acrylates, including the following groups/chemicals in separate sheets:
  - All acrylates together
  - Methyl methacrylate
- Amines, including the following groups/chemicals in separate sheets:
  - All amines together
  - Aliphatic amines
    - Ethylenediamine
    - Triethylene tetramine
    - Aminoethylethanolamine
    - Triethanolamine
  - Heterocyclic amines
    - Piperazine
    - Piperazine dihydrochloride
    - N-methyl-piperazine
  - Piperazine
  - Others
    - EPO60
    - Hydroxylamine
    - Trimethylhexane diamine
- Anhydrides, including the following groups/chemicals in separate sheets:
  - All anhydrides together
  - Maleic anhydride
  - Phthalic anhydride
  - Pyromellitic dianhydride
  - Trimellitic anhydride
  - Hexahydrophthalic acid anhydride
  - Methyltetrahydrophthalic acid anhydride
- Biocides, including the following groups/chemicals in separate sheets:
  - Biocides
  - Glutaraldehyde
  - Chloramine T
- Chemicals, including the following groups/chemicals in separate sheets:
  - All chemicals
  - Azobisformamide
  - Ethylene oxide
- Colophony
- Diazo reactive dyes
  - All diazo reactive dyes
  - Diazonium salt
  - Drimaren brillant yellow K-3GL
  - Lanasol yellow 4 G
  - Drimaren brilliant blue K-BL
- Formaldehyde
  - Formaldehyde
  - Urea formaldehyde
- Isocyanates, including the following groups/chemicals in separate sheets:
  - All isocyanates
  - Diphenylmethane diisocyanate
  - Hexamethylene diisocyanate
  - Toluene diisocyanate
  - Prepoly
  - Naphthylene diisocyanate
  - Others
    - ICA/MIC
    - Isophorone diisocyanate

- Metals, including the following groups/chemicals in separate sheets:
    - All metals
    - Chromium
    - Nickel
    - Cobalt
    - Zinc
    - Platinum
    - Others
        - Palladium
        - Stainless steel
        - Tungsten carbide
- Persulfates
- PVC phtalates
    - Phthalate
    - PVC flooring
    - PVC heating
    - DEHP
- Styrene
- Wood
    - All woods
    - Plicatic acid

ANNEX VI CHEMICAL REPORTS

For the skin sensitizing chemicals, a chemical report for each individual compound is added in this annex, when enough information was found concerning time trends and/or regional differences. Other compounds are summarized in the table at the end. Information about sources of exposure, gender, age, latency, regional differences and time trends are discussed in these reports.

For the respiratory sensitizers, chemical reports have been grouped per chemical class (comparable to Annex V), because few information is available for each individual compound. Here, the same information as for skin is reported, although information on time trends is scarce here. Additionally, information about reported symptoms is added here.