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Bronchial Asthma and COPD due to Irritants in the Workplace – an evidence-based Approach

Dissertation

zur Erlangung des Grades eines Doktors der Medizin

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1. INTRODUCTION

1.1 Subgroups of occupational asthma (OA) with focus on irritant-induced OA including reactive airways dysfunction syndrome (RADS)

Bronchial asthma is defined as a chronic inflammatory disorder of the airways with recurrent episodes of coughing, wheezing, chest tightness, dyspnea, shortness of breath at rest and reversible airflow limitations [1].

Work-related asthma (WRA) as a subgroup of bronchial asthma is characterized by a causative association between work and the asthmatic disorder [2]. Bernstein et al. (1999) [3] defined WRA as a category of asthma and conditions attributable to a particular occupational environment. WRA is subdivided into OA (i.e. new onset WRA) and work-aggravated asthma (i.e. pre-existing or concurrent non-occupational asthma worsened by work factors [4] (Fig.1)).

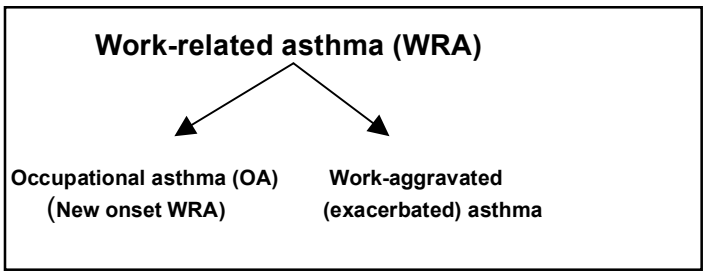

Figure 1. Subgroups of WRA

Occupational agents eliciting bronchial asthma comprise occupational allergens, with their well-defined etiological role and IgE-mediated pathomechanism, as well as occupational agents with unknown pathomechanisms and occupational respiratory irritants, mainly representing low molecular weight chemicals (LMW; <5000 Daltons) causing irritant-induced OA (Fig. 2). The latter agents may also elicit occupational COPD (see chapter 1.2) and include chlorine, acids, welding fumes, as well as isocyanates. However, the etiological role of many low molecular chemicals has not yet been clarified, primarily because of the lack of specific diagnostic tests.

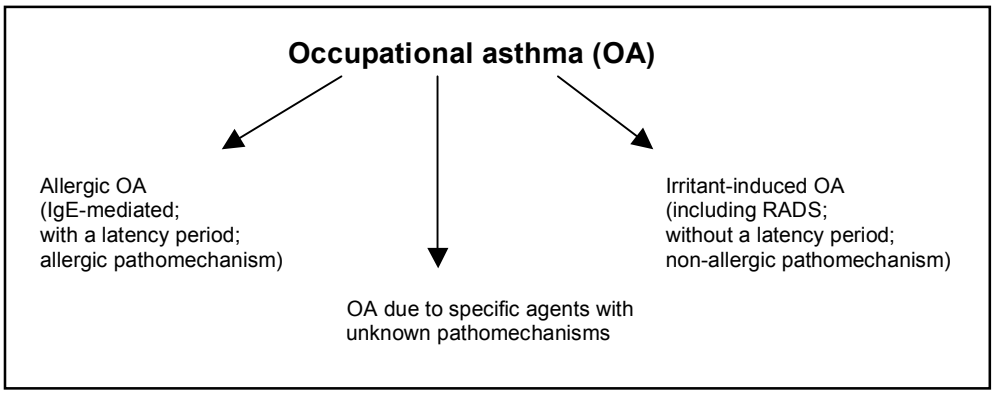

Figure 2. Subgroups of OA

There is increasing evidence that irritant-induced asthma can be further subdivided into three subcategories as outlined in Table 1.

Table 1 Subcategories of irritant-induced OA

Subcategories of irritant-induced OA	**Exposure concentration**	**Duration of exposure**
RADS	Extremely high, > OEL	≤ 1 day
Not so sudden onset of irritant-induced OA	Moderate, OEL range	> 1 day < 4 months
Low dose irritant-induced OA	Low, below OEL	> 4 months

OEL = occupational exposure limit

Many case reports, case series and a few cross-sectional studies demonstrate that a single short-term accidental massive exposure or several short-term high-level exposures to a respiratory irritant can cause asthma within 24 hours without a latency period. Brooks et al. (1985) [5] defined this disorder as “reactive airways dysfunction syndrome” (RADS). This term was later extended to irritant-induced asthma from multiple, somewhat lower, exposure incidents with a less sudden onset that were also shown to cause this disorder [6-11].

Furthermore, there is evidence that a susceptible subgroup of subjects mainly atopics with non-specific bronchial hyperresponsiveness (NSBHR) suffering from irritant-induced OA, is also affected by chronic exposures to relatively low concentrations of irritant gases, fumes or aerosols [11-13]. This disorder has been called “low-dose irritant asthma” (or “low-dose RADS”). Corresponding studies

indicate respiratory effects including asthma from mainly chronic or repeated exposure to a single irritant or a mixture.

The pathophysiological mechanisms of irritant-induced asthma are not well known, and they may be heterogeneous. Airway inflammation, including neutrophils, obviously is commonly involved [14]. At least some irritants induce damage of airway epithelia. Direct activation of nonadrenergic noncholinergic pathways via axon reflexes and onset of neurogenic inflammation may also occur [8]. This may be associated with alteration of epithelial permeability due to release of proinflammatory mediators, such that subepithelial irritant receptors are more likely to be exposed to non-specific stimuli such as cold air or inhaled irritants. Stimulation of these receptors further increases the likelihood of persistence of airway inflammation and of non-specific airway hyperresponsiveness (NSBHR). With increasing level of injury, complete recovery is rare, because airway remodelling due to deposition of type III collagen under the basement membrane occurs [15]. Alberts et al. (1996) [16] demonstrably argued the pathomechanism of RADS to be the predominance of lymphocytes in bronchoalveolar lavages, with evidence of subepithelial thickening and fibrosis. The process is postulated to be the result of extensive denudation of bronchial epithelium, followed by inflammation, release of proinflammatory chemotactic and toxic mediators. Demonstrably causative concentrations of a particular irritant are often below the range of their occupational exposure limits (OELs) or permissible exposure limits (PELs). Irritant examples include swine confinement facilities [17, 18], exposures to cleaning agents [19, 20], solvents, ozone, endotoxin, formaldehyde, quaternary ammonium compounds, chlorine, bisulfite and SO_2, or acid mist [12, 21-24], fumigant residues [25], dusts in the textile paper, mineral fiber or construction industries [21] or in mines [19]. Also encompassed are a proportion of cases of potroom asthma and meatwrappers' asthma . Asthma in cold-air athletes may also be relevant [28, 29]. A summary of the literature on respiratory effects due to irritants below their OELs/PELs is available [30]. Many of the earlier exposure limits have been lowered repeatedly in the light of subsequent clinical or epidemiological findings on their respiratory effects. Other limits remain obstinately high, given their known irritative effects and/or that they are based on sparse data [30]. Accordingly, adherence to OELs/PELs does not prevent the onset of WRA disorders in susceptible subjects.

The broader definition of this disorder (e.g. used in the legal definition in Germany) includes all irritant-induced obstructive airway diseases irrespective of the causative concentrations. Most recurrent exposures to high concentrations are causative [31].

1.1.1 Frequency of OA

OA has become the most prevalent occupational lung disease in developed countries [32] and it is one of the most frequent diagnosis among occupational diseases in general [33]. The annual incidence of WRA is in the range of 50 per million with extremes up to 140 per million workers and even up to 1.300 per million in specific workplace [31].

The available epidemiological and comparative studies and reviews provide evidence that occupational agents cause 5 to 25% of all asthma cases [34-45]. However, complete registries of OA do not exist and therefore the true frequency of the disease is unknown. Ameille et al. (2003) [46] and Fernández-Nieto et al. (2006) [33] stated that OA is underestimated among occupational diseases, because many OA cases are not subjected to diagnostic tests.

Irritant-induced OA is most likely to occur in approximately 5 to18% of all OA cases and is followed by allergic OA as the second most common form [24, 47]. Many individuals with RADS generally continue to report asthma symptoms and demonstrate ongoing evidence of bronchial hyperresponsiveness for years, in addition to persistent airway obstruction [24].

1.2 Chronic obstructive pulmonary disease (COPD) due to occupational exposure

The diagnosis of COPD is based on chronic cough, phlegm during coughing, airflow limitation that is not fully reversible, and a progressive, abnormal inflammative response of the lungs to noxious particles or gases [1]. During ongoing causative exposure (e.g. smoking), airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles, droplets and/ or gases. Patients with COPD have greater numbers of neutrophils and alveolar macrophages in bronchoalveolar lavage fluid than healthy non-smokers [48]. Sites of emphysema, which are frequently found in COPD patients, contain large numbers of lymphocytes, and the extent of lymphocyte accumulation correlates with reduction of FEV_1. It was suggested that the released cytokines released by these lymphocytes might be responsible for matrix destruction of mesenchymal cells surrounding lung elastin and collagen. The CD8+ T cell is the lymphocyte subtype that is found in numerous lung tissue samples from patients with COPD [49].

In their reviews of the literature, Hnizdo et al. (2006) [50], Trupin et al. (2003) [51] and Balmes et al. (2003) [1] found an occupational contribution of about 15% in COPD cases. Occupational COPD is, on epidemiological basis, identified by observing increased frequencies of COPD among certain working groups [15], e.g. in construction workers [14]. Some occupational exposures (e.g. welding fumes, aluminum, potroom fumes, cadmium) may cause COPD associated with emphysema [52, 53].

At later stages of OA, the condition of some subjects does not improve over weekends or during holidays and coincides with symptoms of COPD patients. This observation also applies to non-occupational pulmonary diseases [54, 55] and indicates that a group with changing diagnoses as well as with some overlap between OA and occupational COPD, does exist [15, 56, 57].

1.3 Economic burden

WRA is a serious and sometimes fatal disease [58], which can lead to ill health, inability to work and lost productivity [59, 60]. Based on estimations of new OA cases in Great Britain in 2003 (n= 631), the total lifetime costs to the British society are in the range of £71.7 to £100.1 million or about £3.4 to £4.8 million per year over a lifetime span [61]. Estimated medical costs for OA in the United States were $1.5 billion in 1999 (Quint et al. (2008) [62] cited in Leigh et al. (2003) [63]), and $ 6.6 billion for combined costs of OA and occupational COPD in 1996 [64].

In 2010, estimated costs in Germany for bronchial asthma were € 2.6 billion and for COPD € 5.93 billlion. Bronchial asthma and COPD belong to the most cost-intensive diseases in Germany [65]. In Germany all workers are insured in the statutory occupational accident insurance system, which is sustained by employer contributions [66].

In the year of 2009, the financial burden from occupational disease claims for "Obstructive respiratory tract diseases caused by chemical irritants or substances with toxic effect", which is officially listed as occupational disease no. 4302 (German Occupational Disease Act) [67], was about € 32 million[68]. This amount of money included all expenditures related to that disease, i.e. compensation for confirmed cases, additionally payments for retraining costs of preventive interventions to avoid the onset of this occupational disease [68]. In 2009, 1.437 possible cases referring to the occupational disease no. 4302 were officially reported to the accident insurance institutions. Less than 10% (n= 128) were acknowledged as new cases of the occupational disease no. 4302 [69].

In order to reduce this enormous social burden, a significant decline of the number of new cases of OA must be realized through the improvement of effective preventive measures. This requires detailed knowledge on causative conditions, however, which remain unclear, given the current lack of evidence-based identification of OA inducing agents [62]

1.4 Scope of the study and key question

The aim of this study is to summarize present knowledge on respiratory irritants causing obstructive airway diseases in the humans in the occupational setting and to provide a rating of the strength of evidence for each irritant. It provides a summary of the present state of knowledge regarding the identification of agents by industrial physicians, clinicians and researchers, which has not been previously available in compiled format. It should be noted however, that there is a lack of standardization, of homogenous definitions and of diagnostic tests of irritant-induced OA. Additionally, there is a lack of high-quality research to guide clinicians in specific diagnostic measures and management [70].
Van Kampen et al. (1998) and subsequently the Zentralinstitut für Arbeitsmedizin und Maritime Medizin (ZfAM) of Hamburg, Germany, (www.uke.de/institute/arbeitsmedizin) created a list of all occupational agents assigned to phrase R37 (“airway-irritating substances”; “Code and documentation on occupational diseases”, according to the European Union directives 67/548/EEC, 2001/59/EC, or 2004/73/EC). However, linkages between the agents with respective clinical studies and current documentation of occupational diseases in Germany (BK-DOK) [67] turned out to be more difficult to assign.

The key question of this study considered which of the respiratory airborne agents, professions or work-sites caused irritant-induced OA or occupational COPD, and on what level of evidence such findings were supported.
To the author’s knowledge this study is one of the first attempts to document irritant-induced OA and occupational COPD along with their causative irritant agents in an evidence-based manner.

2. Methodology

The author conducted a systematic review of the literature on occupational irritant-induced asthma and occupational COPD due to occupational irritants.

2.1 Selection criteria

2.1.1 Occupational respiratory irritants

To identify the evidence of irritants of the respiratory tract, all agents denoted as "irritating the respiratory system" by the phrase R 37 [4] and/or as "irritants" by ACGIH 2002 [71] were initially listed.
(http://www.uke.de/institute/arbeitsmedizin/downloads/universitaetsprofessur-arbeitsmedizin/R42_und_R37A-EU09.pdf).
Publications about occupational agents which do not have an irritant effect on the respiratory tract (e.g. about IgE-sensitizing agents) or with unrelated issues (e.g. studies on immunological questions), were excluded.
Irritating gases mainly occurring in the general environment, such as ozone, and inorganic dusts, including silica, talcum, silicates and other fibers known to cause pneumoconioses, were not considered even though exposure to them is frequently associated with mixed ventilation patterns.

2.1.2 Population

The author searched for publications, reporting studies performed exclusively with humans (i.e. animal or in-vitro research was excluded). Studies with non-occupational disorders were also excluded.

2.1.3 Condition

Four different conditions were accepted for inclusion:

1. Irritant-induced OA including RADS
   - Asthma caused by single or multiple occupational exposures to airway irritants.
   - Asthma within 24 hours without a latency period caused by short-term high-level exposures to a respiratory irritant known as acute irritant-induced asthma, or as RADS [5].

2. Work aggravated (exacerbated) irritant-induced OA

- Pre-existing or concurrent asthma worsened by work factors [4].

3. Occupational COPD

- On epidemiological basis, identified by observing increased frequencies of COPD among certain working groups [15].

4. Obstructive ventilation pattern

- Studies about irritant agents, where obstructive ventilation patterns or a significant decrease of FEV1 or FEV1/VC were demonstrated.

2.1.4 Study design, publication type and diagnostic tools

Studies were selected when they met the following design:

- Systematic reviews of cohorts, case-control or cross-sectional studies, cohort studies (prospective/retrospective), longitudinal follow-up, case-control studies, cross-sectional studies, surveys, case series, follow-up of cases or case reports.

Methodological studies (effects of study design and subsequent procedures) were excluded.

Publications were included when they met any of the following criteria:

- examining the frequency of irritant-induced OA or asthmatic work-related symptoms in occupationally exposed groups or individuals
- reporting the causative role of the specific agent or mixture of agents for irritant-induced OA or COPD

Study groups, participants; included if they comprise (any)

- occupationally exposed subjects to airway irritants
- de novo irritant-induced OA
- a previous diagnosis of asthma that is aggravated due to work
- subjects with work-related asthmatic symptoms, if not differentiated whether new-onset or work-aggravated

Studies were included when they applied any of the following diagnostic tools:

- description of work-related asthmatic symptoms (questionnaire)
- lung function test (LFT)
- testing for non-specific bronchial hyperresponsiveness (NSBHR) by means of methacholine, histamine or other pharmacological agents

- serial spirometry or expiratory peak flow rate (PEFR) monitoring or supervised exposure testing in the workplace, challenge with the help of lung function measurements (SFT)
- specific inhalation challenge testing (SIC)
- clinical diagnosis of OA by an expert (occupational or pulmonary physician) and exposure to an irritant agent.

2.1.5 Others

Publication date:

- No restriction for publication dates were made

Language:

- English, German, Spanish, Italian or French

2.2 Strategy of literature search

2.2.1 Database search

MEDLINE®-Database was searched with PubMed® until December 2007 with the following medical subject headings (MeSH) combinations:
“Agent”[MeSH] AND "Humans"[MeSH] AND (("Asthma"[MeSH] OR "Asthma/chemically induced"[MeSH] OR “Asthma/immunology”[MeSH]) OR "Pulmonary Disease, Chronic Obstructive"[MeSH] OR "Lung Diseases, Obstructive/*chemically induced"[MeSH] OR "Respiratory Function Tests"[MeSH]) AND ("Accidents, Occupational"[MeSH] OR "Occupational Exposure"[MeSH] OR "Occupational Diseases"[MeSH] OR "Occupational Diseases/chemically induced"[MeSH]).
If more than 20 publications per agent were found, the search was more specified:
“Agent”[MeSH] AND "Humans"[MeSH] AND ("Cohort Studies"[MeSH] OR "Case-Control Studies"[MeSH] OR "Case-Control Studies"[All Fields] OR "Longitudinal Studies"[MeSH] OR "Longitudinal Studies"[All Fields] OR "Cross-Sectional Studies"[MeSH] OR "Cross-Sectional Studies"[All Fields] OR "Epidemiologic Studies"[MeSH] OR "Epidemiologic Studies"[All Fields] OR "Case Reports"[Publication Type] OR "Meta-Analysis"[MeSH] OR "Meta-Analysis"[All Fields]) AND "adverse effects"[Subheading] AND (("Asthma"[MeSH] OR "Asthma/chemically induced"[MeSH] OR “Asthma/immunology”[MeSH]) OR "Pulmonary Disease, Chronic Obstructive"[MeSH] OR "Lung Diseases,

Obstructive/*chemically induced"[MeSH] OR "Respiratory Function Tests"[MeSH]) AND ("Accidents, Occupational"[MeSH] OR "Occupational Exposure"[MeSH] OR "Occupational Diseases"[MeSH] OR "Occupational Diseases/chemically induced"[MeSH]).

Non-analytic[1] studies (i.e. case reports or case series) were not selected, on the basis that inclusion of these papers would not change the evidence level.

2.2.2 Reference list screening

A second approach consisted of checking reference lists of systematic reviews (until December 2007), identified through database search (until December 2007).

2.2.3 Occupational disease statistics

Further, the author considered occupational disease statistics based either on statutory surveillance or registration systems of occupational diseases, identified through database search (until December 2007).

[1] Epidemiologic study design which is generally (...) employed to test one or more specific hypotheses, typically whether an exposure is a risk factor for a disease (...) (Schoenbach 1999)[72. Schoenbach, V.J. *Understanding the fundamentals of epidemiology: an evolving text. Chapter 8: Analytic study designs*. 1999 [cited; Available from: www.epidemiologic.net.

2.3 Quality assessment

The study quality was assessed with the help of the following check list.

2.3.1 Check list

Design:

- randomized/controlled clinical trial
- systematic review of cohort, case control or cross-sectional studies.
- cohort study (prospective/retrospective), longitudinal follow-up
- case control study
- cross-sectional study, survey
- review
- Case series, follow-up of cases, case reports

Data collection:

- prospective (may be selected retrospectively, but data is collected prospectively)
- unclear

Description of population:

- adequate (i.e. patients described in terms of age, gender and presenting signs and symptoms)
- inadequate

Patient selection:

- consecutive or random selection
- other - specify_____
- not reported

Selection bias:

- yes (i.e. high risk of patient selection related to results)
- no

Description of reference standard:

- adequate (e.g. referral to standard SIC methodology, timing of lung function tests, referral to standard challenge dosages and methodology, involvement of an OA specialist for establishing the diagnosis; sufficient information to reproduce the test)
- inadequate

Description of test (referral to standard methodology; adequate: sufficient information to reproduce the test/ inadequate):

- case history (questionnaire) (adequate/inadequate)
- lung function test (adequate/inadequate)
- pulmonary function test (adequate/inadequate)
- non-specific bronchial challenge (adequate/inadequate)

- specific bronchial challenge (adequate/inadequate)
- other test (adequate/inadequate)

Partial verification bias (i.e. decision to perform the reference test is based upon the results of the test under examination; result of the test predicts patient moving on to the reference standard or vice versa):

- yes
- no

Reporting results:

- allows re-creation of contingency tables
- does not allow re-creation of contingency tables

Confounding (co-exposure; exposure not measured):

- yes
- no

Precision of the study:

- n (study size)
- OR
- P > 0.05

2.3.2 The revised Scottish Intercollegiate Guideline Network (SIGN) grading system [73]

Based on the information with the check list the evidence level of each study was graded according to the revised Scottish Intercollegiate Guidelines Network (SIGN) grading system [73]. Since population-based randomized assignment to different levels of irritant exposure are unethical, no randomised controlled trials (RCTs) could be expected on this topic and, thus, no level 1 evidence would be available, as defined by the revised SIGN grading system. In order to achieve more differentiation among lower evidence grades, the author modified the SIGN grading system and added an additional grade (3+), see Table 2 below.

Table 2 The revised Scottish Intercollegiate Guidelines Network (SIGN) grading system, additionally with the author's modifications [73]

Grading	Description adapted to present study	The revised Scottish Intercollegiate Guidelines Network (SIGN) grading system [73]
1++	High quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a very low risk of bias	High quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a low risk of bias	Well conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a low risk of bias
1-	Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a high risk of bias	Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	High quality systematic reviews of case-control or cohort studies. High quality case control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal. Well-conducted systemic reviews of analytical cross-sectional studies	Well-conducted case control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal. Well-conducted analytical cross-sectional or longitudinal studies with low risk of confounding, bias or chance	Case control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
3+	Cross-sectional, longitudinal studies or surveys with high risk of confounding, bias or chance and a significant risk that the relationship is not causal, non-analytical studies with $n \geq 5$ cases	-
3	Non-analytic studies, e.g. case reports, case series	Non-analytic studies, e.g. case reports, case series
4	Expert opinion	Expert opinion

2.4 Strength of evidence

The strength of evidence for each agent was graded using the Royal College of General Practitioners (RCGP) three-star system of 1995 [74], which also considers quantity (number of studies per agent) and consistency of reported findings with regard to the irritant cause of the asthma.

2.4.1 The Royal College of General Practitioners (RCGP) three-star system (modified by BOHRF (1999)** [75])

The author applied the RCGP three-star system as modified by the British Occupational Health Research Foundation (BOHRF) [75] for rating the strength of evidence. Some additional modifications were necessary for this study, as shown in Table 3.

Table 3: The modified RCGP three-star system of the BOHRF (1999) [75]

Three-star grading[2]	**Description adapted to present study**	**Modified RCGP system of BOHRF (1999)**
***	Strong evidence – provided by generally consistent findings in numerous, high quality scientific studies	Strong evidence – provided by generally consistent findings in numerous, high quality scientific studies
**	Moderate evidence – provided by generally consistent findings in fewer, smaller or lower quality scientific studies	Moderate evidence – provided by generally consistent findings in fewer, smaller or lower quality scientific studies
*[*][2]	Moderate evidence – provided by generally consistent findings in fewer, smaller or lower quality scientific studies, based on questionnaires or other weak evidence	-
*	Limited or contradictory evidence – provided by one scientific study or inconsistent findings in multiple scientific studies	Limited or contradictory evidence – provided by one scientific study or inconsistent findings in multiple scientific studies
[*][2]	Limited or contradictory evidence – provided by one scientific study based only on questionnaires or other weak evidence	-
(*)[2]	Very limited or contradictory evidence – provided by case reports, case series or one occupational disease statistic study with at least five asthma cases	-
-	No scientific evidence – based on clinical studies, theoretical considerations and/or clinical consensus	No scientific evidence – based on clinical studies, theoretical considerations and/or clinical consensus

[2] : Further modifications, see below

The author modified the RCGP three-star grading by using notations with square brackets [ ], in consideration of the level of the underlying studies [*] or *[*], as follows: a collection of studies was graded as "*[*]" (instead of "**"), when it was determined that the clinical investigation was of low quality relative to the scientific rigour of the study, i.e. the clinical findings were mainly based on questionnaires without objective diagnostic parameters, e.g. lung function data. The notation "[*]" was used for a scientific study with weak evidence, i.e. the diagnosis was only based on a questionnaire and/or showed a high risk of confounding.
The RCGP three-star grading system was also modified by changing "-" to "(*)" if there were only non-scientific studies demonstrating causative irritant-induced OA or occupational COPD in at least 5 cases per agent and where no contradictory findings were reported.

For example:

The agent "sodium metabisulfite" showed 4 asthma cases in 4 case reports. The agent was graded with "-", i.e. no scientific evidence, as less than 5 asthma cases. The agent "lubricants" was graded with "(*)", i.e. very limited evidence, because it showed more than 5 asthma cases in occupational disease statistics.

2.5 Data extraction and synthesis

Relevant data from the chosen publications was added to an Excel spreadsheet as explained below. The following information was included in evidence tables (see Table 9, adnex):

Agent (latin)

- CAS no.

Publication [Reference]

- first two authors and year of publication

Strength of evidence

- modified RCGP three-star system applied to the whole study group per agent

Evidence grading, applied to individual study and study types

- modified SIGN system

Occupational exposed subjects studied

- n: number of exposed workers examined

Total no. of irritant-induced OA/ COPD, cases per agent

- n: number of cases

Irritant-induced OA or occupational COPD cases

- n: number of cases and prevalence in %

Diagnostic tests for irritant-induced OA or occupational COPD

- Work-related symptoms, i.e. i.) asthmatic symptoms or physician diagnosed asthma or COPD (symptoms beginning after employment/exposure); ii.) symptoms compatible with RADS (+/(+))

Dependent on the study design, diagnosis of irritant-induced asthma or COPD was based on different diagnostic procedures according to the author. The definitions of confirmed cases were different. At least one of the following diagnostic tests had been used to confirm the diagnosis:

- LFT (lung function test, spirometry). Positive result(s) (obstructive ventilation pattern, i.e. number of cases with reduced FEV1/FVC according to Brändli et al. [76] / all tested subjects; n/n; %)
- SFT (serial lung function testing by spirometry or expiratory flow rate (PEFR) measuring cross-shift (pre-, during, and post-shift) PEFR). Positive result(s) (i.e. number of cases with fall in FEV1 or PEFR during exercise of 15 or 20% according to the author) / all tested subjects; n/n; %

- NSBHR: Positive result(s) (pathologically reduced PC20 (or PD20), i.e. number of cases with 8 or 16 mg/L according to the author) / all tested subjects; n/n; %
- SIC (specific inhalation challenge test). Positive result(s) (i.e. number of cases with fall in FEV1 (PEFR) of 20% according to the author) / all tested subjects; n/n; %

  reaction type:

  i : immediate asthmatic reaction (0-60 min)

  l: late asthmatic reaction (>60 min-24h)

  d: dual asthmatic reaction (immediate and late)

Remarks

- occupation
- clinical tests:
  - immunological testing, such as skin-prick test, specific IgE
  - SFT: detailed description of serial PEFR if > 1 shift (1 day), for example: serial PEFR at work and off-work for x weeks
  - SIC: if tested agent not identical with first column of the Table 9 (adnex)

For example:

SIC with “component of agent” (chlorine)

4/10 SIC+ with “a second agent Y” (1 immediate, 3 late)

dose-response relationship, co-exposure to other irritant agents

3. Results

3.1 Overview on publications retrieved

Three search strings were developed to filter the available literature up until the end of 2007, which include an extreme early study from the year 1932 [77].
254 publications were retrieved from the MEDLINE/ PubMed search. 480 additional publications were retrieved from 12 systematic reviews [5, 14, 16, 24, 66, 78-84], the Occupational Disease Statistics (SWORD 1994-1997 [85-87]; SHIELD 1993 [59]; SORDSA 2001 [88]; SENSOR 2003 [89]; BK-DOK 2007 [67]) and from the library of the Institute of Occupational Medicine, Hamburg (see selection flow diagram, Figure 3).

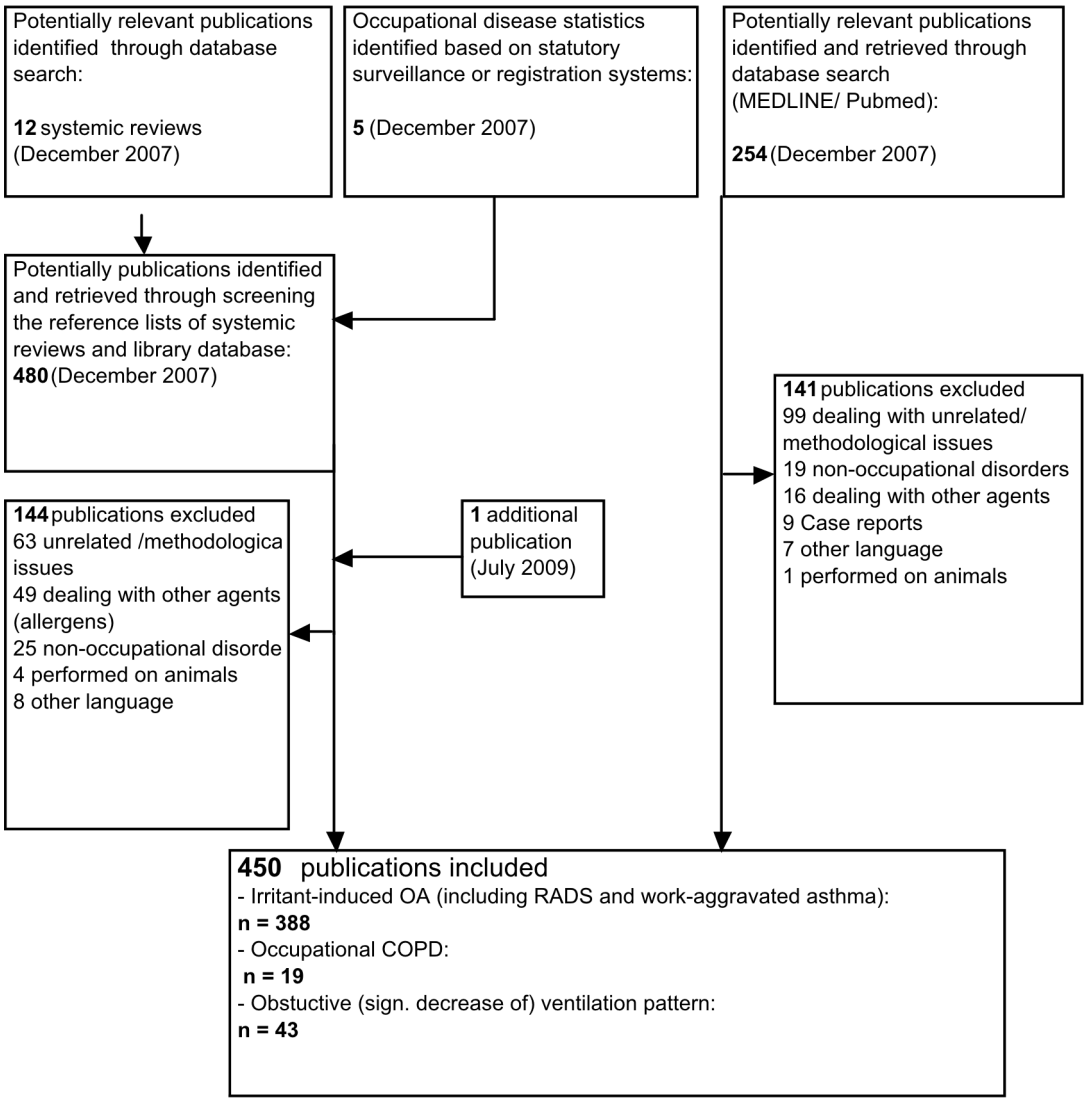

Figure 3: Selection flow diagram

A total of 450 publications were assessed in full-text for reference. 284 were excluded, because they dealed mainly with other agents, such as allergens.
The author's approach corresponds to the procedure of the guidelines of the British Occupational Health Research Foundation (BOHRF) [2].
The 450 publications used for analyses included 113 of the 254 publications obtained from MEDLINE/PubMed search and 337 publications from systematic reviews, or from the library database, as mentioned above.
The 450 publications refer to 129 individual agents, 46 "mixed" agents and 9 work-sites or professions reported to cause OA and/ or occupational COPD.

3.2 Diagnostic aspects

Many different ways of confirming irritant-induced OA were used, with specific inhalation challenge (SIC) and lung function tests (LFT) being the most reliable diagnostic aids.
The SIC was used as the "gold standard" in confirming irritant-induced OA in non-scientific studies (n= 187 studies), and only in a few scientific studies (n= 15).
Another diagnostic method used for irritant-induced OA or occupational COPD was lung function testing (LFT; showing an obstructive ventilation pattern and/or NSBHR related to occupational exposures), mostly in combination with WRA symptoms (n= 180).
Self-reported asthma symptoms or physician reported asthma as documented in questionnaires as an alternative diagnosis for irritant-induced OA, was identified in 27 studies.
Other studies (n=43) were not clearly apportionable to irritant-induced OA, because the results did not specify a causation for irritant-induced OA or occupational COPD. The number of subjects with asthma symptoms and frequencies of obstructive ventilation patterns and/or NSBHR are provided for each study (see Table 9, Adnex).

3.3 Irritant-induced OA as outcome

Irritant-induced OA was the focus of most studies and was the predominant diagnosis.
RADS, as a subgroup of irritant-induced OA, was reported to be due to 46 different agents, with the most prevalent being the World Trade Center disaster in 2001, chlorine, cleaning agents and isocyanates. These were followed by cases, caused

by metam sodium (17), ammonia (11), diesel exhaust (10), acids (9), solvents (8), sulfur dioxide (7), dinitrogen tetraoxide (6), hydrogen chloride (4), smoke (fires, pyrolysis products) (4), chlorofluorocarbons (3), spray paint (3), tear gas (3), bromine (2), dichlorvos (2), sodium azide (2), acrylates (1), amprolium hydrochloride (1), phthalic anhydride (1), bromochlorodifluoromethane (1), bromotrifluoromethane (1), chloramine T (1), chromate (1), hydrazine (1), hydrogen fluoride (1), methylmercaptan (1), phosgene (1), uranium hexafluoride (1), airbag content (1), bleaching agent (1), floor sealant (1), fumigant (1), metal coat remover (1), metal oxide fume (1), pesticides (1), refractory ceramic fibers (1), swine confinement (1).
The preponderance of asthma-inducing agents elicited OA after prolonged exposure and rarely after a single exposure.

Work-aggravated asthma was of less importance in the literature and occurred in only a few studies [5, 90-95].

3.4 Occupational COPD as outcome

Ten agents and four professions or work-sites were reported to cause occupational COPD, as shown in Table 4.

Agents, number of studies (n)	Work-sites or professions, number of studies (n)
○ ammonia (1) ○ cement dust (4) ○ chlorine (1) ○ cleaning agent (1) ○ mustard gas (1) ○ diesel exhaust (2) ○ environmental tobacco smoke(1) ○ isocyanate (1) ○ smoke (1) ○ sulphur dioxide (1)	○ construction work (2) ○ swine confinement (1) ○ farming (1) ○ foundry (1)

Table 4. Agents and professions showing evidence of occupational COPD

As already mentioned, occupational COPD is not specifically addressed in most of the studies. Some describe respiratory symptoms, such as chronic bronchitis (n=17), which may be associated with COPD. One of the few studies which focused on COPD including a large retrospective cohort study on diesel exhaust is Hart et al. (2006 and 2009) [96, 97]. A significantly increased COPD mortality in railroad workers was identified after the introduction of diesel engines in 1945, and so the actual frequencies of occupational COPD may be underestimated in the available literature. Construction work was identified as a cause of occupational COPD, which was demonstrated in 2 out of 4 studies [98, 99]

3.5 Evidence level of the literature (SIGN)

Each considered study was graded for the strength of its scientific evidence using the modified SIGN grading system.

258 of the 450 publications refer to non-analytic studies and were rated according to SIGN as 4, 3 or 3+ and consisted of case reports (n= 225), case series (n= 62), occupational disease statistics (n=33) and reviews (n=7). The other publications comprised analytical studies and were individually rated by SIGN as 2+ (n= 15), 2- (n= 103), or 3+/3 (n= 79).

The highest level by SIGN grading was 2+, indicating a well conducted scientific study (case control or cohort studies) with a low risk of confounding or bias (n= 15 studies). Other studies with a similar design had a higher risk of confounding or bias and were individually rated lower by SIGN grading of 2- (n= 30 studies). Most of the other analytical studies were rated with a SIGN grade of 2-, because their design (cross-sectional or longitudinal study) was limiting (n= 69 studies). Cross-sectional studies, e.g. those with high risk of confounding or bias, were rated even lower with 3/ 3+ (n= 26 studies). A couple of study designs were difficult to classify epidemiologically, including those which were surveys, mostly with very low scientific evidence, rated 3/ 3+ (n= 52 studies), or larger surveys with a lower risk of confounding or bias, which were graded with 2- (n= 4 studies).

Investigations involving dose-response relationship as a form of scientific evidence were performed in 30 out of 450 studies analyzed [53, 96, 97, 100-125].

Another assessment of the level of evidence found in individual studies is to consider in their OR > 2 or < 0.5 for irritant-induced OA or occupational COPD;

this was done in 39 publications [21, 36, 39, 96, 97, 99, 101, 105, 109-112, 114, 118, 120, 126-149].
When the publications were related to the individual (mixed) agent, work-site or profession, the strength of the scientific evidence was always assessed according to the modified RCGP three-star grading, as shown in chapter 2.4.

3.6 Strength of evidence per agent, work-site or profession (RCGP)

The highest evidence level (using the RCGP grading) was found to be moderate, i.e. –"**" for 17 (mixed) agents, work-sites or professions. For six of them (chlorine, platinum salts, environmental tobacco smoke, welding fumes, construction work, World Trade Center disaster in 2001), this level was based on well-conducted studies with low risk of confounding and/or bias (SIGN 2+) (see Table 5). For 11 of these 17 (mixed) agents, SIGN levels of individual studies were lower (benzene-1, 2, 4-tricarboxylic acid; 1,2- anhydride [trimellitic anhydride], cobalt, isocyanates, cement dust, grain dust, animal farming (pig, beef/veal, dairy, poultry), or swine confinement).

Agent	Professions
○ chlorine ○ platinum salts ○ environmental tobacco smoke ○ welding fumes	○ construction work ○ World Trade Center disaster 2001

Table 5. Agents, profession or work-site showing the highest evidence level for irritant-induced OA or occupational COPD by three-star (**2+)

Moderate scientific evidence – provided by generally consistent findings in fewer, smaller or lower quality scientific studies, based on questionnaires or other inadequacies, i.e. "*[*]", was found, that implicated seven agents (phthalic anhydride, glutaraldehyde [glutaral], sulfur dioxide, cotton (dust, raw) CNT 750, potroom aluminum smelting, farming (various) or foundry).

Limited or contradictory evidence – provided by one scientific study or inconsistent findings in multiple scientific studies, i.e."*", was identified 40 times, and after down-grading because of inadequate methodological aspects, i.e. "[*]" on three

occasions. For the majority of agents, only non-scientific studies were reported for ≥ 5 cases, i.e. “(*)” or less than 5 cases, i.e. “-“ (see Table 7).
Of the 450 studies examined 254 were classified as non-analytical studies, mainly consisting of case reports and case series.

The evidence level for agent involvement in these non-analytical studies was raised if at least 5 cases were identified by the case reports/ case series or occupational disease statistics for which proof of irritant-induced OA or occupational COPD existed. When graded according to the three-star system, the evidence level ranged from “very limited or contradictory evidence” in 29 studies, i.e. “(*)”, to “no scientific evidence” “-” 92 times (see Table 6).

Evidence level (modified RCGP three star grading)	Number of agents/ professions or work-sites
***	0
**	17
*[*]	7
*	40
[*]	3
(*)	29
-	92

Table 6. Evidence level of individual agents/professions and work-sites according to the modified RCGP three-star system

The compiled assessment of the individual studies, along with their relevant clinical data and strength of evidence for irritant agents, professions or workplaces causing asthma or COPD, is presented as an overview in Table 7. (See Table 9 in the Adnex for full information).
The outcome for each agent causing OA or occupational COPD was graded according to the modified RCGP three-star system to classify the strength of evidence of its causative role in irritant-induced OA/ occupational COPD. The highest evidence achieved was two stars ”**”, indicating a moderate degree of

evidence provided by generally consistent findings in fewer, smaller or lower quality scientific studies.

The evidence levels for agents, professions and work-sites according to the modified RCGP three-star grading are listed in Table 8 (see below).

For additional findings as well as details of individual studies, see Table 9 in the Adnex.

Table 7: Overview of individual irritant agents causing irritant-induced OA or occupational COPD

Agent CAS	Evidence level (modified RCGP three-star grading)	Number of studies per agent	References
Acids			
", acetic 64-19-7	*	**3**	[101, 150, 151]
", not specified	(*)	**2**	[5, 12]
", various	-	**1**	[9]
", " (hydrochloric, hydrofluoric, nitric, perchloric, sulfuric)	-	**1**	[152]
", hydrochloric 7647-01-0	(*)	**6**	[9, 90, 153, 154]
", hydrofluoric 7664-39-3	-	**1**	[155]
", sulfuric 7664-93-9	*	**3**	[90, 102, 156]
Acrylates			
", not specified	-	**1**	[157]
", alkyl cyanoacrylates	(*)	**4**	[158-161]
", cyanoacrylate glue	-	**1**	[162]
", " [loctite] 53858-53-0	*	**4**	[131, 161, 163, 164]
", methacrylates	*	**1**	[130]
", methyl 2-cyanoacrylate 137-05-3	-	**3**	[158, 161, 165]
", methylmethacrylate 80-62-6	-	**2**	[161, 166]
Aluminum salts aluminum fluoride: 7724-18-1 aluminum sulfate: 10043-01-3	*	**1**	[91]
2-Aminoethanol [2-ethanolamine] 141-43-5	-	**1**	[167]
Amino-ethyl-ethanolamine 111-41-1	-	**1**	[168]
3-Amino-5-mercapto-1,2,4-triazole 16691-43-3	(*)	**1**	[169]
Ammonia 7664-41-7	*	**6**	[20, 170-174]
Ammonium chloride (triple salt) 12125-02-9	-	**1**	[175]

Ammonium thioglycolate 5421-46-5	**-**	**1**	[176]
Amprolium hydrochloride 137-88-2	**-**	**1**	[177]
Anhydrides			
", various	*	**2**	[178, 179]
", dioctyl phthalate 117-81-7	**-**	**1**	[180]
", hexahydrophthalic 37226-48-5	**-**	**1**	[181]
", himic 2746-19-2	**-**	**1**	[182]
", maleic 108-31-6	**-**	**2**	[183, 184]
", methyltetrahydrophthalic 26590-20-9	**-**	**1**	[185]
", phthalic anhydride 85-44-9	***[*]**	**5**	[186-190]
", pyromellitic dianhydride 89-32-7	**-**	**1**	[191]
", tetrachlorophthalic anhydride 117-08-8	*	**4**	[192], [193], [194], [195]
", benzene-1, 2, 4- tricarboxylic acid 1,2- anhydride [trimellitic anhydride] 552-30-7	**	**5**	[189, 196-199]
Aziridine, polyfunctional (dust) 64265-57-2	**(*)**	**2**	[200, 201]
Azobisformamide [azodicarbonamide] 123-77-3	*	**5**	[202-206]
Benzalkonium chloride (fumes) 8001-54-5	**-**	**2**	[207, 208]
1, 2-Benzisothiazoline-3-one (fumes) 2634-33-5	**-**	**1**	[209]
Bisulfite, *SO2* *SO2: 7446-09-5*	**-**	**1**	[12]
Bromine, hydrobromic acid	**-**	**1**	[210]
Bromochlorodifluoromethane (Halon 1211) 353-59-3	**-**	**1**	[92]
Bromotrifluoromethane (Halon 1301) 75-63-8	**-**	**1**	[211]
Cadmium (fumes) 7440-43-9	*	**4**	[53, 212-214]
Calcium carbonate [chalk powder]	**-**	**1**	[103]
Calcium oxide 1305-78-8	**-**	**1**	[9]
Captafol (chlorinated thiocarboximide fungicide) 2425-06-1	**-**	**1**	[215]
Chloramine T (powder dust) 7080-50-4	**(*)**	**5**	[216-220]
Chlorhexidine 55-56-1	**-**	**1**	[221]
Chlorine 7782-50-5	**	**11**	[9, 157, 222-230]
Chromate (not specified) [see also cement]	**(*)**	**9**	[231, 232] [77, 233-238]

Cobalt 7440-48-4	**	**15**	[59, 105, 238-250]
3-(Diamino-amino)propylamine [3-(dimethylamino)propylamine] 109-55-7	**(*)**	**1**	[251]
Diamine, aliphatic + cycloaliphatic (hardener) 2855-13-2 (isophorone diamine)	**-**	**1**	[252]
Diazonium tetrafluoroborate 14239-22-6	**-**	**2**	[253, 254]
Dichlorodiethyl sulfide [mustard gas] +505-60-2	**(*)**	**1**	[255]
Dichlorvos (organophosphate) 62-73-7	**-**	**2**	[256, 257]
Diethanolamine 111-42-2	**-**	**1**	[258]
2-Diethylaminoethanol [diethyl aminoethanol] 100-37-8	**(*)**	**1**	[259]
2-Dimethylaminoethanol [dimethyl ethanolamine] 108-01-0	**-**	**2**	[260, 261]
Diinitrogen tetraoxide [dinitrogentetroxide] 10544-72-6	**(*)**	**1**	[262]
Ethylenediamine [ethylene diamine] 107-15-3	*	**6**	[160, 176, 263-266]
Ethylene oxide 75-21-8	**-**	**2**	[267, 268]
Formaldehyde (gas, dust) 50-00-0	*	**9**	[269-274], [275, 276]
Freon, (freon-22)	**-**	**2**	[277, 278]
Glutaraldehyde [glutaral] 11-30-8	***[*]**	**9**	[59, 87, 279-285]
Hexachlorophene 70-30-4	**-**	**1**	[286]
Hexamethylenetetramine 100-97-0	*	**3**	[176, 287, 288]
Hydrazine 302-01-2	**-**	**1**	[5]
Iridium salt	**-**	**1**	[289]
Isocyanates, isocyanurate			
", various (HDI, MDI, TDI)	**	**11**	[31, 87, 141, 142, 157, 272, 290-294]
", Diphenylmethane diisocyanate [MDI] 5873-54-1	**	**6**	[295-300],
", " prepolymers	**-**	**1**	[301]
", Hexamethylene diisocyanate [HDI]; plus isodurane diisocyanate 822-06-0	**(*)**	**3**	[302, 303]
", HDI biuret plus 4035-89-6			[304]
", 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate [isophorone diisocyanate, IPDI] 4098-71-9	**-**	**1**	[305]

", Methyl isocyanate [MIC] 624-83-9	*	**6**	[306-311]
", 1,5-Naphthylene diisocyanate [NDI] 3173-72-6	**(*)**	**(3)**	[312-314]
", Polymethylene polyphenyl isocyanate 9016-87-9	*	**1**	[315]
", Toluene diisocyanate, TDI 2,4: 584-84-9; 2,6:91-08-7	**	**12**	[9, 117, 157, 316-324]
", Triglycidil isocyanurate 2451-62-1	-	**1**	[325]
", Triphenylmethane triisocyanate	-	**1**	[326]
Isothiazolinone 55965-84-9	-	**1**	[327]
Lauryl dimethyl benzyl ammonium chloride 139-07-1	-	**1**	[328]
Metam sodium [methyldithiocarbamate] 144-54-7	-	**1**	[93]
Methylmercaptan 74-93-1	-	**1**	**[157]**
Monoethanolamine 141-43-5	-	**1**	[176]
N-methylmorpholine 109-02-4	**[*]**	**1**	[329]
Nickel sulphate →anhydrous 7786-81-4 →hexahydrate 10101-97-0	**(*)**	**5**	[237, 330-333]
Ninhydrin 485-47-2	-	**1**	[325]
Nitrogen chloride [nitrogen trichloride, trichloramine] 10025-85-1	**[*]**	**2**	[143, 334]
Ozone (gassings) 10028-15-6	*	**1**	[335]
Palladium 7440-05-3	-	**1**	[336]
Paraphenylenediamine 106-50-3	**(*)**	**1**	[337]
Paraquat 4685-14-7	*	**2**	[120, 144]
Persulfate			
", not specified	**(*)**	**2**	[338, 339]
", ammonium	-	**1**	[340]
", potassium (7727-21-1) and ammonium peroxydisufate (7727-54-0)	**[*]**	**5**	[341]
", alcalic	-	**1**	[342]
", Sodium persulfate 7775-27-1	-	**1**	[343]
", Dipotassium peroxo-peroxodisulfate [potassium persulfate] 7727-21-1	-	**1**	[344]
", Diammonium peroxodisulfate [ammonium persulfate] 7727-54-0	*	**4**	[345-347]
Phenylglycine acid chloride	*	**1**	[348]

39478-47-2			
Phosgene 75-44-5	**-**	**2**	[9, 349]
Piperazine dihydrochloride 142-64-3	*	**3**	[122, 168, 265]
Platinum salts (7440-06-4)	**	**8**	[123, 168, 350-355]
Polyethylene 9002-88-4	**-**	**3**	[356-358]
Polymethyl-methacrylate [plexiglas powder] 9011-14-7	**-**	**1**	[359]
Polypropylene, heated to 250 °C 9003-07-0	**[*]**	**2**	[360, 361]
Polyvinyl chloride (fume) 9002-86-2	*	**8**	[27, 362-366] [367, 368]
Potassium dichromate 7778-50-9 (see also chromium;cement)	**(*)**	**1**	[369]
Potassium aluminum tetrafluoride 14484-69-6	**(*)**	**1**	[370]
Rosin core solder, thermal decomposition [colophony] 8050-09-7	*	**6**	[59, 87, 371-373]
Sodium azide (powder dust) 26628-22-8	**-**	**1**	[374]
Sodium iso-nonanoyl oxybenzene sulphonate [SINOS] 123354-92-7	**(*)**	**3**	[375-377]
Sodium metabisulfite [metabisulfite sodium] 7681-57-4	**(*)**	**4**	[94, 378-380]
Styrene monomer 100-42-5	**(*)**	**3**	[124, 381, 382]
Sulfur dioxide 7446-09-5	***[*]**	**5**	[9, 147, 383-385]
Sulfathiazole 72-14-0	**-**	**1**	[386]
Terpene (3-carene) 13466-78-9	**-**	**2**	[387, 388]
Tetrachloroisophthalonitrile (fungicide)	**-**	**1**	[389]
Tetrahydrothiophene 110-01-0	**-**	**1**	[390]
Tetramethrin [1-(5-tretrazoly)- 4-guanyl-tetrazene hydrate] 7696-12-0	**-**	**2**	[328, 391]
Tributyl tin oxide [carpet fungicide]	**-**	**1**	[392]
Triethanolamine 102-71-6	**-**	**1**	[167]
Tungsten carbide 11130-73-7	**-**	**1**	[393]
Tylosin tartrate	**-**	**1**	[394]
Uranium hexafluoride 7783-81-5	**-**	**2**	[5, 395]
Urea (fume) 57-13-6	**-**	**1**	[95]
Urea formaldehyde foam 64869-57-4*/*	**-**	**1**	[396]

Phenol-formaldehyde resin 9003-35-4			
Vanadium 7440-62-2 **+ divanadium pentoxide** 1314-62-1	*	**5**	[88, 397-400]
Zinc (fume) 7440-66-6	-	**3**	[401-403]
Zinc chloride (fume) 7646-85-7	-	**1**	[175]
Mixed agent	**Evidence level**	**Number of studies per agent**	
Acid fluxes	-	**1**	[59]
Acrylic acid	-	**1**	[158]
Airbag content	-	**1**	[404]
Bleaching agent (fumes)	-	**1**	[90]
Cement (dust)	**	**13**	[104, 125, 226, 405-414]
Chlorofluorocarbons (degradation products)	-	**1**	[415]
Cleaning agents (not specified)	*	**8**	[12, 20, 39, 100, 129, 416-418]
", detergents	-	**2**	[419, 420]
Coffee, green (dust)	*	**4**	[421-424]
Cotton (dust, raw) CNT 750	*[*]	**(11)**	[21, 106-108, 411, 425-430]
Cutting oil	-	**2**	[12, 431]
Diesel exhaust	*	**5**	[96, 97, 432-434]
ECG ink	-	**2**	[435, 436]
Endotoxin (see also cotton dust, swine confinement, poultry confinement, house dust)	*	**2**	[20, 437]
Environmental tobacco smoke	**	**10**	[109, 110, 128, 132-136, 438, 439]
Floor sealant (aromatic hydrocarbons)	-	**1**	[5]
Fumigating agent	-	**1**	[5]
Furan-based binder	-	**1**	[440]
Grain (dust)	**	**9**	[21, 114-116, 441-445]
", rice (dust)	[*]	**1**	[446]
Hairdressing chemicals	(*)	**1**	[272]
Lubricants (not specified)	(*)	**2**	[31, 432]
Metal coat remover (coating removing chemical)	-	**1**	[5]
Metal oxide (fume)	-	**1**	[447]
Metal working fluids [MWF]	-	**1**	[448]
Oil (spill)	*	**1**	[118]
Paint (fumes)	*	**3**	[9, 119, 449]
Paper dust A111	(*)	**1**	[21]
Perfume agents (research lab)	-	**1**	[12, 450]
Pestcides (not specified)	*	**4**	[121, 145, 257, 451]
Polyamines, aliphatic	[*]	**1**	[452]
Polyester	(*)	**2**	[453, 454]
Potroom aluminum smelting	*[*]	**10**	[26, 238, 455-462]
Powder paints	(*)	**1**	[463]
Pyrazolone (see reactive dye)	-	**1**	[464]
Reactive dyes	*	**5**	[465-469]

Refractory ceramic fibers [RCF]	*	**2**	[470, 471]
Smoke (fires, pyrolysis products)	*	**4**	[5, 20, 472, 473]
", **(oil fire and dust storm)**	*	**1**	[474]
", **(biomass, indoor)**	**(*)**	**1**	[475]
Soldering flux (fumes)	*	**4**	[175, 476-478]
Solvents (not specified)	*	**3**	[21, 432, 479]
Spray paint	-	**1**	[5]
Tall oil	-	**1**	[480]
Tear gas	-	**4**	[481-484]
Welding fumes	**	**17**	[20, 21, 31, 87, 238, 272, 485-495]
Work-site or profession	**Evidence level**	**Number of studies per work-site or profession**	
Construction work (dust, agent not specified)	**	**4**	[98, 99, 127, 496]
Farming			
", (various)	***[*]**	**8**	[111, 112, 137-139, 497-499]
", animals (pig, beef/veal, dairy, poultry)	**	**3**	[500-502]
Foundry [see also isocyanates (MDI)]	***[*]**	**4**	[113, 140, 503, 504]
Health care workers	*	**2**	[36, 505]
Poultry confinement	***(*)**	**4**	[146, 506-508]
Poultry confinement, slaughtery house	*	**3**	[509-511]
Swine confinement	**	**8**	[17, 18, 134, 148, 512-515]
World Trade Center disaster 2001	**	**7**	[125, 149, 516-520]

Table 8: Evidence level for agents, professions and work-site according to the modified RCGP three-star system

Evidence level (modified RCGP three-star grading)	Number of agents/work-sites or professions	Agents, work-site or profession [Synonym] (CAS)
***	0	-
**	17	Benzene-1, 2, 4-tricarboxylic acid; 1,2- anhydride [trimellitic anhydride] (552-30-7); chlorine (7782-50-5); cobalt (7440-48-4); various isocyanates, isocyanurate (HDI, MDI, TDI), diphenylmethane diisocyanate [MDI] (5873-54-1), toluene diisocyanate, TDI 2,4 (584-84-9), TDI 2,6: (91-08-7); platinum salts (7440-06-4); cement (dust); environmental tobacco smoke; grain (dust); welding fumes; construction work (dust, agent not specified); farming, animals (pig, beef/veal, dairy, poultry); swine confinement; World Trade Center disaster 2001
*[*]	7	Phthalic anhydride (85-44-9); glutaraldehyde [glutaral] (11-30-8); sulfur dioxide (7446-09-5); cotton (dust, raw) CNT 750; potroom aluminum smelting; farming (various); foundry
*	41	Acetic acid (64-19-7); sulfuric acid (7664-93-9); metacrylates, loctide® (53858-53-0); aluminum salts [aluminum fluoride] (7724-18-1); aluminum sulfate: (10043-01-3); ammonia (7664-41-7); various anhydrides; tetrachlorophthalic anhydride (117-08-8); azobisformamide (123-77-3); cadmium (fumes) (7440-43-9); ethylenediamine (107-15-3); formaldehyde (gas, dust) (50-00-0); hexamethylenetetramine (100-97-0); methyl isocyanate [MIC] (624-83-9); naphthylene diisocyanate (3173-72-6); polymethylene polyphenyl isocyanate (9016-87-9); N-methylmorpholine (09-02-4); ozone (gassings) (10028-15-6); paraquat (4685-14-7); diammonium peroxodisulfate (7727-54-0); phenylglycine acid chloride (39478-47-2); piperazine dihydrochloride (142-64-3); polyvinyl chloride (fume) (9002-86-2); rosin core solder; thermal decomposition (8050-09-7); vanadium (7440-62-2) + divanadium pentoxide (1314-62-1); cleaning agents (not specified); green coffee (dust); diesel exhaust; endotoxin; oil (spill); paint (fumes); pesticides (not specified); reactive dyes; refractory ceramic fibers [RCF]; smoke (fires, pyrolysis products; oil fire and dust storm); soldering flux; solvents (not specified); health care workers; poultry confinement; slaughtery house
[*]	3	Nitrogen chloride (10025-85-1); polyamines, aliphatic; potassium persulfate (7727-21-1) and ammonium peroxydisufate (7727-54-0); grain rice (dust)
(*)	28	Acids not specified; hydrochloric acids (7647-01-0); alkyl cyanoacrylates; 3-amino-5-mercapto-1,2,4-triazole l(16691-43-3); aziridine, polyfunctional (dust) (64265-57-2); chloramine T

		(powder dust) (7080-50-4); chromate (not specified); 3-(diamino-amino)propylamine (109-55-7); dichlorodiethyl sulfide (505-60-2); 2-diethylaminoethanol (100-37-8); diinitrogen tetraoxide (10544-72-6); hexamethylene diisocyanate [HDI], plus isodurane diisocyanate (822-06-0); HDI biuret plus (4035-89-6); nickel sulphate anhydrous (7786-81-4); hexahydrate (10101-97-0); paraphenylenediamine (106-50-3); persulfate (not specified); polypropylene, heated to 250 °C (9003-07-0); potassium dichromate (7778-50-9); potassium aluminum tetrafluoride (14484-69-6); sodium iso-nonanoyl oxybenzene sulphonate [SINOS] (123354-92-7); sodium metabisulfite (7681-57-4); styrene monomer (100-42-5); hairdressing chemicals; lubricants (not specified); paper dust A111; aliphatic polyamines; polyester; powder paints; smoke (biomass, indoor)
-	93	Acids various; hydrofluoric acids (7664-39-3); cyanoacrylate glue; methyl 2-cyanoacrylate (137-05-3); methylmethacrylate (80-62-6); 2-aminoethanol (141-43-5); amino-ethyl-ethanolamine (111-41-1); ammonium chloride (triple salt) (12125-02-9); ammonium thioglycolate (5421-46-5); amprolium hydrochloride (137-88-2); dioctyl phthalate (117-81-7); hexahydrophthalic anhydrides (37226-48-5); himic anhydrides (2746-19-2); maleic anhydrides (108-31-6); methyltetrahydrophthalic anhydrides (26590-20-9); pyromellitic dianhydride (89-32-7); benzalkonium chloride (fumes) (8001-54-5); 1, 2-benzisothiazoline-3-one (fumes) (2634-33-5); bisulfite*, SO2*:(7446-09-5*);* hydrobromic acid bromine; bromochlorodifluoromethane [halon 1211] (353-59-3); bromotrifluoromethane [halon 1301](75-63-8); calcium carbonate [chalk powder]; calcium oxide (1305-78-8); captafol (2425-06-1); chlorhexidine (55-56-1); aliphatic + cycloaliphatic diamine, (hardener) (2855-13-2) [isophorone diamine]; diazonium tetrafluoroborate (14239-22-6); dichlorvos [organophosphate] (62-73-7); diethanolamine (111-42-2); 2-dimethylaminoethanol [dimethyl ethanolamine] (108-01-0); ethylene oxide (75-21-8); freon-22; hexachlorophene (70-30-4); hydrazine (302-01-2); iridium salt; isocyanate prepolymers; 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (4098-71-9); triglycidil isocyanurate (2451-62-1); triphenylmethane triisocyanate; isothiazolinone (55965-84-9); lauryl dimethyl benzyl ammonium chloride (139-07-1); metam sodium (144-54-7); methylmercaptan (74-93-1); monoethanolamine (141-43-5); ninhydrin (485-47-2); palladium (7440-05-3); ammonium persulfate; alcalic persulfate; sodium persulfate (7775-27-1); dipotassium peroxo-peroxodisulfate (7727-21-1); phosgene (75-44-5); polyethylene (9002-88-4); polymethyl-methacrylate (9011-14-7); sodium azide (powder dust) (26628-22-8); sulfathiazole (2-14-0); terpene (3-carene) (3466-78-9); tetrahydrothiophene (110-01-0); tetrachloroisophthalonitrile (fungicide); tetramethrin (7696-12-0); tributyl tin oxide; triethanolamine (102-71-6); tungsten carbide (11130-73-7); tylosin tartrate; uranium hexafluoride (7783-81-5); urea (fume) (57-13-6); urea formaldehyde foam (64869-57-4); phenol-formaldehyde resin (9003-35-4); zinc (fume) (7440-66-6); zinc chloride (fume) (7646-85-7); acid fluxes; acrylic acid; airbag content; bleaching agent (fumes); chlorofluorocarbons (degradation products); detergents; cutting oil; ECG ink; floor sealant (aromatic hydrocarbons); fumigating agent; furan-based binder; metal coating remover (coating removing chemical); metal oxide (fume); metal working fluids; perfume agents (research lab); pyrazolone; spray paint; tall oil; tear gas

4. DISCUSSION

The main objective of this study is to give an evidence-based overview of the literature on irritative agents, professions or work-sites causing irritant-induced OA and occupational COPD. To the author's knowledge, this study is the first of such an initiative.

The 450 publications retrieved (Table 9, see Adnex) in this work mainly refer to individual agents (n=129), but also to mixed exposure(s) or multicomponent work-sites or professions (n=59), where heterogeneous exposure to irritating substances is common, e.g. swine confinement, "construction work" or "farming", giving 184 different causes of irritant-induced OA and/or occupational COPD in total.

4.1 Methodological aspects

4.1.1 Evidence-based approach

As quoted by the AHRQ in 2002 [521] it is not easy to find a fitting evidence-based grading system to adequately rate studies at a scientific level. Evidence-based guidelines are an important tool for an appropriate decision-making process in clinical practice, as Guyatt et al. (2008) has pointed out: "Busy clinicians require succinct, transparent, easily digested summary on evidence" [522]. In this study it is important for identification and management of workers with suspected WRA or occupational COPD [523-525],

4.1.2 Grading systems

Literature grading for guidelines is mainly based on randomised controlled trials (RCTs) [526]. It is obvious that the level of scientific evidence in the analyzed studies is generally low, mainly because of the absence of RCTs and other high-level studies. Tarlo et al. (2008) [4] therefore stressed that "(…) case reports (…) must be relied on to supplement traditional randomized controlled trial (RCT) evidence". Thus, the procedure used e.g. by the American College of Chest Physicians (ACCP) was not suitable for application to the key question of this study. RCTs are not ethical for studying exposition to agents expected to produce damage.

The author used the revised SIGN system (2000) [73] for quality grading of each study and the RCGP three-star system (1995) [74] for grading the strength of evidence referring to a single agent, work-site or profession causing irritant-induced OA or occupational COPD. This approach corresponds to the guidelines commissioned and funded by the BOHRF for prevention, identification and management of irritant-induced OA using evidence statements [2]. The objective was to obtain precise information on the strength of evidence for causation of irritant-induced OA or occupational COPD by irritant agents. It was necessary to amend the grading in order to meet the objectives of this study because of numerous study designs offering a low level of evidence. The RCGP three-star system and the revised SIGN grading system were adjusted to take into account the level and the amount of diagnostic tests, as well as the number of examined cases.

The author modified the RCGP three-star grading system to reflect the quality of the diagnostic setting, i.e. a study was graded as "*[*]" instead "**" when there were no objective diagnostic parameters. Frequently findings were almost exclusively based on questionnaires without any objective diagnostic parameters. All study types of various scientific strength, such as cohort studies and cross sectional studies, were taken into account. The author up-graded summarized case studies or case series to (*) if a total of ≥ 5 affected subjects was investigated. For example the agent "sodium metabisulfite" which was shown to cause asthma in 4 case reports, was graded with (-), i.e. no scientific evidence, because it showed less than 5 asthma cases. The agent "lubricants" was graded with (*), i.e. very limited evidence, because it showed more than 5 asthma cases in 2 studies of occupational disease statistics (see Tables 2 and 3, chapter "Methodology").

4.1.3 Individual diagnostic methods

Irritant-induced OA cannot usually be diagnosed in one clinical visit and, instead, follow-up and/or detailed clinical investigations are necessary. The diagnostic "gold standard" for OA is SIC obtained using a specific occupational agent in an exposure chamber. It is particularly indicated in the clinical setting where new causative substances with still unknown adverse respiratory sensitization potentials are suspected. A modified SIC method, consisting of closed-circuit equipment, can also be used to generate well-defined stable concentrations of

occupational agents [527]. SIC was mainly applied in case reports, case series and other non-scientific studies (n= 187), presumably because SIC is time-consuming, needs experienced personnel, is only available in a limited number of centers and because it is not of diagnostic use in RADS or occupational COPD cases.

Serial PEF or FEV1 cross-shift measurements combined with registration of WRA symptoms are an alternative approach to confirm irritant-induced OA. The use of serial FEV1 measurements is even better validated than serial NSBHR in the occupational setting [528, 529] and was carried out in n= 180 studies (see Table 9 in the Adnex).
Leuenberger et al. (2000) [37] stressed that occupational exposure, particularly from dust and fumes, was associated with increased NSBHR.
Boutet et al. (2007) [530] concluded in a prospective study that NSBHR in asymptomatic subjects exposed to high molecular weight allergens is an important determinant for the development of respiratory symptoms. This supports the approach using NSBHR as one of the major screening items in the diagnosis of irritant-induced OA.
A questionnaire is a good tool to detect occupational sensitization and/or respiratory symptoms [531, 532]. Its sensitivity is high, but its specifity is low [533-536].

4.2 Basis and quality of data

The scientific quality of each individual study was rated using a SIGN grading system. Non-analytic studies, such as case reports or case series, were rated low at 3 or 3+ and comprised more than half of the considered studies (254 of 450 studies). According to the SIGN grading system (see Table 1 in chapter “Methodology”), only 113 of the 450 publications provided evidence regarded as scientific, such as cross-sectional, case-control or (prospective) cohort studies. The highest SIGN quality for individual studies by SIGN was 2+ and was achieved in only 15 studies. Additionally 69/ 450 studies were cross-sectional or longitudinal studies based on low-level scientific evidence (2-).
The highest strength of evidence for an agent obtained for 17 agents was two stars “**”, (see Table 5 and Table 6, chapter “Results”). The lowest level without

scientific evidence, rated as "-" using the RCGP three-star grading system, applied to 92 agents.

The strongest evidence of causation indicated by the RCGP three-star system requires at least three high-quality cohort or case-control studies with a 2++ by SIGN. Population-based randomization to exposure of irritants is unethical and RCTs are not available, i.e. none of the studies could be rated by 1-, 1+ or 1++ in the SIGN system.

So, the evidence levels to confirm irritant-induced OA or occupational COPD for the listed irritant agents, professions or work-sites (see Table 7 in chapter "Results") are mainly low to very low with the major reasons that high-quality studies were missing and the quality of the available studies was low. Nevertheless, this knowledge is the best available and may help physicians to identify a suspected irritant agent as causative in irritant-induced OA and/ or occupational COPD [62]. As also recently stressed by Quint et al. (2008) [62], "implementing an evidence-based identification and regulatory process for OA will help to ensure primary prevention of OA". In cases of low evidence level of an agent that does not exclude a causative role, caution should be exercised and a more detailed diagnostic testing of relevant exposure should be performed.

4.3 Occupational COPD, an underestimated category

The population-attributable fraction for COPD associated with occupational exposure was estimated between 9% and 31 % [51]. However, the true population-attributable risk due to occupational exposure is unclear [537] as occupational COPD is rarely clinically diagnosed. Blanc et al. (2009) [538] recently published an ecological analysis using data from three large studies, comprising the Burden of Obstructive Lung Disease study (BOLD), the Latin American Project for Investigation of Obstructive Lung Disease (PLATINO) and the European Community Respiratory Health Survey follow-up (ECHRS II), where occupational COPD was also not a primary goal. The original publications are mainly concerned with OA or asthma symptoms, but a history of pre-existing OA or RADS cannot be allowed to exclude occupational COPD [539].

Only 19 out of 450 publications that referred to occupational COPD were identified, with most implicating inorganic or organic dust or fumes, such as cement dust, construction work and diesel exhaust, as the causative agents.

As an example, the mixed agent cement dust was investigated in 13 studies, but only four studies documented cement dust as an causative agent in occupational COPD [104, 406, 407, 410]. The remaining nine studies described irritant-induced OA cases [226, 411-414] or identified significant asthma symptoms/ obstructive ventilation patterns without a clear diagnosis [170, 405, 408, 540]. It can be assumed that if it had been considered on the other 9 studies, occupational COPD caused by cement dust would have been frequently observed.

Blanc et al. (2009) [538] stressed that the contribution of occupational exposure can not be ignored, because “the association between adverse working conditions and COPD (…) carries significance as a global finding (…), alongside the (…) critical contribution of cigarette smoking to disease prevalence”.
General acceptance of this statement does not exist [15, 539], although evidence for an association between individual exposure levels and COPD is accumulating in the latest literature [1, 97, 488, 537, 541-543].

4.4 Irritant-induced OA – a broader definition

Irritant-induced OA includes three subcategories that predominantly differ according to the concentration of irritants in the workplace atmosphere. It can occur without a latency period, such as RADS, as was shown for 46 causative agents in this study, with the highest prevalence after spills of acids or tear gas (see Table 9, Adnex). Other agents, e.g. isocyanates or welding fumes, usually induce a slower onset of low dose irritant-induced asthma with a latency period and mostly without evidence of an IgE-mediated pathomechanism (see Table 9, Adnex).
The ACCP also stated in their last Consensus Statement in 2008 [4] that cases who do not meet the stringent criteria of RADS [5] (e.g. where is a lag of several days before the onset of symptoms or where there is no single massive exposure but rather repeated exposure over days and weeks) should be subsumed into a broader category of irritant-induced asthma. Burge (2010)[11] suggested using the term “not so sudden onset of irritant-induced asthma” for those developing the disorder after such exposure within a period of 2 days to 4 months. In a definition similar to the author’s, he used the term “low dose irritant-induced asthma” for those developing the disorder after relatively low repeated exposure for more than 4 months.

Bardana (1999) [544] and Vandenplas and Malo (2003) [545] questioned whether such rather low concentrations could actually cause irritant-induced OA. These different opinions about the pathogenetic role of chronic or recurrent exposure(s) to low concentrations of respiratory irritants seem to be due to inadequate considering of the increased susceptibility of a small group of workers. Occupational disease statistics do not contain such cases so far.

4.5 Comparison to occupational guidelines or consensus statements – what is new?

In the current analysis the focus has been on irritant agents causing irritant-induced OA and occupational COPD. Both entities have been underestimated or even overlooked in the past. Occupational COPD has not been considered as a subgroup of COPD thus so far [539, 546]; and the definition of irritant-induced OA has been heterogenous at best [4, 70, 547, 548]. Furthermore, the guidelines dealing with respiratory disorders have not even considered causation by individual irritant agents so far.

The ACCP published a Consensus Statement in 2008 [4] which focuses on the diagnosis and management of WRA after a latency period, i.e. due allergens and "sensitizers" with unknown pathomechanisms, effectively sidelining irritant-induced asthma to RADS.

The Agency for Healthcare Research and Quality (AHRQ) published the Evidence Report Number 129 "Diagnosis and Management of WRA", a systematic review [70]. The key question of the report was to ascertain the best diagnostic approach for a patient with suspected WRA. In respect of irritant-induced asthma, they only considered RADS as a non-allergic asthma due to mainly low molecular weight compounds of unknown pathomechanism.

The Canadian Thoracic Society "Guidelines for OA" [549] was the first evidence-based guideline, although irritant-induced OA was limited to RADS. If criteria were not fulfilled, irritant-induced OA was discussed as a controversial diagnosis. The three evidence levels in the "Guidelines for OA"[549] were based on quality of scientific evidence within analyzed studies [550]. Compared with the modified RCGP three-star grading (see Table 3 in chapter "Methodology"), the different levels are defined in a more general way, i.e. not considering the quantitative aspect if only studies with lower scientific evidence exist.

The evidence review and recommendations for OA by the BOHRF [2] were designed to improve the prevention, identification and management of OA. This work mainly deals with asthma after a latency period and irritant-induced OA closely and RADS to be related entities. The difference in comparison with the analysis of this study is obvious even though the author's evidence-based approach was closely related to the BOHRF guidelines and used the same grading systems.

In summary, the existing guidelines or statements mostly define irritant-induced OA as RADS. Occupational COPD as a distinct entity has not been considered in any guideline, although it is becoming recognized as such in more recent publications [537, 539, 546].

This evidence-based approach is the first which especially focuses on irritative agents within the broader definition of irritant-induced OA and occupational COPD. For clarification the grading systems were modified in accordance with BOHRF [2] when considering the extent and quality of the clinical investigations, with the goal of creating evidence levels for causative irritative agents as precisely as possible.

4.6 Possible tools to identify irritant-induced OA or occupational COPD and future aspects

The diagnosis of the subgroup irritant-induced OA should be considered if:

- there has been exposure to high concentration of an irritative agent identified in this study and the development of asthma without a latency period (original definition of RADS) or
- there has been chronic or repeated exposures to moderate (in the TLV ranges) concentrations of an identified irritative agent and the development of asthma with a latency period, but without evidence of an IgE-mediated pathomechanism
- there is evidence that a highly susceptible subject (e.g. with pre-existing NSBHR) develop new onset (or aggravation) of asthma upon occupational exposure to an identified irritative agent even at concentrations below the TLV.

The diagnosis of occupational COPD should be considered if:

- there has been exposure to an agent capable of causing occupational COPD, and
- demonstration of not reversible chronic airway disease is found and
- there is a temporal relationship between the period of exposure (mostly cumulative exposures to identified irritants play the causative role and acute WRA symptoms are frequently missing) and development of COPD.

Occupational COPD has to be taken into consideration especially in non-smokers, i.e. when dominating non-occupational causes for COPD are obviously not present.

The estimated high population-attributable risk in the range of 15 % for OA and COPD from occupational exposure indicates that more detailed and intensive research as well as strategies designed to prevent these disorders should receive high priority in the global efforts to reduce the burden of these diseases. This implies amplified evidence-based diagnostic procedures that help to optimize primary and secondary prevention by the physicians dealing with occupational diseases.

Adequate primary prevention is the best and favoured way for intervention. If this is not possible, effective secondary preventive measures, such as wearing adequate respiratory devices, are required [551-554].

4.7 Limitations of the study

4.7.1 Evaluation of evidence

The paradigm of “evidence-based medicine” has been criticized by leading scientists [555-558]. Bias in the selection of information may be a problem for generalization of findings in single studies [559, 560]. In spite of these limitations, approaches as an alternative to evaluation of the literature have not been generally accepted. Evaluation of the evidence depends on the domain which means the factors to be considered in assessing the extent to which the study results are reliable or valid.

Kunz et al. (2008) [561] stressed the approach of grading scientific studies on basis of additional qualified data, i.e. dose response relationships. The latter was seen in 30/450 individual studies in this current work. Other studies were based on

evidence by OR >2 or < 0.5 for irritant-induced OA and occupational COPD which was applied as an approach in 40/450 individual studies (see Table 9, Adnex). There are numerous procedural methods for rating the strength of scientific evidence. The AHRQ emphasized in 2002: “Systems for grading the strength of a body of evidence are much less uniform than those for rating study quality” [521].

4.7.2 Possible confounding and selection bias

It is possible that not all relevant studies were found in the search of literature. The selection of literature was made by one person and this may have introduced a personal bias. Additionally, the author searched the Internet using Pubmed® for relevant studies that were identified using by MeSH terms. Some known studies could not be found by the MeSH term raster (see chapter ‘Methodology’), usually because of missing key words. As stressed by the AHRQ 2002 [521], MeSH terms are not very sensitive for identifying systems grading evidence. This might also be a problem in the identification of studies of irritant-induced OA or occupational COPD.

Possible risks due to confounding (e.g. exposure to multiple agents) and selection bias (e.g. healthy worker effect) were taken into consideration.

The search was terminated by the end of December 2007. Only one further study (Hart et al. 2009 [97]) has been added, because it was important for the evidence-level of a currently discussed agent with just a few low level studies so far(diesel exhaust).

4.8 Concluding remarks

OA is the most common chronic occupational lung disease in many industrialized countries [2].

COPD is the fourth leading cause of death worldwide of which the occupational contingent is a significant portion [15]. The term occupational COPD does not officially exist. However, it has to be considered as a subcategory of COPD [539]. This study shows that reliable, sensitive and specific methods are required in the diagnostic approach for confirming irritant-induced OA or occupational COPD. The concrete diagnostic set-up in a suspected subject depends on the individual clinical data and on the knowledge of asthma-inducing agents in the workplace.

SIC is a cumbersome test that is costly, not standardized and not always available, meaning that it is frequently difficult to get a reliable diagnosis. On this basis, these investigations may help in diagnostics especially for agent exposures where the author was able to relate irritant-induced OA or occupational COPD to a high evidence-based level (i.e. two stars according to the RCGP grading).

A list representing the strength of evidence for irritating agents to be causative in irritant-induced OA or occupational COPD has been created (see Table 7, chapter “Results”). A low level or absence of evidence for many agents in causing irritant-induced OA or occupational COPD is sometimes due to contradictory findings in literature, but it is mostly due to the absence of rigorous scientific studies, with many gaps remaining in the knowledge of a causative role for individual agents and conditions. Therefore and because of rarely applied diagnostic approach in the clinical setting, the author’s literature search and evaluation lead assume that irritant-induced OA and occupational COPD are considerably underreported in cross-sectional studies and occupational disease statistics. This list needs updating in the light of recent literature in order to provide a realistic overview of agents and evidence level in their causation of irritant-induced OA or occupational COPD.

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5. Summary

WRA is a frequent occupational lung disease in an industrialized environment. It is subdivided into OA and work-aggravated asthma. The main objective of this study was to give an evidence-based overview of the literature on irritative agents, professions or work-sites causing irritant-induced OA and/or occupational COPD. The key question of this study was: Which respiratory airborne agents cause irritant-induced OA or occupational COPD, and on what level of evidence can such findings be supported?

A database search provided 450 studies dealing with irritant-induced OA or occupational COPD.

An evidence-based approach was realized by applying two suitable grading systems. The modified SIGN grading was used for rating the quality of all considered studies individually. The modified RCGP three-star system was applied for grading each irritant agent with regard to cause irritant-induced OA or occupational COPD. This permitted all study types of different scientific strength. Irritant-induced OA was the focus of most studies and was the predominant diagnosis. Different ways of confirming irritant-induced OA were used by the author. SIC and lung function tests were the most important diagnostic instruments. Occupational COPD was mainly not the specified target. Some studies described respiratory symptoms such as chronic bronchitis which may be associated with COPD. One of the few studies which focused on occupational COPD was a large retrospective cohort study on diesel exhaust.

According to the SIGN grading system more than half of the publications represent non-scientific studies and were rated with the lowest level, this comprises case reports/case series and occupational disease statistics. The highest level realized by SIGN grading was 2+, which means a well-conducted scientific study with a low risk of confounding or bias. On the basis of the modified RCGP three-star grading, strengths of evidence of the individual/ mixed agent, profession or work-site could be identified. The highest evidence achieved was two stars.

Only a few agents, professions or work-sites were found with moderate evidence level for causing irritant-induced OA or occupational COPD. These include chlorine, welding fumes or construction work (see Table 5, chapter “Results”). For most agents only limited evidence was found, e.g. for acids, acrylates or diesel exhaust (see Table 7, chapter “Results”).

It is possible that not all relevant studies were found in the literature search. Other limitations of this work may be due to the possibility that selection and information bias cannot be totally excluded.

In conclusion, the diagnosis of irritant-induced OA should be especially considered if there has been a single or repeated exposures to high concentration or chronic exposures to moderate (in the TLV ranges) concentrations of an identified irritative agent without evidence of an IgE-mediated pathomechanism.

The diagnosis of occupational COPD should be considered if there have been mainly chronic exposures to an agent capable of causing occupational COPD, not reversible chronic airway disease is found, there is a temporal relationship between the period of exposure and development of COPD, and no other cause of COPD is obviously present.

Based on the estimated population-attributable risk due to occupational exposures for OA and occupational COPD, which are still considerably underreported occupational diseases, strategies designed to prevent these disorders should receive high priority in global efforts to reduce their burden. This study might amplify adequate diagnostic procedures and may help to optimize primary and secondary prevention. Since there is still a lack of knowledge on the causative role of irritant agents and conditions, more research should focus on this issue in order to improve further respective evidence-based diagnostic procedures and preventive strategies.

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9. Declaration of authorship

I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Hamburg. The work is original except where indicated by special reference in the text and no part of the dissertation has been submitted for any other degree. Any views expressed in the dissertation are those of the author and in no way represent those of the University of Hamburg. The dissertation has not been presented to any other University for examination.

SIGNED: .....

10. Adnex

10.1 Abbreviations

ACCP = American College of Chest Physicians

AHRQ = Agency For Healthcare Research and Quality

BK-DOK = Dokumentation des Berufskrankheiten-Geschehens in Deutschland

BOHRF = British Occupational Health Research Foundation

COPD = Chronic obstructive pulmonary disease

LFT = lung function test

LMW = low molecular weight

HMW = high molecular weight

MeSH = Medical Subject Headings

NSBHR = non-specific bronchial hyperresponsiveness

OA = occupational asthma

OELs = occupational exposure limits

PEFR = serial exspiratory peak flow rate

PELs =permissible exposure limits

RADS = reactive airways dysfunction syndrome

RCGP = College of General Practitioners

RCT = randomized controlled trial

SENSOR = Sentinel Event Notification Systems for Occupational Risks

SFT = serial lung function testing

SHIELD = scheme in the West Midlands Region, United Kingdom

SIC = specific inhalative challenge test

SIGN = Scottish Intercollegiate Guidelines Network

SORDSA = occurrence and causes of occupational asthma in South Africa

SWORD = surveillance of work-related and occupational respiratory disease

WRA = Work-related asthma

10.2 Table 9: Irritants, work-sites or professions reported to cause irritant-induced OA or occupational COPD

Agents (specification) [synonyms], CAS No.	Publication [Reference]	Strength of evidence per agent (three star system of RCGP)	Evidence grading, applied to individual study (modified SIGN system); Study type	Occupationally exposed subjects studied, n	Total no. of irritant-induced occupational asthma/ occupational COPD cases per agent	Irritant-induced occupational asthma/ occupational COPD cases, n (prevalence, %)	EVIDENCE (pathological results)													Remarks
							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC					
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Acids																					
", not specified	Kipen, Blume et al. 1994 [12]	(*)	**3**; Case reports	4	**5**	4	4/4			nd		4/4		nd		nd					1 fire inspector and 3 hazardous waste investigators exposed to fumes of acid drum waste
","	Brooks, Weiss et al. 1985 [5]		**3**; Case report	1		1	1/1		+	1/1		1/1		nd		nd					Welder. Co-exposure to welding fumes
", various	Tarlo and Broder 1989 [9]	-	**3**; Case report	1	**1**	1	1/1		+	x*		1/1		x*		nd					Profession not mentioned. *Individual data for LFT/SFT not given
", " (hydrochloric, hydrofluoric, nitric, perchloric, sulfuric)	Musk, Peach et al. 1988 [152]	*	**3**; Survey	20	**4**	4 (20.0)	9/20			2/ 20		5/20		1/4		nd					20 Workers in a mineral analysis laboratory
", glacial acetic, 64-19-7	Kern 1991 [99]	*	**2-**; Cross-sectional	51	**6**	4(7.8)*	15/ 51	29.4	+	4/ 51	7.8	9/24	37.5	nd		nd					Hospital employees exposed to spill. *Cases for RADS sign. dose-response related, OR for RR in subjects with high exposure 9.8, ns
","	Rajan and Davies 1989 [150]		**3**; Case report	1		1*	1/1			x**		nd		nd		nd					Maintenance fitter exposed to massive spill. *Development of interstitial pneumonitis (P+); **reversible FVC and FEV1 decline
","	Kivity, Fireman et al. 1994 [151]		**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1			1		Cannery worker
", hydrochloric, 7647-01-0	Deschamps. Soler et al. 1994 [153]	-	**3**; Case report	1	**3**	1	1/1		+	1/1		1/1		nd		nd					Profession not mentioned. Co-exposure to sodium hypochlorite. Resp. symptoms after 5 min inhalation; duration of asthma post exposure > 2 years
","	Boulet 1988 [89]		**3**; Case report	1		1*	1/1		+	1/1		nd		nd		nd					Pool cleaner; exposure to agent for 1 hour. *Severe work-exacerbated asthma
","	Boulet 1988 [89]		**3**; Case report	1		1	1/1		+	0/1*		1/1		nd		0/1*					Cleaner. *LFT and SIC normal at examination 2 yrs post exposure
", sulfuric, 7664-93-9	Gamble, Jones et al. 1984 [100]	*	**2-**; Cross-sectional	248	**25**	13	13/248*	5,2		x**		nd		nd		nd					Lead acid battery workers.*WRS (' wheeze') ns vs. controls; **individual data not given; dose-response relationship ns
"	El-Sadik, Osman et al. 1972 [156]		**3+**; Survey	33		11	11/33*	33.3		x**		nd		nd		nd					Workers of battery manufacturing plants. *Cases defined as chronic bronchitis/chronic asthmatic bronchitis; sign. higher prevalence of cases in smokers (13/20) vs. non-smokers (2/13). **Individual data not given, decline of FEV1 and FVC ns vs. controls
	Boulet 1988 [89]		**3**; Case report	1		1	1/1			0/1*		1/1		nd		0/1*					Cleaner. *LFT and SIC normal at examination 2 yrs post exposure
Acid fluxes	Gannon and Burge 1993 [58]	-	**3**; Occupational diseases statistics (SHIELD)	4	**4**	4	4/4			nd		nd		x		x					4/500 OA cases in 1989-1991
Acrylates																					
", not specified	Chatkin, Tarlo et al. 1999 [157]	-	**3**; Occupational diseases statistics (WCB), survey	2	**2**	2	2/2		+	nd		x*		nd		nd					2/469 asthma claims between mid 1984 and mid 1988, identified by retrospective review; *2/2 NSBHR+ and/or BD+
", alkyl cyanoacrylates	Savonius, Keskinen et al. 1993 [158]	(*)	**3+**; Case reports	11	**13**	10	10/ 11			nd		x*		nd		10/11		1	6	3	Factory employees working with glue. *Individual data not given.
","	Yacoub, Lemière et al. 2005 [159]		**3**; Case report	1		1	1/1			0/1		nd		nd		1/1			1		Exposure while making miniature planes
","	Nakazawa 1990 [160]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1*		1	1		Worker of hearing aids industry. *SIC done twice on different days using "Aron Alpha".
","	Lozewicz, Davison et al. 1985 [161]		**3**; Case report	1		1	1/1			nd		0/1		1/1		1/1			1		Forklift operator in loudspeaker production industry
", cyanoacrylate glue	Chan, Cheong et al. 1994 [162]	-	**3**; Case report	1	**1**	1	1/1			1/1		nd		1/1		1/1			1		Door factory worker

Agents (specification) [synonyms], CAS No.	Publication [Reference]	Strength of evidence per agent (three star system of RCGP)	Evidence grading, applied to individual study (modified SIGN system); Study type	Occupationally exposed subjects studied, n	Total no. of irritant-induced occupational asthma/ occupational COPD cases per agent	Irritant-induced occupational asthma/ occupational COPD cases, n (prevalence, %)	EVIDENCE (pathological results)													Remarks
							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
", " [loctite®]	Toren, Järvholm et al. 1999 [125]	*	**2-**; Population based case referent study	15	**21**	15	15			nd		nd		nd		nd					15/251 OA in 1996 (physician-diagnosed). OR 1.8, sign.
", "	Quirce, Baeza et al. 2001 [163]		**3**; Case reports	2		2	2/2			0/2		1/2		2/2		2/2			2		2 Assembly operators in weather strips and rubber-processing factory
", "	Lozewicz, Davison et al. 1985 [161]		**3**; Case reports	3		3	3/3			nd		0/3		nd		3/3			1	2	Solderer of electronic industry, 2 factory workers assembling lampshades
", "	Kopp, McKay et al. 1985 [164]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1			1		Accountant and computer representative building remote control model airplanes
", mecrilate [methylcyanoacrylate], 137-05-3	Weytjens, Cartier et al. 1999 [165]	-	**3**; Case report	1	**4**	1	1/1			0/1		0/1		nd		1/1			1		Auto bodyshop worker. Preceeding rhinitis
", "	Savonius, Keskinen et al. 1993 [158]		**3**; Case reports	4		2	2/4			nd		x*		nd		2/4			1	1	Factory workers: 1 working with glue, 1 in manufacture of earplugs, 1 producing dental fillings, 1 working with dentin primer. *Individual data not given
", "	Lozewicz, Davison et al. 1985 [161]		**3**; Case reports	1		1	1/1					0/1		nd		1/1			1		Worker of instrument manufacture
", methacrylates	Jaakkola, Leino et.al. 2007 [126]	*	**2-**; Cross-sectional	512	**29**	29 (5.7)*	26	5.1		x*		x*		nd		nd					799 female dental assistants in Finland of whom 512 were exposed. *sign. OR 2.76 for risk of doctor-diagnosed asthma in the last 12 months vs. non-exposed group (n=287)
", methylmethacrylate, 80-62-6	Lozewicz, Davison et al. 1985 [161]	-	**3**; Case report	1	**2**	1	1/1			nd		0/1		nd		1/1		1			Dental assistant
"	Pickering, Bainbridge et al. 1986 [166]		**3**; Case report	1		1	1/1			0/1		nd		nd		1/1			1		Theatre sister handling bone cement
Acrylic acid	Savonius, Keskinen et al. 1993 [158]	-	**3**; Case report	1	**1**	1	1/1			x**		x**		nd		1/1*		1			Mechanic in paper mill. *SIC with ink containing acrylic acid (30%), hydroxy-propanolic cid (30%), bronze powder (25%), white spirit (4%), ethanol (10%); **Individual data not given.
Airbag content	Hambrook, Fink et al. 2006 [404]	-	**3**; Case report	1	**1**	1	1/1		+	nd		1/1		nd		nd					Head-on motor vehicle accident
Aluminum salt (al.fluoride), 7724-18-1 (al.sulfate), 10043-01-3	Simonsson, Sjöberg et al. 1985 [90]	*	**3+**; Case series with follow-up	19	**19**	19	19/19*			2/19***		17/ 19***				0/2**					Aluminum salt workers. *Average of 4.1 months of exposure before having WRS; 2/19 work-exacerbated asthma. **SIC done with al. fluoride (1person) and al. sulfate. ***At follow-up changes of LFT and NSBHR ns. Mean aluminum dust exposure between 0.2 and 4 mg/m³
2-Aminoethanol [2-ethanolamine], 141-43-5	Savonius, Keskinen et al. 1994 [167]	-	**3**; Case report	1	**1**	1	1/1			nd		0/1		1/1		1/1				1	Cleaner. Subfebrile temperature 7h after SIC
Amino-ethyl-ethanolamine, 111-41-1	Pepys, Pickering et al., 1972 [168]	-	**3**; Case reports	3	**3**	3	3/3			2/3		nd		nd		3/3			1	2	Cable joiners
3-Amino-5-mercapto-1,2,4-triazole, 16691-43-3	Hnizdo, Sylvain et al. 2004 [169]	(*)	**3+**; Survey of Case series indentified by System of Occupational Risks (SENSOR)	106	**6**	6* (5,6)	6/ 106	5.6		x**		6/6		3/6		nd					Chemical plant workers. Co-exposure to N-(2,6-difluorophenyl)-5-methyl-[1,2,4]triazolol (1,5-a]pyrimidine-2-sulfonamide); *6/106 physician-diagnosed OA; **individual data not given
Ammonia, 7664-41-7		*			**≥ 15**																
"	Ali, Ahmed et al. 2001 [170]		**2-**; Cross-sectional	73		x*	33/ 73	45.2		x*		nd		nd		nd					Ammonia workers. *FEV1 sign. reduced in symptomatic nonsmokers and high cumulative exposure group (> 50 mg/m3·of air-years) vs. controls, individual data not given
"	Reinisch, Harrison et al., 2001 [20]		**3+**; Occupational diseases statistics (SENSOR), survey	7		7	7/7		(+)	x*		nd		nd		nd					7/430 new-onset asthma in 1993-1996. *Individual data not given

Agents (specification) [synonyms], CAS No.	Publication [Reference]	Strength of evidence per agent (three star system of RCGP)	Evidence grading, applied to individual study (modified SIGN system); Study type	Occupationally exposed subjects studied, n	Total no. of irritant-induced occupational asthma/ occupational COPD cases per agent	Irritant-induced occupational asthma/ occupational COPD cases, n (prevalence, %)	EVIDENCE (pathological results)													Remarks
							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	de la Hoz, Schlueter et al. 1996 [172]		**3**; Case reports	3		3*	3/3		+	3/3		1/1		nd		nd					Factory worker, engine testing operator, truck driver. Exposure to massive leaks of refrigerators/spill of tank. *Development of restr., COPD and small airway disease over the years after accident
", (fumes)	Bernstein and Bernstein 1989 [171]		**3**; Case reports	4		4	4/4		+	1/4		3/3		nd		nd					Profession not mentioned. Massive accidental exposure, 4/4 P+, resp. symptoms persisted for 12-32 months
"	Leduc, Gris et al. 1992 [173]		**3**; Case report with 12 year follow-up	1		1	1/1		+	1/1		nd		nd		nd					Solderer of industrial butter plant. Massive accidental exposure; P+; persisting severe airflow obstruction over 12 years
"	Flury, Dines et al. 1983 [174]		**3**; Case report	1		1	1/1		+	1/1		nd		nd		nd					Profession not mentioned. Pulmonary edema with acute pulmonary distress after massive exposure
Ammonium chloride (triple salt), 12125-02-9	Weir, Robertson et al. 1989 [175] **s. Soldering flux**	-	**3**; Case report	2	**2**	2	2/2			2/2		2/2		2/2		1/1			1		1 tin maker, 1 car radiator repair man; use of soft corrosive soldering fluxes. Co-exposure to zinc chloride (see also zinc chloride). Also 2/2 SIC+ with soldering flux (2 immediate)
Ammonium thioglycolate, 5421-46-5	Gelfand 1963 [176]	-	**3+**; Case series	14	**10**	10	14/ 14			nd		nd		nd		10/10*					14 subjects exposed in the beauty culture industry. Co-exposure to monoethanolamine and ethylene diamine; *individual reaction type not given
Amprolium hydrochloride, 137-88-2	Greene and Freedman 1976 [177]	-	**3**; Case report	1	**1**	1	1/1		+	0/1		nd		nd		1/1		1			Worker of poultry-food additive manufacturing (Pancoxin). Massive accidental exposure
Anhydrides																					
", various	Baur, Czuppon et al. 1995 [162]	*	**2-**; Cross-sectional with follow-up of cases	92	**10**	8* (8.7)	18/ 92			11/90		4/90		nd		nd					Chemical workers. *8/18 dyspnoeic subjects with sign. obstr.; 15/92 spec. IgE+
","	Drexler, Weber et al. 1994 [179]		**3+**; Survey	110		2 (1.8)	14/ 110			nd		nd		nd		2/8*					Employees of epoxy resin plant. *Individual reaction type not given; 16/109 spec. IgE+
", dioctyl phthalate, 117-81-7	Cipolla, Belisario et al. 1999 [180]	-	**3**; Case report	1	**1**	1	1/1			1/1				1/1*							Bottle stopper production worker. *SFT+: immediate
", hexahydrophthalic, 37226-48-5	Chee, Lee et al. 1991 [181]	-	**3**; Case report	1	**1**	1	1/1			0/1		nd		1/1*		1/1			1		Laboratory technician. *SFT done over one month
", himic, 2746-19-2	Rosenman, Bernstein et al. 1987 [182]	-	**3+**; Survey	20	**3**	3* (15.0)	3/20			nd		nd		nd		nd					Chemical plant workers. 3/20 wheezing and spec. IgE+; 7/20 rhinitis
", maleic, 108-31-6	Lee, Wang et al. 1991 [183]	-	**3**; Case report	1	**4**	1	1/1			0/1		1/1		nd		1/1				1	Assistant technician in chemical plant
", "	Graneek, Durham et al. 1987 [184]		**3**; Case reports	4		3	x*			x*		3/3		x*		3/4			3		Profession not mentioned. *Individual data not given
", methyltetrahydrophthalic, 26590-20-9	Nielsen, Welinder et al. 1989 [185]	-	**3**; Case report	1	**1**	1	1/1			0/1		1/1		nd		nd					Worker of plastic manufacturing factoy. SPT+ and spec.IgE+. resp. symptoms exposure
", phthalic anhydride, 85-44-9	Nielsen, Welinder et al. 1988 [186]	**	**2-**; cross-sectional	60	**30**	5* (8.3)	5/60			nd		nd		nd		nd					Workers of plants producing alkyde and unsaturated polyester resins. Average conc. 0.4 mg/m³, peaks 6.6 mg/m³; *all cases in high exposed group; 7/60 chronic bronchitis (6/7 heavily exposed); 4/60 spec. IgE+, exposure-related
","	Wernfors, Nielsen et al. 1986 [187]		**3+**; Survey	118		21 (17.8)	21/ 118			8/ 55		7/36		nd		2/2				2	Workers of plants producing alkyde and/or unsaturated polyester resins. Average conc. 3-13 mg/m³. 3/37 skin scratch test +; 4/54 spec. IgE+
","	Frans and Pahulycz 1993 [188]		**3**; Case report	1		1	1/1		+	0/1		1/1		nd		nd					Tanker driver exposed to massive spill. At follow-up after about 1.5 years asymptomatic and NSBHR-

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
","	Fawcett, Newman Taylor et al. 1977 [189]		**3**; Case reports	5		2	5/5			2/5		nd		nd		2/5				2	Workers of plastic and paint industry
","	Maccia, Bernstein et al. 1976 [190]		**3**; Case report	1		1	1/1			nd		nd		nd		1/1		1			Chemical foreman. SPT+; spec. IgE+
", pyromellitic dianhydride, 89-32-7	Meadway 1980 [191]	-	**3+**; Case series	7	**2**	2	2/7			0/7		nd		2/4*		nd					Employees working with epoxy resins. *SFT done while exposed to a.) already mixed and b.) while mixing adhesives (a.1 immediate with FEV1 of 15% decline, b.1 late with FEV1 of 18% decline)
", tetrachlorophthalic anhydride, 117-08-8	Venables, Topping et al. 1985 [562]	*	**3**; Survey with follow-up	330	**24**	9* (2.7)	9*/330	2.7		nd		nd		nd		nd					Factory workers.*9/396 WR chest symptoms, not related to IgE+; 24/300 IgE+, related to smoking
","	Howe, Venables et al. 1983 [194]		**3+**; Case series	7		4	7/7			0/7		nd		nd		4/4			2	2	Factory workers with epoxy resin systems. 7/7 spec. IgE+
","	Venables, Topping et al. 1987 [193]		**3+**; Case series with follow-up	7		7	7/7			0/7		5/5		nd		nd					Factory workers with epoxy resin systems. 4 yrs follow-up; 7/7 spec. IgE+ and SPT+; persistent asthmatic symptoms over 4 years in spite of avoidance
","	Schlueter, Babaszak et al. 1978 [195]		**3+**; Case series	5		4	5/5			3/5		1/1		nd		3/5		1	2		5 plastic industry workers
", benzene-1, 2, 4- tricarboxylic acid 1,2-anhydride [trimellitic anhydride] 552-30-7	Grammer, Zeiss et al. 2000 [196]	**	**2-**, Case control study	80	**43**	12*	12/80	15.0		12/80*	15.0	nd		12/80*	15.0	nd					Workers of TMA manufacturing plant. *Individual data not given for LFT/PFT. 17/80 positive for late resp. systemic syndrome. Difference in frequency of any HLA antigens vs. controls ns
", "	Grammer, Shaughnessy et al. 1999 [197]		**2-**; Survey with follow-up	286		14* (4.9)	14*/286	4.9		x**		nd		nd		nd					Workers of TMA manufacturing industry. Average conc. < 0.00045-1.7 mg/m³. *14/286 developed TMA-related resp. symptoms within 3 years; **Individual data not given ; 18/286 spec. IgE+; IgG sign. disease- and exposure-related
	Grammer, Shaughnessy et al. 1998 [198]		**2-**; Cross-sectional with 5-year follow-up	119		10*(9,1%)	x**			x**		x**		x**		x**					Workers of TMA factory. *Individual data not given, details of investigation see study above. **Before follow-up, 3 subjects with OA, additionally 7 new OA cases within follow-up; 9/10 spec. IgE+
","	Zeiss, Patterson et al. 1977 [199]		**3+**; Case series	14		6*	14/14			nd		nd		nd		1/1		1			Chemical plant workers. 2/14 asthma-rhinitis syndrome (mediated by spec.IgE for TMA hapten), *4/14 late-onset asthma, 2/14 both diseases; 6/14 irritant syndrome; 3/14 spec. IgE+
","	Fawcett, Newman Taylor 1977 [189]		**3**; Case report	1		1	1/1			1/1		nd		nd		1/1				1	Maintenance fitter
Aziridine, polyfunctional (dust), 64265-57-2	Kanerva, Keskinen et al. 1995 [200]	(*)	**3+**; Case series	9	**8**	7	7/9			nd		2/9		nd		7/9		1	5	1	5 parquet varnishers, 1 spray painter, 2 painters, 1 sales agent. 3 subjects also dermatitis. 4/7 SIC+ also SPT+;4/7 SIC+ with rhinitis
"	Leffler and Milton 1999 [201]		**3**; Case report	1		1	1/1			1/1		1/1		0/1*		nd					Spray painter. *5% across-shift drop in PEF rate; contact dermatitis
Azobisformamide [azodicarbonamide], 123-77-3	Slovak 1981 [202]	*	**3+**; Survey	151	**36**	28* (18.5)	28/ 151			0/ 28		13/ 28	46.4	0/ 11		nd					Profession not mentioned. Average conc. 2-5 mg/m³ .*Asthma type at onset of symptoms: 6 immediate, 16 late, 6 dual
"	Kim, Cho et al. 2004 [203]		**3**; Case report	1		1	1/1			1/1		1/1		0/1		1/1			1		Factory worker. Resp. symptoms after a latency period of 7 years; SPT negative
"	Normand, Grange et al. 1989 [204]		**3**; Case reports	4		4	4/4			1/2*		nd		nd		2/2			1	1	Workers of plastic industry. *For 2/4 subjects individual data not given.
"	Valentino and Comai 1985 [205]		**3**; Case report	1		1	1/1			0/1		nd		nd		1/1		1			Factory worker

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Malo, Pineau et al. 1985 [206]		**3**; Case reports	2		2	2/2			2/2		2/2		nd		2/2			1	1	Profession not mentioned
Benzalkonium chloride (fumes), 8001-54-5	Purohit, Kopferschmitt-Kubler et al. 2000 [207]	-	**3**; Case report	3	**4**	3	3/3			nd		2/3		3/3		3/3			3		Medical, surgical and paediatric nurses
"	Bernstein, Stauder et al. 1994 [208]		**3**; Case report	1		1	1/1			nd		nd		nd		1/1			1		Worker in cleaning products manufacturing
1, 2-Benzisothiazoline-3-one (fumes), 2634-33-5	Moscato, Omodeo et al. 1997 [209]	-	**3**; Case report	1	**1**	1	1/1			0/1		0/1		nd		1/1		1			Worker of chemical factory
Bisulfite [SO_2], 7446-09-5	Kipen, Blume et al. 1994 [12]	-	**3**; Case report	1	**1**	1	1/1			1/1		nd		1/1		nd					Profession not mentioned
Bleaching agent (fumes)	Boulet 1988 [89]	-	**3**; Case report	1	**1**	1	1/1		+	1/1		1/1		nd		nd					Acute accidental exposure to fumes, with low density phosphate, sodium metasilicate, chloride 18%. Patient tested 6 years after accident
Bromine, hydrobromic acid	Burns and Linden 1997 [210]	-	**3**; Case reports	2	**2**	2/2	2/2		+	nd		2/2		nd		nd					Non-occupational exposure during single hot tube bathing for 5-10 min
Bromochlorodifluoromethane [Halon 1211], 353-59-3	Matrat, Laurence et al. 2004 [91]	-	**3**; Case reports	4	**3**	3	2/4		+	4/4		4/4		nd		nd					Accidental release of fire extinguisher content. 1/4 subjects with exacerbated asthma
Bromotrifluoromethane [Halon 1301], 75-63-8	de la Hoz 1999 [211]	-	**3**; Case report	1	**1**	1	1/1		+	1/1		1/1		nd		nd					Accidental exposure to fumes, caused by leak of a tank (belonging to a fire extinguishing system). Obstructive lung patterns for > 7 years; BD+
Cadmium (fumes), 7440-43-9	Davison, Fayers et al. 1988 [52]	*	**2-**; Cross-sectional	101	**≥ 36**	33* (32.7)	33/ 101	32.7		33/77	42.8	nd		nd		nd					Cadmium workers. *33/101 FEV1 or FEV1/VC sign. reduced (average 30% below predicted), cumulatively dose-related; lung function and chest X-ray indicate emphysema in 14/75
"	Chan, Poh et al. 1988 [212]		**2-;** Cross-sectional with 3-year follow-up	44		**	14***; (3)*	31.8; (6,8)*		6/44; (3/44)*	13.6; (6,8)*	nd		nd		nd					Battery workers. Data consisting of previous and *current results (3 years later, see in brackets). sign. reduction of cadmium in-air-levels acchieved; sign. reduction of resp. symptoms and sign. improvement of LFT. **Asthma was not a spec. target. ***Definition of WRS not specified
"	Leduc, Francquen et al. 1993 [213]		**3;** Case report	1		1	1/1			1/1		nd		nd		nd					Furnace worker producing cadmium salts and -oxides. Chest X-ray and lung funcion indicates emphysema. Severe impairment of symptoms within 10 years of follow-up. Additional development of pulmonary adeno-carcinoma
"	De Silva, Donnan et al. 1981 [214]		**3+;** Case series	11		2*	3/6			4/11		nd		nd		nd					Workers of cadmium pigment manufacturing plant. *Asthma cases with moderate and severe emphysema. 6/12 with chronic cadmium poisoning, of these 2/6 with asthma and LFT+
Calcium Carbonate [chalk powder], 471-34-1	Bohadana, Massin et al. 1996 [101]	*	**3+;** Cross-sectional	158			5/158	3.0		x*		nd		nd		nd					Workers of chalk powder plant. sign. highest FEV1/FVC decline in workers of chalk sacking correlated with sign. dose-response relationship, *individual data not given
Calcium oxide 1305-78-8	Tarlo and Broder 1989 [9]	-	**3**; Case reports	2	**2**	2	2/2			x*		2/2		nd		nd					Profession not mentioned. Persistent asthmatic symptoms for 1.5 to 3 years; 1/2 co-exposed to welding fumes; *individual data for not given
Captafol [chlorinated thiocarboximide fungicide], 2425-06-1	Royce, Wald et al. 1993 [215]	-	**3**; Case report	1	**1**	1	1/1			0/1		1/1		nd		1/1				1	Chemical worker
Cement dust (see also chromate)		**			**≥ 267**																

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Mwaiselage, Bråtveit et al. 2005 [102]		**2-**; Cross-sectional	117		22* (18.8)	22/ 117	18.8		22/ 117	18.8	nd		nd		nd					117 cement workers vs. 105 controls. *22/117 COPD (18.9% vs. 4.8% of controls), sign. dose-response relationship for asthma symptoms (10mg/m³ daily for ≥ 2 years) and the risk of developing COPD (10mg/m³ daily for ≥ 10 years)
"	Yang, Huang et al. 1996 [405]		**2-**; Cross-sectional	412			36/ 412	8.7		x*		nd		nd		nd					412 portland cement workers vs. 179 controls. Dyspnea sign. increased (8.7 vs. 7.2% of controls); wheezing also sign. increased (7.6 vs. 6.2% of controls); *LFT sign. reduced (FVC, FEV1, FEF50, FEF75) with individual data not given
"	Abrons, Petersen et al. 1988 [406]		**2-**; Cross-sectional	2738		112* (4.1)	148**	5.4		x*		nd		nd		nd					Cement workers. *COPD inreased (4.1% vs. 3% of controls);**dyspnea sign. increased (5.4% vs. 2.7% of controls); no sign. lung function changes, individual data not given
"	Fell, Thomassen et al. 2003 [407]		**3+**; Cross-Sectional	119		17 (14.3)*	32/119**			x*		nd		nd		nd					Former Portland cement workers . *14.3% COPD cases with mean reduction of FEV1/FVC of 74.3%, sign.; prevalence of COPD ns vs. controls (exposed to ammonia, high risk of confounding) ; **attacks of dyspnea selected as asthma symptoms
"	Al-Neaimi, Gomes et al. 2001 [408]		**3+**; Cross-sectional	67			4/ 67	6.0		x**		nd		nd		nd					67 cement workers vs. 134 controls. *4/67 asthma symptoms (6% vs. 3% of controls); 9/67 bronchitis; other chronic resp. symptoms: dyspnea 14/67 (20.9% vs. 4.5%). **individual data not given
"	Ali, Ballal et al. 1998 [409]		**3+**; Cross-sectional	149			nd			x*		nd		x*		nd					Cement factory workers. *Sign. post-shift reduction in FEV1, FEV1/FVC, FEF25-75 with exposure related decreases compared to controls.
"	Kalacic 1973 [410]		**3+**; Cross-sectional	847		95* (11.2)	95	11.2		nd		nd		nd		nd					Cement workers. *COPD sign. increased (11.2% vs. 4.3% of controls); wheezing sign. increased (7.4% vs. 3.7% of controls, more pronounced in smokers); *high risk of selection-bias/ confounding because study based on questionnaire
"	Mengesha and Bekele 1998 [411]		**3+**; Comparative survey	53		17** (32.1)	17/ 53	32.1		x*		nd		nd		nd					Workers of a cement factory. 14/53 chronic bronchitis; *individual data not given; high risk of confounding and selection-bias, because inadequate description of controls and **asthma diagnose based on questionnaire (32.1% vs. 8.5% of controls, ns)
"	Prezant, Weiden et al., 2002 [124]		**3+**; Cross-sectional	348			55/ 348	15.8		x*		nd		nd		nd					Portland cement workers; asthma symptoms sign. dose-response related; *individual data not given; high risk of confounding and selection bias.
"	Lockman, 2002 [412]		**3**; Case report	1		1	1/1			nd		nd		nd		nd					Leather tanning worker. SPT+ with potassium dichromate
"	de Raeve, Vandecasteele et al. 1998 [413]		**3**; Case report	1		1	1/1			0/1		1/1		1/ 1**		1/1*				1	Floorer. *SIC with potassium dichromate;**SFT done for 50 days (17 days at work, 33 days off work); first symptoms after 34 years of exposure
"	Leroyer, Dewitte et al., 1998 [226]		**3**; Case report	1		1	1/1			nd		1/1		nd		1/1*		1			Roofer. *SIC with potassium dichromate
"	Shirakawa and Morimoto, 1996[424]		**3**; Case and control	1		1	1/1			nd		nd		nd		1/1		1			Worker of metal plating factory. Spec. IgE+
Chloramine T (powder dust), 7080-50-4	Bourne, Flindt et al. 1979 [216]	**(*)**	**3+**; Case series	7	20	7	7/7			nd		nd		nd		nd					Brewery workers. Recovery after removal; 7/7 SPT+ done with clortol
"	Feinberg and Watrous 1945 [217]		**3+**; Case series	6		6	6/6		(+)*	nd		nd		nd		nd					Co-exposure to halazone; *1/6 RADS

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Kujala, Reijula et al. 1995 [218]		**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1				1	Cleaner
"	Jouannique, Pillière et al. 1992 [219]		**3**; Case reports	2		2	2/2			1/2*		1/2*		nd		1/1**		1			Laboratory workers. *1/2 with normal LFT only nasal provocation test (positive)
"	Dijkman, Vooren et al. 1981 [220]		**3+**; Case series	5		4	4/5			1/5		nd		nd		3/3			1	2	2 cleaners, 2 technicians, 1 nurse. 4/4 SPT+
Chlorhexidine, 55-56-1	Waclawski, McAlpine et al. 1989 [221]	-	**3**; Case reports	2	**2**	2	2/2			0/2		1/2*		1/ 2**		1/ 2**		1			1 nursing auxiliary with *NSBHR+ and FEV1 decline of 13% after SIC; 1 midwife with **SIC+ and **SFT+
Chlorine, 7782-50-5		**			**299**																
"	Glindmeyer, Lefante et al. 2003 [222]		**2+**; Retrospective cohort study	19601		226	x*			nd		nd		nd		nd					Workers of U.S.pulp/ paper mills (RR 1.3, sign. for new asthma cases).*Individual data not given.**Annual incidence 0.16 vs. 0.13% of controls. Additionally 5/447 new asthma cases in group of gassed (highly exposed) workers
"	Andersson, Olin et al. 2003 [223]		**2-**; Cross-sectional	385		12	53/345	15.3		nd		nd		nd		nd					*99 workers of paper department and 210 workers of bleachery department exposed to gassing (Cl2/ClO2, also to SO2). HR 5.6, sign., for gassing as a strong risk factor of asthma
"	Gautrin, Leroyer et al. 1995 [224]		**2-**; Cross-sectional	239		9* (3.8)	38/ 239**	15.9		x***		x***		nd		nd					**38/239 workers from the smelting area with accicental puffs over a 3 year period. *9/239 current asthma; ***LFT (FEV1, FVC, FEV1/FVC) and NSBHR sign. lower and increased respectively in group with >10 puffs compared to other exposed groups; 3/239 chronic bronchitis
"	Bhérer, Cushman et al. 1994 [225]		**3+**; Survey with follow-up	64		29*** (45.3)	58/ 64	90.6	(+)*	15/ 51**	31.4	29/ 51**	56.9	nd		nd					289 contruction workers. After multiple exposures, *71/289 with resp. symptoms and possible RADS; at follow-up 18 to 24 months **51/58 symptomatics underwent pulmonary testing; ***29/51 with obstr. and/ or NSBHR+
"	Leroyer, Dewitte et al. 1998 [226]		**3+**; Longitudinal study with follow-up of case series	13		3	13/ 13		(+)	1/ 13*		2/ 13*		nd		nd					13/278 workers of metal production plant with accidental exposure. *3/13 transient FEV1 or NSBHR deterioration
"	Chatkin, Tarlo et al. 1999 [157]		**3+**; Occupational diseases statistics (WCB), survey	5		5	5/5		(+)**	nd		x*		nd		nd					5/469 asthma claims between mid 1984 and mid 1988 identified by retrospective Review. *All 5 cases accident-related with BD+ and/or NSBHR+; **1/5 RADS
"	Chester, Gillespie et al., 1969 [227]		**3**; Survey	58		2	34/ 58	58.6		2/ 58	3.4	nd		2/2		nd					139 men of a chlorine gas-production plant
"	Ferris, Burgess et al., 1967 [228]		**3+**; Survey	147		8*	13/67	19.4		nd		nd		nd		nd					Pulpmill workers. Co-exposure to sulphur dioxide. *7 COPD, *1 asthma (physician-diagnosed)
"	Lemière, Malo et al. 1997 [229]		**3**; Case report	1		1	1/1*		+	1/1		1/1		nd		1/1			1		Worker of water-filtration plant.*Persistent symptoms and steroid medication until 5 months after accidental inhalation; P+
"	Tarlo and Broder 1989 [9]		**3**; Case report	1		1	1/1			x*		1/1		x*		nd					Profession not mentioned. Persistent asthmatic symptoms for 6 months; *individual data for LFT/SFT not given.
"	Schönhofer, Voshaar et al. 1996 [230]		**3**; Case reports	3		3	3/3		+	nd		3/3		nd		nd					Policemen exposed to chlorine gas spill. resp. symptoms > 2.5 years
Chlorofluorocarbons (degradation products)	Piirilä, Espo et al. 2003 [415]	-	**3+**; Case series	7	**3**	3	5/7		+	0/7		3/7		nd		nd					6 restaurant employees and 1 refrigerator maintenance worker; refrigerator fluid spill
Chromate (not specified, see also cement dust)		(*)			**38**																

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC					
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Olaguibel and Basomba 1989 [231]		**3+**; Case series	5		5	5/5			nd		3/5		nd		5/5*		1	2	2	2 workers of concrete industry, 1 tanning, 1 metal plating, 1 construction worker. *SIC done with potassium dichromate
"	Onizuka, Tanabe et al. 2006 [232]		**3**; Case report	1		1	1/1			1/1*		nd		nd		1/1**					Stone mason. *individual data not given. **SIC done with chrome dust, reaction type not given; asthma onset after 8 years of exposure, contact dermatitis after 3 years; SPT+/spec IgE+ to potassium dichromate and nickel sulfate
	Fernadez-Nieto, Quirce et al. 2006 [33]		**3**; Case reports	4		4	4/4			0/4		4/4		nd		4/4*		1	2	1	2 electro-plating, 1 welder, 1 cement worker. *SIC done with potassium dichromate. 3/4 co-exposure to nickel with 2/3 SIC+ to nickel. 2/4 SPT+ to chromium and nickel
"	Sastre, Fernandez-Nieto 2001 [234]		**3**; Case report	1		1	1/1			1/1		1/1				1/1*				1	Electro-plating employee. Co-exposure to nickel sulfate, gold and silver. SPT+ to NiSO4 and potassium dichromate. *SIC done with potassium dichromate, additionally SIC+ to NISO4 (dual reaction type)
"	Nagasaka, Nakano et al. 1995 [235]		**3**; Case report	1		1	1/1		+	nd		1/1		nd		1/1			1		1 worker with accidental exposure of a chrome pellet manufacturing plant. 1/1 SPT+ to potassium dichromate
"	Park, Yu et al. 1994 [236]		**3**; Case reports	4		4	4/4			nd		3/4		2/2		4/4*		1		3	2 metal plating, 1 construction worker, 1 worker of cement industry. *SIC done with potassium dichromate
"	Novey, Habib et al. 1983 [237]		**3**; Case report	1		1	1/1			1/1		nd		nd		1/1*		1			Metal plating worker. SIC done with chromium sulfate, additionally SIC+ to nickel sulfate (late reaction type)
"	Joules 1932 [76]		**3**; Case report	1		1*	1/1			nd		nd		nd		nd					Chromium plating. Asthma with subsiding dermatitis; *1/1 SPT+ with potassium dichromate
"	Bernstein and Merget 2006 [14]		**4**; Review	20		20	20/ 20			nd		20/ 20		nd		20/20		7	4	9	
Cleaning agents		*			**≥ 267**																
", (not specified)	Mirabelli, Zock et al. 2007 [416]		**2-**; prospective cohort study	60*		7* (11,7)	7	11,7		nd		nd		nd		nd					Nurses or nurses related occupations. Population-based study in the Communitty Respiratory Health Survey (ECRHS II). *60/332 nurses exposed to ammonia and/ or bleach with new onset asthma (RR 2.16, sign.)
","	Massin, Hecht et al. 2007 [103]		**2-**; Cross-sectional	175		x*	12/175			25/ 175*		32/ 165*		nd		nd					Food industry cleaners. *Results vs. controls ns; exposure mainly to chlorine and nitrogen trichloride; sign. dose-response relation between upper resp. symptoms and exposure level
","	Medina-Ramón, Zock et al. 2005 [127]		**2-**; Nested case control	40		x*	24/ 40			2/35**		4/22*	18.2	nd		nd					Workers of different cleaning professions. *22/40 cases tested for BHR, not clear if cases with NSBHR+ additionally asthma symptoms; **2/35 COPD cases, not clear if work-related; asthma symptoms associated with high level ammonia exposure (OR 3.1,sign.)
","	Medina-Ramón, Zock et al. 2003 [38]		**3+**; Cross-sectional	4521		x*	12.0% vs. 5.0%**			nd		nd		nd		nd					593 women (13%) employed in domestic cleaning work. *Inadequate, because cases not given, asthma sign. more prevalent than in non-cleaning workers (OR 1.46); **prevalence of WR resp. symptoms in cleaning workers 12% vs. 5% in non-cleaning workers
","	Rosenman, Reilly et al. 2003 [417]		**3+**; Occupational diseases statistics (SENSOR)	236		236*	236/236		(+)**	x***		nd		nd		nd					*236/1915 OA cases 1993- 2001. 189 new-onset asthma including **42 cases of RADS; ***individual data not given

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
","	Reinisch, Harrison et al. 2001 [20]		**3+**; Occupational diseases statistics (SENSOR), survey	22		22	22/ 22			x*		nd		nd		nd					22/430 new-onset asthma in 1993-1996. *Individual data not given.
","	Kipen, Blume et al. 1994 [12]		**3**; Case report	1		1	1/1			x*		nd		nd		nd					Profession not mentioned. Low dose irritant-induced asthma; *BD+
","	Tabar, Álvarez 1998 [418]		**3**; Case report	1		1	1/1			0/1		1/1		nd		nd					Worker of bottle-filling process with cleaning agents. Low dose irritant-induced asthma. At follow-up 6 months after leaving the workplace cessation of symptoms and NSBHR
", detergents	Murphy, Fairman et al. 1976 [419]	-	**3**; Case report	1	**2**	1	1/1			1/1		nd		nd		nd					Housewife. Symptoms started 6-8 weeks after mixing several cleansing agents to unstop a kitchen drain
","	Mapp, Pozzato et al. 2000 [563]		**3**; Case report	1		1*	1/1			nd		1/1		nd		nd					*22 year old cleaner with preexisting asthma. Immediate-onset asthma followed by toxic lung oedema
Cobalt, 7440-48-4		**			**≥ 78**																
"	Linna, Oksa et al. 2003 [239]		**2-**; Case-control	110		15*	15/ 110			0/ 110		nd		nd		1/1					Cobalt production workers. Co-exposure to nickel; *15/110 suspected asthma cases by questionnaire (sign.), high risk of confounding
"	Kusaka, Iki et al. 1996 [240]		**2-**; Cross-sectional	345		x*	41/317**	12.9		nd		nd		nd		nd					Former and current hard metal industry workers. *Asthma cases were not a spec. target. **Low cobalt concentration (<50micg/m³) as a sign. risk factor. Relation between sensitivity to cobalt and asthmatic symptoms not sign.
"	Kennedy, Chan-Yeung et al. 1995 [241]		**2-**; Cross-sectional	118		x*	11/118**	9.0		18/118***	15.3	nd		12/118***		nd					Saw filers.*Asthma cases were not a specified target; **wheezing sign. related to work; ***sign. FEV1<80% only for tungsten carbide wet grinding (current job) with average cobalt exposure of 5,6micg/m³. ****sign. FEV1 drop >5% average change
"	Sprince, Oliver et al. 1988 [104]		**2-**; Cross-sectional	1039		x*	113/ 1039**	10.9		209/ 1039*		nd		nd		nd					Tungsten carbide production workers. *WR wheezing dose-response related (Cobalt>50micg/m³, OR 2.1, sign.); **workers with asthma symptoms more affected with obstr., but no further specification
"	Roto 1980 [242]		**2-**; Case referend study	21		6	21/ 21			x*		x**		nd		6/ 15**					Cobalt industry workers. *For a case definition either LFT+ and/or NSBHR+; **5/6 SIC with cobalt chloride, 1/6 SIC with cobalt dust, individual reaction types not given
"	Pisati and Zedda 1994 [243]		**3+**; Case series with follow-up	9		9	9/9			5/9		9/9		nd		9/9			8	1	9 cobalt industry workers. 3 year follow-up: 1/9 still exposed (with obstr.), 7/9 NSBHR+, 1/1 SIC+ (late reaction type)
"	Shirakawa, Kusaka et al., 1989 [244]		**3+**; Case series	8		8	8/8			8/8		7/8		nd		8/8*		2	4	2	Workers in shaping, grinding, sintering. *SIC with cobalt chloride; 4/8 IgE+
"	Shirakawa, Kusaka et al. 1988 [245]		**3+**; Case series	12		12	12/ 12			nd		nd		12/12		12/12*		5	4	3	Workers in grinding, sintering, powdering. *SIC with cobalt chloride; 6/12 spec.IgE+
"	Shirakawa, Kusaka et al. 1990 [246]		**3+**; Case series	8		8	8/8			8/ 8*		7/8		nd		8/8**		3	3	2	Hard metal plant workers. **SIC with cobalt chloride; *NSBHR before SIC with nickel; 6/8 SPT+; 5/8 spec.IgE+; co-sensitization to nickel sulfate
"	Gheysens, Auwerx et al. 1985 [247]		**3**; Case reports	3		3	3/3			1/3		2/3		nd		3/3*			1	2	Diamond workers. *SIC done with cobalt powder
"	Gannon and Burge 1993 [58]		**3**; Occupational diseases statistics (SHIELD)	4		4	4/4			nd		nd		x		x					4/500 OA cases in 1989-1991
	Baik, Yoon et al. 1995 [248]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1			1		Worker of glassware factory. After SIC also systemic response

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Wilk-Rivard and Szeinuk 2001 [249]		**3**; Case report	1		1	1/1			nd		nd		1/1		nd					Diamond grinder
"	Krakowiak, Dudek et al. 2005 [250]		**3**; Case report	1		1	1/1			1/1		1/1				1/1*			1		Diamond polishing disc former. SIC with cobalt chloride; SPT+ with cobalt chloride
"	Bernstein and Merget 2006 [14]		**4**; Review							nd		x		nd		x*					Largest work population in hard metal industry; *SIC+ (mostly late)
Coffee, green (dust)	Jones, Hughes et al. 1982 [421]	*	**2-**; Cross-sectional	372	**13**	7 (1.8)	10/372	2.6		x*		nd		nd		nd					7/372 new onset asthma; *exposure-time-related FEV1 decline; 35/362 SPT+; 24/331 IgE+
","	Zuskin, Kanceljak et al. 1985 [422]		**3+**; Case series	9		4	9/9			2/9		nd		nd		4/9		4			9 coffee industry workers; SIC done with aqueous extract; 5/9 symptomatics SPT+; 4/9 BD+
", " (roasted)	Lemière, Malo et al., 1996 [423]		**3**; Case report	1		1	1/1			1/1		nd		1/1		1/1		1			Factory worker (at machine roasting green coffee beans). Asthma symptoms after 3-4 years of work. SPT+, spec.IgE+ for roasted coffee beans
","	Johansen and Viskum 1987 [424]		**3**; Case report	1		1	1/1			1/1		nd		1/1		nd					Worker in coffee-roasting establishment. Spec.IgE+, SPT+
Construction work (dust, agent not specified)	Sauni, Oksa et al. 2003 [128]	**	**2+;** Retrospective cohort study	7513	**≥ 179**	133	x*			x*		x*		x*		x*					Contruction workers (CW) with new OA between 1991-1995 in Pikanmaa region of Finland from register of *Employment Pension Fund of CW and hospital records. OR for OA of male and female workers: 1.81, sign. and 2.5, sign. respectively (compared with Pirkanmaa population); annual incidence 3730/1.000.000
"	Ulvestad and Lund 2003 [98]		**2+;** Prospective cohort study	212		30 (14.2)*	56/212			x**		nd		nd		nd					Tunnel workers. *COPD cases: 14.2% vs. 8% of controls with OR 2,5, sign.; **Mean FEV1 decline 74.4% for exposed, individual data not given
"	Bergdahl, Torén et al. 2004 [97]		**2+;** Prospective cohort study	200.735		(10.7% overall/ 52.2% never-smokers)*	x*			x*		nd		nd		nd					Contruction workers exposed to different agents (inorganic dust, irritants, fumes, wood dust). *COPD cases within the follow-up 1971-1999; ** individual data not given; increased mortality rate from COPD, except for wood dust, RR 1.12, sign. (n=523)
"	Oliver, Miracle-McMahill et al., 2001 [496]		**2-**; Cross-Sectional	389		16 (4.1)*	48/389	12,3		16/330	4.1	nd		nd		nd					Contruction workers (laborers, tunnel workers, operating engineers). *Not clear, if obtruction correlates with WRS.
Cotton (dust, raw) [CNT 750] (see also endotoxin)		*[*]			**≥124**																
"	Christiani, Wang et al., 2001 [425]		**2+**; Prospective cohort	447		(25%-33%)*	x*			x**		nd		nd		nd					15-yr follow-up of 447 cotton textile workers. *25-33% chest symptoms; 67/447 dyspnea; **across-shift FEV1 decline is correlated with longitudinal FEV1 decline, also FVC decline
"	Latza, Oldenburg et al. 2004 [426] ; Oldenburg, Latza et al. 2007 [427]		**2-**; Cross-sectional	150		12** (8.0)	12/ 150	8.0		x***		12/ 74**	13.5	x*		nd					Cotton-spinning mill workers. *74/74 subjects with sign. FEV1/FVC% declines across-shift and current endotoxin exposure-related; **sign. NSBHR+ increase across-shift; ***individual data not given

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC					
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Hayes, Ye et al. 1994 [428]		**2-**, Cross-sectional	355		x*	x**			x***		nd		x****		nd					Workers of textile cotton industry. *Asthma cases not mentiontioned; **sign. elevation of resp. symptoms (chronic cough 18.3%, chronic bronchitis 21.7%); *** in baseline preshift ns; ****sign. FEV1, FVC mean decline across-shift (-2.07 vs. 0.05%) and also sign. in FEF25-75 (-0.03 vs. 0.18)
"	Woldeyohannes, Bergevin et al. 1991 [105]		**2-**; cross-sectional	595		64 (10.8)	64	10.8		x*		nd		x*,**		nd					Cotton mill workers. *Individual data not given; **dose-response relationship across-shift ns; duration of exposure over years with prevalence of asthma sign. correlated; 100/ 595 cases with byssinosis
", yarn	Toren, Balder et al. 1999 [21]		**2-**; Case control	22		22	x*			x*		x*		nd		nd					22/294 OA cases in 1996 (textile factory workers) with OR 1.9, sign.; *individual data not given
","	Rylander and Bergström, 1993 [106]		**2-**; Cross-sectional	35			nd			x*		0/34**		nd		nd					Textile cotton workers. **Decline of FEV1 >20,0% ns, 4/34 >10% FEV1 decline after NSBHR testing NSBHR. FEV1 decline dose-response related to endotoxine
","	Wang, Pan et al. 2003 [429]		**3+;** Longitudinal study with 18 months follow-up.	225			x*			x**		x***		x****		nd					Cotton mill workers. 31/101 SPT+(atopics); *asthma or asthma symptoms were not a specific target; **sign. longitudinal decline in FEV and FVC in overall group (atopics/ non-atopic) after 12 and 18 months of follow-up; ***sign. FEV1 decline at highest methacholine dose in atopics after 18 months; ****trend of greater FEV1 decline cross shift in atopics.
", yarn	Mengesha and Bekele 1998 [411]		**3+**; Comparative survey	91		24 (26.4)	24/91	26.4		x*		nd		nd		nd					Workers of a cotton-yarn factory. sign. prevalence of 24/91 subjects with asthma symptoms (26.4% vs. 8.5% in controls) and 25/91 (27.5% vs. 9.5) with chronic bronchitis;* individual data not given
","	Li, Zhong et al. 1995 [430]		**3+**:Longitudinal study with 1year follow-up	110			nd			nd		x**		x***		nd					Cotton mill workers.*Increase in non-spec. BHR during follow-up in the atopic group (for cotton dust SPT+), -8.1% vs. -4.2%, ns. **FEV1 decline across-shift 3.3% and 5.2% after 1 year for atopics, for NSBHR and SFT indiviidual data not given; exposure range of cotton dust 0.2 - 2.01mg/m³, of endotoxin 0.004-1.73 µg/m³
", "	Rylander, Haglind et al. 1985 [107]		**3+**; Case series	15		2	15/ 15			2/ 15		nd		nd		x*					Cotton mill workers. *SIC with cotton samples in experimental cardroom, sign. mean FEV1 declines in 8/15; FEV1 declines and symptoms related to endotoxin exposure; dose-response relationship between cotton dust level and individual FEV1 changes ns
Cutting oil	Kipen, Blume et al. 1994 [12]	-	**3**; Case report	1	**2**	1	1/1			nd		1/1		nd		nd					Profession not mentioned
"	Hendy, Beattie et al. 1985 [431]		**3**; Case report	1		1	1/1			1/1		nd		1/1*		1/1**		1			Toolsetter. *SFT over a period of 5 months; **also SIC+ with reodorant (immediate), heated colophony (immediate) and artists' turpentine (immediate)
3-(Diamino-amino)propylamine [3-(dimethylamino)propylamine], 109-55-7	Sargent, Mitchell et al. 1976 [251]	**(*)**	**2-**; Survey	25	**5**	5(20.0)	5/25			x		nd		x*		nd					Assemblers, pressmen and other mold room workers. use of an epoxy resin system; *sign. FEV1 and FEF50 decreases across-shift and cross-week of slightly exposed and symptomatics
Diamine, aliphatic + cycloaliphatic (hardener), 2855-13-2 (isophorone diamine)	Aleva, Aalbers et al. 1992 [252]	-	**3**; Case report	1	**1**	1	1/1			0/1		1/1		nd		1/1			1		Salesman selling industrial floor-covering materials

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Diazonium tetrafluoroborate, 14239-22-6	Luczynska, Hutchcroft et al. 1990 [253]	-	**3**; Comparative study	45	**3**	2	25/45	55.6		1/2*		nd		nd		2/2*		1		1	Workers manufacturing flourine polymer precursor. 9/43 spec.IgE+; *hospital admission 2/45 for LFT and SIC
"	Graham, Coe et al. 1981 [254]		**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1*			1		Production of photocopy paper. *SIC with diazonium chloride
Dichlorodiethyl sulfide [mustard gas], 505-60-2	Emad and Rezaian 1997 [255]	*	**3**; Cross-sectional	197	**15**	15*(7.6)	197/197			15/197		nd		nd		nd					Iranian veterans. Single massive exposure 10 years ago; 116 with chronic bronchitis, *89 COPD cases
Dichlorvos [dimethyl dichlorovinyl phosphate], 62-73-7	Deschamps, Questel et al. 1994 [256]	-	**3**; Case report	1	**2**	1	1/1		+	1/1		1/1		nd		nd					Cook. Persistent asthma
"	Barthel 1983 [257]		**3**; Case report	1		1	1/1		+	1/1		1/1		nd		nd					Cook. First, symptomless in between usages; after repetitive use of insecticide within years, development of asthma symptoms independantly of usage.
Diesel exhaust	Hart, Laden et al. 2006 and 2009 [95, 96]	*[*]	**2-**; Retrospective cohort study	536 (3913**)	**303**	75* (217**)	nd			nd		nd		nd		nd					*COPD mortality cases of railroad workers. *75/536 conductors and engineers with exposure ≥ 16 years of operating trains had a sign. increase in COPD mortality (OR 1.35 (1.17-2.39)), sign. dose-response relationship.**For workers employed after 1945 after the conversion to diesel locomotives, the risk of COPD mortality increased by 2.5% (sign.) for each additional year of work.
"	Henneberger, Derk et al. 2003 [432]		**3+**; Occupational diseases statistics (SENSOR)	7		7	7/7		+	x		x		nd		nd					7/424 OA cases between 1993-1995 (7/123 RADS)
"	Wade and Newman 1993 [433]		**3**; Case reports	3		3	3/3*		+	3/3		3/3		nd		nd					Railroad workers. RADS after a high exposure over several hours in second locomotive units 2/3 “reversible restrictive” ventilation pattern; twice hospital administration after high exposure
"	Makker and Ayres 1999 [434]		**3**; Case report	1		1	1/1			1/1		nd		1/1*		nd					Aircraft engine mechanic.*SFT done over a 50 days' period with sign. PEF decline over 5-day working week and improvement on weekends
Diethanolamine 111-42-2	Piipari, Tuppurainen et al. 1998 [258]	-	**3**; Case report	1	**1**	1	1/1			nd		1/1		1/1*		1/1		1			Metal worker. *SFT for 12 days
2-Diethylaminoethanol [diethyl aminoethanol], 100-37-8	Gadon, Melius et al. 1994 [259]	(*)	**3+**; Case series	14	**7**	7	14/14			4/12		nd		10/11		nd					Steam leak in heating system of a State office building. 7 asthma cases and 7 suspected asthma cases
2-Dimethylaminoethanol [dimethyl ethanolamine], 108-01-0	Vallières, Cockcroft et al. 1977 [260]	-	**3**; Case report	1	**3**	1	1/1			0/1		1/1		1/1		1/1				1	Spray painter
"	Cockroft, Cotton et al. 1979 [261]		**3**; Case report	2		2	2/2			0/2		0/2		nd		2/2			1	1	Profession not mentioned, occupational exposure to hardeners in paints. Co-exposure to HDI
Diinitrogen tetraoxide [dinitrogentetroxide], 10544-72-6	Conrad, Lo et al. 1998 [262]	(*)	**3+**; Case series	234	**6**	6	6/6		+	4/6		6/6		nd		nd					6/234 symptomatics developed RADS after massive release from a railroad tanker; 207/234 shortness of breath, 151/231 wheezing after massive exposure
ECG ink	Keskinen, Nordman et al. 1981 [435]	-	**3**; Case report	1	**2**	1	1/1			nd		1/1		nd		1/1				1	Laboratory nurse. Also SIC+ with methyl blue (immediate) and Patent Blau V; SPT+ to methyl blue, Patent Blau V, methylene blue
"	Rodenstein and Stanescu 1982 [436]		**3**; Case report	1		1	1/1			nd		1/1		nd		1/1		1			Technician. SIC+ also with methyl blue (immediate)

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Endotoxin (see also cotton dust, swine confinement, poultry confinement, house dust)	Reinisch, Harrison et al. 2001 [20]	*	**3+**; Occupational diseases statistics (SENSOR), survey	8	**15**	8	8/8			x*		nd		nd		nd					8/430 new-onset asthma between 1993-1996. *Individual data not given
"	Milton, Wypij et al. 1996 [437]		**3+**; Cross-sectional	37		6*	14/37			x**		nd		x***		nd					Maintenance and production workers of fiberglass manufacturing.Co-exposure to phenolics and formaldehyde. *6/37 new-onset asthma; **FEV1 and FVC reduction exposure-related; ***endotoxin-related PEF decline across-shift with SFT over 10 days
Environmental tobacco smoke, 1-09-0		**			≥268																
"	Jaakkola, Piipari et al., 2003 [129]		**2+**; Incident case control	239		117	x**			x**		x**		x**, ***		nd					*49.2% of asthma attributable to ETS (workplace + home) during the past year (among 239 ETS-exposed). 8% attributable fraction for the whole working-age population (n=487), resp. in asthmatics lifetime workplace ETS sign. increased, OR 2.16, > 150 cigarette-years adjusted OR 2.21. In total population for lifetime workplace ETS OR 1.84; **no individual data given.; ***SFT for 2 weeks
"	Greer, Abbey et al. 1993 [130]		**2+**; Prospective cohort study	3119		45	x**			nd		nd		nd		nd					Cohort of n=3914 in 1977 and again in 1987. ETS in the workplace increases asthma sign., OR 1.45; *45 subjects wirh new onset asthma between 1977 and 1987; **individual data not given
"	Eisner, Balmes et al. 2005 [131]		**2-**; Cross-sectional	2113			x			42/47*		nd		nd		nd					Population-based sample. COPD sign. increased (OR for > 23 yrs workplace ETS 1.36); population-attributable fraction of ETS exposure at work = 7%; subpopulation n=47: *42/47(89.4%) obstuctive ventilation pattern
"	Fidan, Cimrin et al. 2004 [132]		**2-**; Cross-sectional	114		44* (38.6)	44/ 114*	38.6		x**		nd		x**		nd					Coffeehouse workers (86% smokers). *Airway disease cases with sign. higher risk of prevalence vs. controls (OR 5.35, sign.), especially for smoking personal (OR 4.52, sign.); **individual data not given; sign. time exposure relationship (OR 3.59 < 4yrs.,sign.; OR 7.89 >13yrs., sign.)
"	Radon, Büsching et al. 2002 [133]		**2-**; Cross-sectional	1890			x			nd		nd		nd		nd					Sample of population-based ECHRS. Increased asthma: OR for ETS at home and in the workplace 1.5; chronic bronchitis (OR 1.9) sign. increased
"	Chen, Tunstall-Pedoe et al. 2001 [108]		**2-**; Case-control (MONICA)	294			x**			x**		nd		nd		nd					Never-smoking workers. Asthma was not a spec. target. **Individual data not given. Sign. dose-response relationship to high level eposure of ETS, increase of resp. symptoms and FEV1-, FVC- declines at work (OR 3.09-3.12 for FEV1, sign., and OR 2.47-2.53, sign.)
"	Janson, Chinn et al. 2001 [109]		**2-**; Cross-sectional	7882			x*			x*		x*		nd		nd					Subjects of 36 centers in 16 countries. ETS in the workplace associated with resp. symptoms and current asthma OR 1.9, sign.; NSBHR+ dose-related trend with ETS; *individual data not given
"	Blanc, Ellbjär et al. 1999 [134]		**2-**; Cross-sectional; survey (ECRHS)	1562		61 (3.9)	61/1562	3.9		x*		x*		nd		nd					Population-based sample of ECHRS resp. work disability; increased asthma PR for workplace ETS, OR 1.8; workplace ETS associated with NSBHR+ and WRS; *individual data not given

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Flodin, Jönsson et al. 1995 [135]		**2-**; Population-based case-referent study				x*			x*		x*		nd		nd					ETS in the workplaces increased asthma cases, OR 1.5 sign.; *individual data not given
	Lambourn, Hayes et al. 1992 [439]		**3**; Case report	1		1	1/1			0/1		0/1		nd		1/1			1		Mould maker and fitter
Epoxy resin system see 3-(dimethylamino) propylamine, 109-55-7																					
Ethylenediamine [ethylene diamine], 107-15-3		*			**≥ 14**																
"	Aldrich, Stange et al. 1987 [263]		**3+**; Cohort study	337		x*	44/337*			nd		nd		nd		nd					Factory workers with EDA exposure of 8 years or more. *High risk of confounding bias, not clear if WR-asthma cases. 38/337 EDA rhinitis, coughing and wheezing; mean latency period for symptoms 15.2 months; 6/38 sensintized had asthma
"	Gelfand 1963 [176]		**3+**; Case series	7		7	7/7			nd		nd		nd		7/7*					6 shellac handlers and 1 rubber industry worker. *Individual reaction types not given
"	Casas, Badorrey et al. 2002 [263]		**3**; Case report	1		1	1/1			0/2		0/1		nd		1/1			1		Worker of laundry powder industry with 14 years of work before symptoms started.
"	Nakazawa and Matsui 1990 [160]		**3**; Case reports	2		2	2/2			0/2		2/2		nd		2/2			2		2 chemical workers. 2/2 i.c.+
"	Hagmar, Bellander et al., 1982 [265]		**3**; Case reports	3		3	3/3*			x**		1/3		nd		nd					Chemical workers; co-exposure to other amines. *Asthma type according to onset of symptoms: 1 late, 2 dual; **individual data not given
"	Lam and Chan-Yeung, 1980 [266]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1			1		Photography laboratory worker. SIC+ also with sulphur dioxide (immediate)
Ethylene oxide 75-21-8	Deschamps, Rosenberg et al. 1992 [267]	-	**3**; Case report	1	**2**	1	1/1			1/1		1/1		nd		nd					Worker of railway station
"	Dugue, Faraut et al. 1991 [268]		**3**; Case report	1		1	1/1			nd		nd		nd		1/1*					factory worker. 1/3 spec.IgE+; *individual reaction type not given
Farming		*[*]			**≥ 944**																
"	Walusiak, Krawczyk-Adamus et al., 2004 [497]		**2-**; Case control	100		38(38.0)	100/100			x*		x*		nd		38/100		23		15	Polish farmers. SIC with grain dust, animal epidermis, furs and feathers; sign. risk factors of resp symptoms, cereal farming, animal breeding; 47/100 SPT+; *individual data not given
"	Eduard, Douwes et al. 2004 [136]		**2-**; Cross-sectional	1614			x*			nd		nd		nd		nd					Norwegian farmers. *asthma sign. elevated in cattle and pig farmers (OR 1.8 or 1.6); exposure to endotoxines, fungal spores and ammonia pos. associated with non-allergic asthma
"	Hoppin, Umbach et al. 2003 [137]; Hoppin, Umbach et al., 2004 [110]		**2-**; cross-sectional (Agricultural Health Study 1994-1997)	20468/ 20898			3838*/ 20 898	18.4		nd		nd		nd		nd					20 468, and 20 898 farmers (pesticide applicators). 3838 wheezing; OR for wheeze 1.26 (dairy), and 1.70 (eggs); wheezing sign. dose-response related for poultry and number of livestock; OR for driving diesel tractor: 1.31 (sign.), for solvents 1.16-1.33 sign.

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Melenka, Hessel et. al 1999 [111]		**2-**; Cross-sectional	781		36*(4.6)	108/781			x**		nd		nd		nd					Farmers, growing grain crops and raising livestock. *36 asthma cases correlated with cumulative dust exposure with OR 1.05, not sign.; **individual data not given. sign. dose-response relationship associated with reduction of FEV1 and FEV1/FVC (%) and cumulative dust exposure
"	Gomez, Hwang et al. 2004 [498]		**2-**; Cross-sectional	1620			295/ 1620**	18.2		nd		nd		nd		nd					Farmers of New York State. Data from telephone interviews with questionaire. *Asthma cases were not a specific target. **Participants were asked for occurrence of wheezing in the past year. Despite smoking and allergic reaction, sign. predictors for wheeze were having goats, more acreage in corn for silage
"	Melbostad, Eduard et al., 1998 [138]		**2-**; Cross-sectional	8482		263*(3.1)	263*/ 8482	3.1		x**		nd		nd		nd					Farmers of Norway. *Cases of self-reported asthma with 'current asthma'. sign. relationship between animal production and prevalence of current asthma without family history with OR 2.16, sign. **Individual data not given. Another important risk factor for asthma was an asthma family history
", (various)	Dosman, Graham et al., 1987 [499]		**3+**; Survey	1824		607(33.3)	607/ 1824			x*		nd		nd		nd					Farmers. 607 dyspnea, 500 wheezing; *sign. declines of FEV1, FVC, FEV1/VCV with individual data not given
", animals (pig, beef/veal, dairy, poultry)	Portengen, Preller et al., 2005 [500]	**	**2-**; Cross-sectional	81	**≥ 54**	36(44.4)	81/81			x*		36/78**	46.1	nd		nd					Pig farmers. *Individual data not given;**. NSBHR sign. increased (46% vs. 17% of controls); FEV1 sign. reduced; endotoxin-associated with BHR or lower lung function
","	Monso, Riu et al., 2004 [501]		**2-**; Cross-sectional	105		18(17.1)	58/105			11/105		nd		nd		nd					58/105 participants of sample of European never-smoking farmers' study reported wheezing. 18 COPD; COPD sign. dust-related
","	Radon, Weber et al., 2001 [502]		**2-**; prospective cohort study	76			36/ 67*			x***		nd		x***		nd					40 pig farmers (Denmark) and 36 poultry farmers (Switzerland), randomly chosen subsample out of a European study (n=3544). Asthma was not a spec. targe;. *spec. asthma symptoms not given; **individual data not given;***sign. Lower FEV1 and MMEF25-75 of farmers with symptoms; sign. lower lung function (FEV1, FVC, MMEF25-75) of pig farmers with higher temperature (>19°C) inside the pig houses
Floor sealant [aromatic hydrocarbons]	Brooks, Weiss et al. 1985 [5]	-	**3**; Case report	1	**1**	1	1/1		+	0/1		1/1		nd		nd					Grocery clerk. RADS for 14 months
Formaldehyde (gas, dust), 50-00-0		*			**≥53**																
"	Nunn, Craigen et al., 1990 [269]		**2-**; Prospective cohort study with 6-year follow-up.	125		*	33/125**			x***		nd		nd		nd					Workers of chemical factory. *Asthma was not a spcific target. **Neither wheezing, nor other resp. symptoms were sign. different from controls; ***FEV1/FVC decline in exposed group ns
"	Nordman, Keskinen et al., 1985 [270]		**3+;** Cross-sectional with Case reports	230		12	230/230			2/5*		29/ 209				12/230		6	4	2	230 formaldehyde workers.; 5 Case reports, *individual data only given in 3 cases

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC					
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Burge, Harries et al., 1985 [271]		**3+**; Case series	15		7	5/15			nd		4/14		nd		7/ 15		4	1	2	1 plastic molder, 1 printer, 1 formaldehyde manufacturer, 1 medicine packer, 1 farmworker, 6 printers/ laminators of flexible packaging, 1 laminated tray worker, 2 core shop workers; 9/15 subjects co-exposed to isocyanates
"	Piipari and Keskinen, 2005 [272]		**3**; Case reports	4		4	4/4			nd		nd		4/4*		4/4*					4/306 OA cases in 2002. *Individual data not given
"	Kim, Song et al., 2001 [273]		**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1*			1		Textile factory worker. *Workplace challenge; average workplace-conc.: 6 ppm, several short-term peaks of 0.12-0.13 ppm
"	Lemière, Desjardins et al., 1995 [274]		**3**; Case reports	3		3	3/3			0/3		3/3		3/3		3/3		1	2		1 chemist, 1 carpenter, 1 wood chips factory worker
"	Porter, 1975 [275]		**3**; Case report	1		1	1/1			1/1		nd		nd		nd					Neurology resident. P+
"	Hendrick and Lane, 1975 [276]		**3**; Case report	1		1	1/1			nd		nd		nd		1/1			1		Nurse
Foundry (see also Isocyanates [MDI])		***[*]**			**≥ 7**																
"	Hansen 1997 [503]		**2-**; historical cohort study with follow-up	3056		x*	x*			nd		nd		nd		nd					Workers of iron- (93%), stell- (3%), or metal- (4%) foundry. Exposure to silica dust, metal fumes, organic combustion products, engine exhaust, pyrolysis products; *within follow-up, 886 deaths with sign. increase of resp. diseases (mainly: chronic bronchitis/emphysema, pneumoconiosis)
"	Ahman, Alexandersson et al., 1991 [112]		**2-**; Cross-sectional	28		*	0/28**			0/28		nd		0/28***		nd					Foundry workers (molding/core making). *Asthma was not a spec. target; **complaints of upper resp. symptoms which show a dose-response relationship to cumulative furan resin sand exposure; ***24/28 with sign. FVC (but not FEV1) decline over a work shift
"	Mastrangelo, Tartari et al., 2003 [139]		**3;** Case control study	7		**7***	7/7			0/7		nd		nd		nd					Foundry workers. *COPD cases selected for study with sign. increased risk, OR 12.0; exposure mainly to mineral dust and irritant gases
"	Hahn, Beck et al.,1986 [504]		**3**; Survey	265		*	x**			50/ 265***	18.8	nd		nd		nd					Foundry workers. *Asthma was not a spec. target. **sign. prevalence of chronic bronchitis symptoms in exposed group (21.1% vs 10.2%); ***individual data not given
Freon 22 [fluorocarbon 22], 75-45-6	Sjögren, Gunnare et al., 2002 [277]	**-**	**3**; Case report	1	**1**	0	1/1			nd		nd		nd		nd					Refrigerator company worker. After massive exposure resp. symptoms with dypnoe, cough and blood-stained sputum; development of pulmonary inflammation, death by myocardial infarction one month later
", (heated)	Malo, Gagnon et al., 1984 [278]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1				1	Refrigerator company worker. Asthma aggravation at work for two years
Fumigating agent	Brooks, Weiss et al., 1985 [5]	**-**	**3**; Case report	1	**1**	1	1/1		+	1/1		1/1		nd		nd					Housewife fumigating her kitchen. Duration of symptoms for 6 months
Furan-based binder	Cockcroft, Cartier et al., 1980 [440]	**-**	**3**; Case report	1	**1**	1	1/1			1/1		1/1		1/1		1/1*			1		Mold maker. *3 SICs+ (late): furfuryl alcohol combined with acid catalyst, sulfuric acid, or butyl alcohol
Glutaraldehyde [glutaral], 11-30-8		***[*]**			**≥ 105**																
"	Vyas, Pickering et al., 2000 [279]		**2-**; Cross-sectional	318		*	17/ 318**	5.3		x***		nd		0/17		nd					Nurses of endoscopy units throughout the UK. *Asthma was not a specific target. **WR chest tightness. ***Individual data not given.

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Curran, Burge et al., 1996 [318]		3+; Cross-sectional	20		7	13/20*	65.0		nd		nd		nd		7/8*					Hospital employees. *SIC done in 8/13 with LFT+, individual data on reaction type not given, 2/13 IgE+ and 3/13 false positive IgE
"	Ross, Keynes et al., 1997 [86]		3+; Occupational diseases statistics (SWORD)	74		74	x*			x*		x*		x*		x*					74/1765 physician-diagnosed asthma cases in 1996
"	Gannon, Bright et al.,, 1995 [281]		3+; Case series	7		7	7/7			1/7		3/7		7/7		7/8			5	2	Workers of endoscopy and X-ray departments
"	Gannon and Burge, 1993 [58]		3+; Occupational diseases statistics (SHIELD)	6		6	6/6			nd		nd		x		x					6/500 asthma cases in 1989-1991
"	Jachuck and Bound, 1989 [282]		3+; Survey	9		1*(11.1)	1/9*			nd		nd		nd		nd					Employees of endoscopy unit. *1subject with breathlessness
"	Ong, Tan et al., 2004 [283]		3; Case report	1		1	1/1			0/1		1/1		1/1*		1/1			1		Laboratory technician
"	Cullinan, Hayes et al. 1992 [284]		3; Case reports	2		2	2/2			0/2		1/2		x*		1/2**			1		Radiographers. *Individual data not given; **SIC done with 11% glutaraldehyde solution in first patient (+); in second patient with SIC-solution of 1 and 2% and additionally with fixative solution (SIC+, imm.), containing acetic/hydrochloric acids
"	Corrado, Osman et al., 1986 [285]		3; Case reports	4		1	4/4			0/4		nd		nd		1/4*			1		Nurses of endoscopy units. *SIC with alkaline glutaraldehyde
Grain dust		**			≥ 133																
"	Toren, Balder et al., 1999 [21]		2-; Case control	7		7	x*			x*		x*		nd		nd					7/294 OA cases in 1996. OR 4.2, sign.; *individual data not given
"	Post, Heederik et al., 1998 [113]		2-; Cross-sectional study with follow-up after 5 years	140		*	8/ 140	6.0		x**		nd		nd		nd					Workers of grain processing and animal feed industry. sign. higher annual FEV1 decline in workers with 5-10 years of exposure vs. workers <5 years of exposure; sign. dose-response relationship to grain dust (>4mg/m³) / endotoxin (>20ng/m³) and rapid annual FEV1 decline (>90ml/s), OR 3.3/OR 3.2, sign.
"	Schwartz, Thorne et al., 1995 [114]		2-; Population based cross-sectional	410		58(14.1)	58	14.1		x*		45/410	11.0	nd		nd					Grain workers. *FEV1 sign. reduced and sign. endotoxin dose-related
"	Chan-Yeung, Schulzer et al., 1980 [441]		2-; Comparative survey	610			x*			x*		nd		x*		nd					Workers of grain elevator terminals. Increased chest symptoms; across-shift and -week decrease in FEV1 and FVC (FEV1 drop of > 10% in 4.3% of the survey)
"	Williams, Skoulas et al., 1964 [442]		3+; Survey	502		35	35/ 502			nd		nd		nd		nd					Grain elevator industry workers. 78 with WR breathlessness; 35 (7.0%) wheezing and breathlessness without cough, 20 (4.0) with cough, breathlessness and wheezing
"	Skoulas, Williams et al., 1964 [443]		3+; Survey	51		31	31*	61.0		x*		nd		nd		nd					51 grain elevator workers out of 175 with resp. symptoms. *Most severe (n=31) symptoms associated with sign. FEV1 decline; 31/51 SPT+(settled barley dust), 61% vs. 32% of controls
"	Pahwa, Senthilselvan et al., 1994 [115]		3; Longitudinal study	1396		*	x**			x**		nd		nd		nd					Grain workers. *Asthma was not a spec. target; **individual data not given; trend of increased annual declines in FEV1 and FVC. Trend of dose-response relationship
"	Baur, Preisser et al., 2003 [444]		3; Case reports	2		2	2/2			2/2		2/2		nd		2/2*		2			1 farmer, 1 manager of grain warehouse (SIC with wheat dust); *SIC in workplace with rye dust

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Chan-Yeung, Dimich Ward et al., 1992 [445]		**4;** Review				nd			nd		nd		nd		nd					across-shift and chronic decreases in lung function exposure-related
", rice dust	Ye, Huang et al., 1998 [446]	**[*]**	**2-**; Cross-sectional	474	**20**	20 (4.2)*	x**			x***		nd		x****		nd					Rice handlers, processors from granaries. *Asthma cases: 4.2%(n=20) vs. 3.0%(n=7) of controls, ns. **sign. higher prevalences of resp. symptoms (e.g chronic cough/bronchitis/phlegm.) in exposed group. ***Individual data not given, no sign. FEV1/FVC changes in exposed vs. controls.****Trend of higher FEV1 decrements aacross-shift in exposed. Range of rice dust concentration at workplace 6.6mg/m3- 59.8mg/m3.
Hairdressing chemicals	Piipari and Keskinen, 2005 [272]	**(*)**	**3+**; Occupational diseases statistics Finland	6	**6**	6	x*			nd		nd		6/6*		6/6*					6/306 OA cases in 2002. *Individual data not given
Health Care Workers	Kogevinas, Zock et al., 2007 [140]	*	**2-**; prospective cohort study (ECRHS II)	913*	**332**	27(3.0)*	27/913*			nd		nd		nd		nd					High risk occupations for WRA. *sign. increase for workers exposed to agents with low-molecular-weight, OR 1.58; Highest sign. risk of WRA was nursing, OR 2.22; exposure to cleaning products also associated with sign. high risk of WRA, OR 1.80
"	Pechter, Davis et al., 2005 [505]		**3+**; Occupational disease statistics (SENSOR 1993-1997)			305*	305			x**		nd		nd		nd					*Majority of cases were nurses (63%) working in hospitals. **Individual data not given. Nurses affected by latex (33%), cleaning products (21%), glutaraldehyde/ formaldehyde (19%)
Hexachlorophene, 70-30-4	Nagy and Orosz, 1984 [286]	-	**3**; Case report	1	**1**	1	1/1			nd		1/1		nd		1/1				1	Children's nurse
Hexamethylenetetramine, 100-97-0	Merget, Topcu, et al. 1999 [287]	*	**3+** ; Cross-sectional	17	**≥ 15**	x**	3/17*	11.8		0/17		4/17**	24	nd		nd					HMT production workers. *Results ns different from controls; **not clear if workers with NSBHR+ additionally asthma symptoms; 0/17 SPT+
"	Gamble, McMichael et al., 1976 [288]		**3+**; Comparative survey	52		8 (15.4)	8/52	15.4		x*		nd		x		nd					Workers of tire manufacturing plant. 8/52 wheezing, 14/52 chest tightness, 10/52 dyspnea; *LFT reduction ns
"	Gelfand, 1963 [176]		**3**; Case series	7		7	7/7			nd		nd		nd		7/7*					Laquer handlers with asthma. 7/7 SPT+
Hydrazine, 302-01-2	Brooks, Weiss et al., 1985 [5]	-	**3**; Case report	1	**1**	1	1/1		+	1/1		1/1		nd		nd					Power plant utility worker. Massive exposure to pouring of 35% solution; symptoms for 34 months
Hydrogen chloride [hydrochloric acid], 7647-01-0	Promisloff, Lechner et al., 1990 [154]	-	**3**; Case reports	3	**5**	3	3/3		+	0/3		3/3		nd		nd					Members of police department. Massive exposure by truck accident
"	Tarlo and Broder, 1989 [9]		**3**; Case report	1		1	1/1			x*		1/1		x*		nd					Profession not mentioned. Asthmatic symptoms persistent for 2 years
"	Boulet, 1988 [89]		**3**; Case report	1		1	1/1		+	0/1		1/1		nd		nd					Profession not mentioned. BD+
Hydrogen fluoride [hydrofluoric acid], 7664-39-3	Franzblau and Sahakian, 2003 [155]	-	**3**; Case report	1	**1**	1	1/1		+	1/1		1/1		nd		nd					Cleaning with HF containing rust stain remover once. Asthmatic symptoms persistent for > 3 years
Iridium salt	Bergman, Svedberg et al., 1995 [289]	-	**3**; Case report	1	**1**	1	1/1			x*		x*		nd		nd					Worker of elctrochemical factory. SPT+ (immediate); individual data not given
Isocyanates, Isocyanurate					**(≥ 1737)**																
", various (HDI, MDI, TDI)	Mastrangelo, Paruzzolo et al., 1995 [141]	**	**2-**; Cross-sectional	121	**1220**	7(5.8)	7/121	5.8		nd		nd		nd		nd					Workers of wooden furniture industry. Exposure to two-component paint (polyalcohols and polyisocyanates) with sign.higher prevalence of WRA vs. non-exposed (n=609), OR 4.61,sign.

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
","	Baur, Dewair et al., 1984 [290]		**2-**; Case series/ cross-sectional	621		179 (28.8)	247/ 621	39.8		179/ 621	28.8	nd		nd		nd					Isocyanate workers of different companies. 26/247 symptomatics exposure-related COPD; spec.IgE+ (14% symptomatic vs. 0.3% asymptomatic isocyanate workers); 26.4% (14/53) symptomatics SPT+ vs. 0% (n=150) asymptomatics
", "	Piirilä, Nordman et al., 2000 [291]		**3+**; Case series	244		236	244/244			x*		3/3**		14/14**		219/ 219**		101	118		Asthma cases diagnosed 1976-1992. Mainly eposed to polyurethane foams production or spray painting;*individual data not given;**case diagnosed by NSBHR or SFT or SIC (mainly); 91 patients re-examined in 1995 with sign. impairment of FEV1
", "	O'Brien, Harries et al., 1979 [292]		**3+**; Case series	24		16	24/24			nd		12/24		nd		16/24			5	11	Profession not mentioned. 8/16 SIC+ also SIC+ with MDI (4 immediate, 4 dual), 3/8 SIC+ with 3rd agent HDI (1 immediate, 2 late)
", "	Cartier, Grammer et al., 1989 [293]		**3+**; Case series	62		29	62/62			14/62		46/62		nd		29/62		7	15	7	Workers of foam industry (spray painters and others. 8/29 SIC+ with spec.IgE+ and
", "	Meredith, Bugler et al., 2000 [142]		**3+**; Case-referent study	78		27*	27			x**		nd		x**		nd					Workers of foam industry. Asthma cases of SWORD-study between 1989-1993.24/27 TDI, 3/27 MDI-exposed. Higher TWA-exposures for cases vs. referents: 1.5ppb vs. 1.2 ppb respectively. OR (for 0.1ppb increase in 8h TWA-exposures) 1.08, ns.
", "	Ross, Keynes et al., 1997 [86]		**3+**; Occupational diseases statistics (SWORD)	310		310	x*			x*		x*		x*		x*					310/1765 physician-diagnosed asthma cases in 1996
", "	Piipari and Keskinen, 2005 [272]		**3+**; Occupational diseases statistics Finland	6		6	6/6*			nd		nd		6/6*		6/6*					6/306 OA cases in 2002. *Individual data not given.
", "	Latza and Baur, 2005 [31]		**3+**; Occupational diseases statistics	54		54	x*			x*		nd		nd		x*					54/835 OA cases in 2003 (54/210 irritant asthma cases). *Individual data not given.
", "	Chatkin, Tarlo et al., 1999 [157]		**3+**; Occupational diseases statistics (WCB), survey	9		9	9/9		(+)**	nd		9/9*		nd		nd					9/465 asthma claims between mid 1984 and mid 1988 identified by retrospective Review. *9/9 BD+ and/or NSBHR+; **2/9 RADS
", "	Tarlo, Liss et al., 2002 [294]		**3+**; Retrospective review of new OA claims of occupational diseases statistics, (WCB) between 1980-1993	425		425	x*			x*		x*		nd		x*					Review of of Ontario Workers' compensation board. Diisocyanates represented 50% of all OA claims. *Individual data not given.
", **Diphenylmethane diisocyanate [MDI],** 5873-54-1	Bernstein, Korbee et al., 1993 [295]	**	**2-**; Cross-sectional	243	**137**	2* (0.8)	9/243			nd		nd		3*/9		nd					Workers of urethane mold plant. *At follow-up,2/3 physician diagnosed OA, additionally showed NSBHR+.
", "	Liss, Bernstein et al., 1988 [296]		**3+**; Comparative survey	26		7 (26.9)	7/26			x*,**		nd		x**		nd					Current mould and core room (foundry) workers. *sign. FEV1 decrease across-shift; **individual data not given; 1/26 IgE+
", "	Woellner, Hall et al., 1997 [297]		**3+**; Case series	18		15	18/18			x*		15/16		nd		nd					Workers of a wood products plant. *Individual data not given.
", "	Mapp, Boschetto et al., 1988 [564]		**3+**; Case series	162		93	162/162			15/93		93/ 162*		nd		93/162		27	32	34	Profession not mentioned. *NSBHR sign. lower in 93 SIC+ vs. 69 SIC-
	Zammit-Tabona, Sherkin et al., 1983		**3+**; Case series	78		6	12/78			5/11		9/11*		nd		6/11			4	2	Foundry workers. 0/6 with SIC+ spec.IgE-
", "	Perfetti, Brame et al., 2003 [300]		**3**; Case report	1		1	1/1		+	1/1		1/1		nd		1/1				1	Spray painter. RADS after accidental spill
", " (prepolymers)	Vandenplas, Malo et al., 1993 [301]	-	**3+**; Case series	8	**2**	2	8/8			0/8		1/8		nd		2/8*					Workers of woodchip board manufacturing; 8/8 SIC+ with sign. declines of FEV1 and FVC, only *2/8 with sign. obstr. (no individual reaction type not given); 7/8 spec IgE+; 4/8 BD+

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
, HDI biuret plus, 4035-89-6	Vandenplas, Cartier et al., 1993 [304]	**(*)**	**3+**; Case series	20	**12**	10	20/20			6/20		15/20		nd		10/20*		4	2	4	Profession not mentioned; *SIC with monomer and prepolymers of HDI (4 only with HDI prepolymers, 1 only with HDI monomer, 5 with both)
, Hexamethylene diisocyanate [HDI] (plus isodurane diisocyanate), 822-06-0	Lemière, Malo et al., 1996 [302]		**3**; Case report	1		1	1/1		+	0/1		1/1		nd		0/1					Mechanic; co-exposure to several organic solvents; P+
, "	Belin, Hjortsberg et al., 1981 [303]		**3**; Case report	1		1	1/1*			1/1		1/1		nd		nd					Gasoline station manager; spec.IgE+; *severe asthma symptoms after exposed to high concn.of car (polyurethane) paint twice
, 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate [isophorone diisocyanate, IPDI], 4098-71-9	Clarke and Aldons, 1981 [305]	**-**	**3**; Case report	1	**1**	1	1/1			1/1		nd		nd		1/1*				1	Spray painter; asthma associated with abnormal chest X-ray (interstitial infiltration); *SIC by increasing exposure on following days
, Methyl isocyanate [MIC], 624-83-9	Kamat, Patel et al., 1992 [306]	*****	**3+**; Longitudinal study, follow-up of cases	113	**≥ 144**	97	97/97			x*		nd		nd		nd					Persistently symptomatic residents exposed to MIC at Bhopal tragedy 1984. 97/113 dyspnea; 32% with lung function fluctuations; *sign. FEV1/FVC decline after 18 months, also gradual FEF25-75 decline over 24 months, in a previous study 24/82 subjects; predominating restr.s; 97/97 BD+
, "	Baur, Chen et al., 2001 [307]		**3+**; Case series	6		3	5/6			nd		3/5*		nd		3/5*		1	1	1	1 elastomer-, 5 synthetic resin production workers. 1/6 rhinitis; *SIC+ workers also NSBHR+
, "	Vijayan and Sankaran, 1996 [308]		**3+**; Case series	54		17	54/54			17/54		nd		nd		nd					Bhopal tragedy. 17 subjects investigated symptomatic and moderately or severely exposed subjects with obstructive lung pattern; FEV1/FVC sign. negatively related to exposure and to BAL neutrophils (P+)
, "	Kamat, Mahashur et al., 1985 [309]		**3+**; Case series	82		24	82/82			24/82*		nd		nd		nd					Exposed residents at Bhopal tragedy. Predominating restr.s (64/82); 24/82 BD+
, "	Harries, Burge et al., 1979 [310]		**3**; Case reports	3		3	3/3			2/3		1/3		nd		3/3			2	1	1 chemist, 1 foreman, 1 polyurethane caster of plastic mould factory
, "	Mehta, Mehta et al., 1990 [311]		**4**; Review	41			nd		+	nd		nd		nd		nd					Bhopal tragedy: Mainly mixed resp ailments
, 1,5-Naphthylene diisocyanate [NDI], 3173-72-6	Fuortes, Kiken et al., 1995 [314]	*****	**2-**; Survey	46	**24**	13*	17/46			x*		2/3	66.6	3/8	37.5	nd					Workers of wheel factory employed in production and administrative section. Co-exposure to MDI; *7 cases reported to NIOSH and 6 additional cases identified by questionnaire; *individual data not given.
,"	Baur, Wieners et al., 2000 [313]		**3;** Case series	5		5	5/5			3/5		3/5		nd		3/5		1	1	1	Workers in production of car equipment
,"	Alexandersson, Gustafsson et al., 1986 [312]		**3+**, Survey	23			8/23			nd		nd		nd		nd					Production of tires. * 12/17 eye irritation, 6/17 productive cough, 2/17 chronic bronchitis, 6 exertional dyspnoe. Significant DV decline in 8 workers after 2 days of work.
, Polymethylene polyphenyl isocyanate, 9016-87-9	Séguin, Allard et al., 1987 [315]	*****	**2-**; Survey	42	**6**	6 (11.8)	14/ 42	33.3		4/ 10	40.0	nd		nd		6/ 10	60		2	4	Paint shop workers
, Toluene diisocyanate [TDI], 2,4: 584-84-9; 2,6:91-08-7	Butcher, Jones et al., 1977 [316]	******	**2-**; Prospective cohort	103	**≥ 152**	9	26/ 89			x**		8/ 11				9/ 13		5	*	*	103 TDI workers of Longitudinal study 1973-1975. 89/103 became continuously/intermittently exposed; *4/9 SIC reaction type late or dual; **LFT not sign.
, "	Ott, Klees et al., 2000 [317]		**3+**; Cohort study	313		19	x*			x*		nd		nd		nd					TDI production employees between 1967-1992.*Individual data not given.

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
", "	Omae, Higashi et al., 1992 [318]		**3+**; Cross-sectional study with follow-up	57		*	**			x*		nd		nd		nd					Workers of polyurethane foam industry. *Asthma and asthma symptoms were not a spec. target; **individual data not given; sign. increase of average annual loss of pulmonary function (FEV1,FEF75, PEF) in high exposuregroup(n=15) with mean and maximal TWA conc. of 8.2 and 30ppb
", "	Chatkin, Tarlo et al., 1999 [157]		**3+**; Occupational diseases statistics (WCB)	5		5	5/5		+	nd		x*		nd		2/5**					5/469 asthma claims between mid 1984 and mid 1988 identified by retrospective review; 5/5 BD+ and/or NSBHR+; for SIC indiviual reaction type not given
", "	Marabini, Brugnami et al., 1994 [319]		**3+**; Case series with follow-up	40		40	x*			x*,**		nd		nd		40/ 40		9	25	6	Profession not mentioned. *Individual data not given.; **at follow-up 4-8 years after first diagnosis sign. decline of FEV1 and FVC of workers with SIC+ (late)
", "	Karol, Tollerud et al., 1994 [320]		**3+**; Case series	63		34	63/ 63			nd		32/34*		nd		34/ 63		12	13	9	63 asthmatic isocyanate workers. *NSBHR+ associated with SIC+
", "	Paggiaro, Bacci et al., 1990 [321]		**3+**; Case series with follow-up	10		10	10/ 10			5/ 10		10/ 10				10/ 10			4	6	Profession not mentioned. At follow-up 3-39 months after cessation no sign. difference in FEV1 and NSBHR. Biopsy of bronchial mucosa with inflammatory changes in 8/8 (P+)
", "	Axford, McKerrow et al., 1976 [322]		**3+**; Case series with 4 year follow-up	35		30	30/35		(+)*	x**		nd		nd		nd					35 firemen at accidental exposure. 20/35 persistent resp. symptoms 4 years later with small **FEV1/FVC decline; *8/35 chest tightness during the fire (immediate), additionally 22 within 8 hours to 3 weeks (delayed symptoms); 7/33 asthmatic symptoms after 6 months, 2/32 after 44 months
", "	Vandenplas, Cartier et al., 1992 [323]		**3**; Case reports	2		2	2/2			1/2		2/2		nd		2/2*			2		Workers of wood roof industry. *SIC with TDI prepolymers, TDI monomers negative
", "	Luo, Nelsen et al., 1990 [324]		**3**; Case reports	2		2	2/2		+	1/2		2/2		nd		nd					Police officers exposed to spill. Persistent asthmatic symptoms > 7years with considerable improvement
", "	Tarlo and Broder, 1989 [9]		**3**; Case report	1		1	1/1		+	x*		1/1		x*		nd					RADS lasting for 1.5 years
", "	Wisnewski, Liu et al., 2005 [116]		**4**; Review																		Accelerated loss of FEV1 within 4-year-period. Dose-response relationship remains unclear
", **Triglycidil isocyanurate,** 2451-62-1	Piirilä, Estlander et al., 1997 [565]	-	**3**; Case report	1	**1**	1	1/1			nd		1/1		1/1		1/1		1			Laboratory technician. Spec.IgE+
", **Triphenylmethane triisocyanate**	Buick and Todd 1997 [326]	-	**3**; Case report	1	**1**	1	1/1			1/1		nd		nd		nd					Salesman, dealing with rubber products. Initially, exacerbation of interstitial lung disease
Isothiazolinone, 55965-84-9	Bourke, Convery et al., 1997 [327]	-	**3**; Case report	1	**1**	1	1/1			1/1		1/1		1/1*		nd					Chemical plant operator; *SFT on 3 consecutive days with I. (asthma onset late)
Lauryl dimethyl benzyl ammonium chloride, 139-07-1	Burge and Richardson, 1994 [328]	-	**3**; Case report	1	**1**	1	1/1			nd		1/1		1/1		1/1			1		Pharmacist
Lubricants (not specified)	Henneberger, Derk et al., 2003 [432]	(*)	**3+**; Occupational diseases statistics (SENSOR)	46	**54**	46	46/46			x		x		nd		nd					46/424 OA cases in 1993-1995
"	Latza and Baur, 2005 [31]		**3**; Occupational diseases statistics	8		8	x*			x*		nd		nd		x*					8/835 OA cases in 2004. 3 classign.ed as allergic asthma, 5 as irritant asthma (total irritant asthma cases = 210); *individual data not given
Metal coat remover (coating removing chemical)	Brooks, Weiss et al., 1985 [5]	-	**3**; Case report	1	**1**	1	1/1		+	1/1		1/1		nd		nd					Remover of coatings from metals and plastics. RADS for 39 months
Metal oxide fume	Dube, Puruckherr et al. 2002 [447]	-	**3**; Case report	1	**1**	1	1/1		+	1/1		nd		nd		nd					Metal industry worker. RADS associated with metal fume fever
Metal working fluids [MWF]	Zacharisen, Kadambi et al., 1998 [448]	-	**3+**; Survey	30	**12**	12 (40.0)	30/ 30	100.0		5/ 30	16.7	12/ 30	40.0	nd		nd					30 workers of an automobile engine manufacturing plant: 12 OA, 6 industrial bronchitis, 7 hypersensitivity pneumonitis

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC					
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Metam sodium [methyldithiocarbamate], 144-54-7	Cone, Wugofski et al., 1994 [92]	-	**3+**; Retrospective case series	197	**20**	20 (10.1)	48/ 197	24.3	(+)*	15/ 30	50.0	23/ 23	100.0	nd		nd					Massive spill of pesticide, 197 out of c. 3,000 exposed subjects clinically examined. 20 new onset asthma (*17/20 RADS) plus 10 work-exacerbated asthma
Methylmercaptan, 74-93-1	Chatkin, Tarlo et al., 1999 [157]	-	**3**; Occupational diseases statistics (WCB)	1	**1**	1	nd		+	nd		x*		nd		nd					1/469 asthma claims between mid 1984 and mid 1988 identified by retrospective review; *1/1 BD+ and/or NSBHR+
Monoethanolamine, 141-43-5	Gelfand,1963 [176]	-	**3+**; Case series	14	**10**	10	14/14			nd		nd		nd		10/10*					Subjects exposed in the beauty culture industry. Co-exposure to ammonium thioglycolate and ethylene diamine; *individual data not given
Mustard gas (see dichlorodiethyl sulfide)																					
N-methylmorpholine, 109-02-4	Belin, Wass et al., 1983 [329]	[*]	**3**; Comparative survey	48		x*	13/ 48			nd		8/44		nd		nd					Polyurethane foam industry workers; 13/48 wheezing and dyspnea (27 vs. 17% of controls, ns); NSBHR sign. increased, *not clear if 8/44 with BHR+ have asthma symptoms; co-exposure to 1.4-diaza-bicyclo-(2,2,2) octane and to isocyanates
Nickel sulphate, →anhydrous 7786-81-4 →hexahydrate 10101-97-0	Estlander, Kanerva et al., 1993 [330]	(*)	**3**; Case report	1	**5**	1	1/1			0/1		0/1		1/1		1/1			1		Manual grinding of metal casting. Co-exposure to chromium; spec. IgE+; allergic contact dermatitis
"	Block and Yeung, 1982 [331]		**3**; Case report	1		1	1/1			0/1		1/1		1/1		1/1		1			Metal polisher. SPT+; contact dermatitis
"	Malo, Cartier et al., 1982 [332]		**3**; Case report	1		1	1/1			0/1		0/1		1/1		1/1		1			Metal plating factory worker. **SFT for 2 weeks; spec.IgE+
"	Novey, Habib et al., 1983 [237]		**3**; Case report	1		1	1/1			1/1		nd		nd		1/1				1	Metal plating worker. Co-exposure to chromium; spec.IgE+
"	McConnell, Fink et al., 1973 [333]		**3**; Case report	1		1	1/1			nd		nd		nd		1/1		1			Metal plating worker. SPT+; contact dermatitis
Ninhydrin 485-47-2	Piirilä, Estländer et al., 1997 [325]	-	**3**; Case report	1	**1**	1	1/1			1/1		1/1		1/1		1/1		1			Forensic laboratory worker; preceding rhinitis; spec.IgE+ (low); SPT+
Nitrogen chloride [nitrogen trichloride, trichloramine], 10025-85-1	Jacobs, Spaan et al., 2007 [143]	[*]	**2-**; Cross-sectional	624	**≥ 3**	x*	x*			nd		x**		nd		nd					Swimming-pool employees. *sign. elevation of asthma attacks during the last 12 months compared to the general Dutch population (OR 2.6 sign.); 60% of pool employees completed questionnaire; **ns
"	Thickett, McCoach et al., 2002 [334]		**3**; Case reports	3		3	3/3			1/3		0/3		2/2*		3/3		2		1	2 life guards of indoor swimming pools, 1 swimming teacher. Latency periods 10-14 years; *SFT over 4 weeks
Oil (spill)	Zock, Rodrigues-Tigo et al., 2007 [117]	*	**2-**; Cross-sectional	6700		x*	x*			nd		nd		nd		nd					Fishermen who participated in clean-up work after wreckage of oil tanker Prestige next to spanish coast. sign. prevalence for lower resp. symptoms, i.e. wheeze and breathlesness, OR 1.73; sign. dose-resp.onse relationship (i.e. number of exposed days)
Ozone (gassings) 10028-15-6	Mehta, Henneberger et al., 2005 [335]	*	**2-**; cross-sectional with follow up	66	**9**	9*	nd			9/66*	13.6	nd		nd		nd					Pulp mill workers. *Asthma was not a spec. target but chronic airflow limitation(FEV1/FVC <70%); higher risk of chronic airflow limitation in group with pre-baseline survey and both pre-baseline and interval of follow-up survey with ozone gassings (PR 4.3-5.5 for chronic airflow limitation, sign.)
Paint (fumes)	Wieslander, Norbäck, et al. 1997 [118]	*	**2-**; Longitudinal study	175	**26**	7(4.0)	7/175	4.0		x*		35	20.0	nd		nd					House painters, working with water based and solvent-based paints. Sign. dose-response relationship; highest TVOC 100-380mg/m³; *individual data not given
"	Wieslander, Janson et al. 1994 [449]		**3+**; Survey and clinical study	415		18 (4.3)	28*	6.7		18/23		20/23		nd		nd					House painters, working with water based paint. *28 with self-reported asthma, 23/28 took part in clinical study
"	Tarlo and Broder, 1989 [9]		**3**; Case report	1		1	1/1			x*		1/1		x*		nd					Consectutive worker; asthmatic symptoms persistent for 3 months

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Palladium, 7440-05-3	Daenen, Rogiers et al., 1999 [336]	-	**3**; Case report	1	**1**	1	1/1			1/1		1/1		nd		1/1		1			Electric industry worker. SPT+
Paper dust A111	Toren, Balder et al., 1999 [21]	(*)	**2-**; Case control	32	**32**	32	x*			x*		x*		nd		nd					32/294 OA cases in 1996. OR 2.1,sign.;*individual data not given.
Paraphenylendiamine, 106-50-3	Silberman and Sorrell, 1959 [337]	(*)	**3+**; Case series	80	**37**	37	59/ 80			nd		nd		nd		*37/ 50					80 fur industry workers. Patch test (2% PPD)+: 12/33; 18/80 contact dermatitis; individual reaction type not given
Paraquat, 4685-14-7	Schenker, Stoecklin et al., 2004 [144]	(*)	2-; cross-sectional (SALUD)	219			41/338**	12.1		10/338*, **	3.0	nd		nd		nd					Workers of banana, coffee and palm oil farms. sign. shortness of breath and wheeze associated with cumulative paraquat exposure, OR 2.3; *association to paraquat exposure ns; **data for overall group: 219 exposed, 119 not exposed
"	Castro-Gutièrrez, McConnell et al., 1997 [119]		**2-**; Cross-sectional	134			20/71*	28.2		14/ 134**	10.5	nd		nd		nd					Workers of banana farms. *Group with intense exposure, OR 2.9 sign.; **NSBHR+ OR 0.93-1.3,ns; dose-response relationship between intensity of exposure and exertional dyspnea, grade 3, OR 2.8-4.6, sign.
Perfume agents (research lab)	Kipen, Blume et al., 1994 [12]	-	**3**; Case report	1	**2**	1	1/1			nd		nd		1/1*		nd					Profession not mentioned. “Low dose RADS” ; *BD+
"	Baur, Schneider et al., 1999 [450]		**3**; Case report	1		1	1/1			1/1		nd		nd		1/1*		1			Saleswoman. *SIC with perfume "Must de Cartier"; SPT- and spec.IgE-
Persulfate																					
", not specified	Moscato, Pignatti et al., 2005 [338]	(*)	**3+**; Case series	47		21	47/ 47			0/21		12/21**	57.1	nd		21/47*	57.0	4	14	3	Hairdressers. SIC with ammonium pesulfate; 11/21 rhinitis; 8/21 dermatitis; 6/21 BD+; **NSBHR+ sign. associated with SIC+
", "	Pankow, Hein et al., 1989 [339]		**3**; Case report	1	**22**	1	1/1			*		1/1		nd		1/1		1			Hairdresser. *LFT could not be finished, because of non-compliance
", **ammonium**	Harth, Raulf-Heimsoth et al., 2006 [340]	-	**3**; Case report	1	**1**	1	1/1			0/1		1/1		nd		1/1			1		Hairdresser
", **potassium,** 7727-21-1 ", **ammonium peroxydisufate,** [7727-54-0]	Wrbitzky, Drexler et al., 1995 [341]	[*]	**3**; Cross sectionel	52			15/52*			x**		nd		nd		nd					Workers of persulphate producing factory (ammonium- and potassium- persulfate). *Resp. symptoms not specified; **trend (ns) of lung function decline in workers with SPT+ (8/52), compared to workers with SPT-
", **alcalic**	Therond, Géraut et al., 1989 [342]	-	**3+**; case series	5	**4**	4	1/5			1/5		nd		nd		4/5		2	2		Hairdressers
", **Sodium persulfate,** 7775-27-1	Parra, Igea et al., 1992 [343]	-	**3**; Case report	1	**1**	1	1/1			nd		1/1		nd		1/1			1		Hairdresser; SPT+, spec.IgE-
", **Dipotassium peroxo-peroxodisulfate [potassium persulfate],** 7727-21-1	Muñoz, Cruz et al., 2003 [344]	(*)	**3**; Follow-up of cases	8	**7**	7	8/8			5/6		7/8		nd		7/7		1	5	1	3 cosmetic industry workers, 5 hairdressers
", **Diammonium peroxodisulfate [ammonium persulfate],** 7727-54-0	Schwaiblmair, Vogelmeier et al., 1997 [566]	*	**3**; Survey	55	**16**	9 (16.4)	38/ 55	69.1		3/ 55		32/ 53		nd		9/ 41	28.0	5		4	Hairdressers; 13/54 SPT+
", "	Blainey, Ollier et al., 1986 [345]		**3**; Survey	23		4 (17.4)	7/23	30.4		0/23		6/23		1/12		4/9			4		Hairdressers. SIC with bleach, 3/4 SIC+ also challenged with potassium peroxodisulfate (3/3 late); 1/23 SPT+
", "	Gamboa, de la Cuesta et al., 1989 [346]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1			1		Hairdresser
", "	Baur, Fruhmann et al., 1979 [347]		**3**; Case reports	2		2	2/2			1/2		nd		2/2		nd					Chemical factory workers
Pestcides (not specified)	Jones, Burks et al., 2003 [120]	*	**2-**; Prospective case-control	135	**≥ 83**	x*	22/ 135**	16.3		11/ 135**	8.0	nd		nd		nd					Pesticide aviators. *Not clear if 11/ 135 with LFT+ additionally asthma symptoms; **symptoms and LFT sign. different vs. controls (community selected). At follow-up, dose-response relationship ns

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Senthilselvan, McDuffie et al., 1992 [145]		**2-**; Cross-sectional	1939		83 (4.3)*	x**			x***		nd		nd		nd					Farmers. *Asthmatic group, asthma physician diagnosed; **sign. higher prevalence of wheezing and shortness of breath in asthmatics; ***sign. reduction of FEV1/FVC ratio in asthmatics; sign. association of carbamate insecticide use with asthma, POR 1.8; co-exposure to grain dust as possible cause for asthma
"	Lings, 1982 [451]		**3+**; Survey	274		*	x**			8/ 181***	4.4	nd		nd		nd					Fruit growers. *Neither asthma nor **asthmatic symptoms were a spec. target (only resp. symptoms: cough, expectoration, dyspnea); ***difference of resp. symptoms in group that used masks compared to group of non-users ns
"	Barthel, 1983 [257]		**3**; Case reports	2		2	2/2		(+)	2/2		1/2		nd		nd					Midwife and insecticide worker.
Phenylglycine acid chloride, 39478-47-2	Kammermeyer and Mathews, 1973 [348]	**(*)**	**3+**; Case series with controls	24	**15**	15	15/ 24			x*		nd		nd		2/2		2			Plant workers. 7/24 allergic, 8/24 irritant resp. symptoms; 9/24 SPT+; *individual data not given
Phosgene, 75-44-5	Tarlo and Broder, 1989 [9]	**-**	**3**; Case report	1		1	1/1			x*		1/1		nd		nd					Profession not mentioned. co-exposure to hydrochloric acid; duration of symptoms 2 years; *individual data not given
"	Wyatt and Allister 1995 [349]		**4**; Case report	1	**2**	1	1/1		+	nd		nd		nd		nd					Refrigeration worker. Asthma symptoms immediate while using hot welding torch to cut refrigeration pipe containing freon (gas); exertional dyspnoe for further 2 weeks
Piperazine dihydrochloride, 142-64-3	Hagmar, Bellander et al., 1982 [265]	*****	**3+**; Survey	130	**185**	13 (10.0)	13/130*	10.0		nd		6/15		nd		1/1			1		Factory workers with co-exposure to other amines. *According to WRS, 12 late and 1 dual asthma type; additionally 16 former employees had suspected OA, exposure-related; also bronchitis increased (24/117)
"	Hagmar, Bellander et al., 1984 [121]		**3+**; Cross-sectional	516		170 (32.9)	170/ 516	32.9		nd		nd		nd		nd					Chemical workers. 33% WR attacks of dyspnea, 27% WR wheezing, 12% chronic bronchitis; sign. dose-response relationship
"	Pepys, Pickering et al., 1972 [168]		**3**; Case reports	2		2	2/2			0/2		nd		nd		2/2			2		Chemical industry workers
Platinum salts, 7440-06-4	Merget, Kulzer et al., 2000 [350]	******	**2+**; Prospective cohort study	227	**≥ 131**	6*(2.6)	9/ 227			x		11/ 187		nd		nd					Catalyst production employees. Exposure related resp. symptoms, lung function decline and NSBHR+; 9/14 with new chest symptoms within 5 yrs, smoking-related; 14/227 SPT+; *6/227 SPT- with new chest symptoms
"	Calverley, Rees et al., 1995 [122]		**2+**; Prospective cohort study	78		7 (9.0)	32/ 78	41.0		7/10*	70.0	nd		nd		nd					New recruits of refinery workers. 32/78 new-onset symptoms (bronchospasm, rhinitis etc.) within 24 months; *10/32 PSS with SPT-; 22/30 SPT+; dose-related increase of risk of asthma for smokers
"	Hnizdo, Esterhiuzen et al., 2001 [351]		**3+**; Occupational diseases statistics (SORDSA)	29		29	x*			x*		x*		nd		x*					29/324 OA cases due to platinum in 1997-1999. Individual data not given
"	Merget, Reineke et al., 1994 [352]		**3+**; Case series with follow-up	24		24	23/ 24			2/ 24		23/ 24		nd		24/ 24*					Refinery workers. *Individual reaction type not given; at follow-up change in NSBHR and SIC ns after removal from exposure for 19 months (1-77)
"	Baker, Gann et al., 1990 [353]		**3+**; Cross-sectional	107		x**	28/ 107			6/ 107		3/ 107*		nd		nd					Current workers in metal industry. 15/107 SPT+; *NSBHR+ done with cold air ;**not clear if people with LFT+ and/or BHR+ additionally combined with asthma symptoms
"	Venables, Dally et al., 1989 [354]		**3+**; Survey with follow-up	91		49 (53.8)	49*/91			nd		nd		nd		nd					Refinery workers; 22/49* SPT+, related to smoking

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Pickering 1972 [355]		3+; Case series	12		6	12/12			nd		nd		nd		6/12*		5		1	Platinum refinery workers; *SIC done with ammonium hexachlorplatinate, 6/7SPT+; SIC additionally done with a.tetra-cl-pl: 4/6 imm., 2/6 late; Sodium hexa-cl-pl:3/7 imm.
"	Pepys, Pickering et al., 1972 [168]		3+; Case series	16		10	16/ 16			5/ 16		nd		nd		10/16		7	2	1	Platinum refinery workers; 10/16 SPT+; 7/11 nasal challenges+
Polyamines, **aliphatic**	Ng, Lee et al., 1995 [452]	[*]	3+; Cross-sectional	12	1	1	4/12			0/12		nd		4/12*		1/2*				1	Polyamide resin factory workers. *SFT for 1-2 weeks with sign. greater diurnal variation (in DV-PEFR%) compared to unexposed workers
Polyester	Zuskin, Mustajbegovic et al., 1998 [454]	*	3+; Comparative survey	400	5	4 (1.0)	4/ 400			x*,**		nd		x**		nd					Synthetic textile workers. Dyspnea sign. increased in male workers (32/92); *sign. FEF75 decline; **individual data not given
"	Cartier, Vandenplas et al., 1994 [453]		3; Case report	1		1	1/1			1/1		1/1				1/1*		1			Painter. Exposure to powder paint, containing polyethylene terephthalate and polybutylene terephthalate; *SIC done with granulated polyester (bisphenol based epoxide); after SIC, additionally occurance of alveolitis-type reaction with leukocytosis, fever and declines of DL,co plus FVC
Polyethylene, 9002-88-4		-			3																
", (heated to 140°C)	Stenton, Kelly et al., 1989 [356]		3; Case report	1		1	1/1			1/1		1/1		1/1		1/1*			1		Electric cable repairer; *SIC with heated repair tape
", (heated to 160°C)	Gannon, Burge et al., 1992 [357]		3; Case report	1		1	1/1			1/1		1/1		1/1		1/1*				1	Paper packer; *SIC with heated polyethylene (76°C)
", (heated to 200°C)	Skerfving, Akesson et al., 1980 [358]		3; Case report	1		1	1/1			1/1		1/1		1/1		nd					Food industry worker. Lowest values of LFT after 5 day working week, normal values of LFT after 5 days holiday
Polymethyl-methacrylate [plexiglas powder], 9011-14-7	Kennes, Garcia-Herreros et al., 1981 [359]	-	3; Case report	1	1	1	1/1			1/1*		nd		nd		1/1**		1			Plexiglass factory worker. *BD+, **SIC done with plexiglas dust, additionally hemoptysis, re-SIC+ (dual) 2 days later
Polypropylene (heated to 250 °C), 9003-07-0	Atis, Tutluoglu et al., 2005 [360]	[*]	2-;Cross-sectional	50	≥ 1	x*	13/50**	26.0		x***		nd		nd		nd					Workers of polypropylene flock processing plant. *Asthma was not a spec. target; **asthma symptoms not spec.; ***individual data only partly given; sign. pulmonary function decline (FEV1,FVC,FEF25-75) in exposed group vs. controls; sign. time-exposure relationship in years for lung function decline. Dust concentration < 0.2 - 4.4mg/m³
"	Malo, Cartier et al., 1994 [361]		3; Case report	1		1	1/1			1/1		1/1		nd		1/1			1		Bag factory worker
Polyvinyl chloride (fume), 9002-86-2	Tuomainen, Stark, Seuri et al., 2006 [362]	**	3+; Survey	10	≥ 8		0/10			0/10		0/10		nd		0/10					PVC workers. SIC done with 2-ethylhexanol, sign. increase of resp symptoms next morning after SIC (n=5) compared to morning after control exposure (n=0)
"	Lee, Ng et al. 1991 [363]		3+; Survey	48		x*	8/48**	16.7		x***		nd		x****		nd					Workers of PVC industry,mixers(n=24) with high PVC exposure (mean conc. 1.6 mg/m3) and non mixers(n=24) with low exposure (mean conc. 0.4 mg/m3). *Asthma was not a spec. target; **sign. wheezing in mixers (n=7/8); ***individual data not given; ****sign. higher diurnal variation (6.5%) of mixer group.
"	Wegman, Eisen et al., 1987 [364]		3+; Cross-sectional	230		x*	x*			24/ 230*		nd		nd		nd					Food store workers. *5% higher prevalence of obstr. vs. unexposed control group; resp symptoms not investigated. At follow-up, lung function decline sign. associated with exposure to PVC-fumes of "hot-wire" cutting of meat wrap

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Baser, Tockman et al., 1985 [365]		**3+**; Cross-sectional	163			57/ 163*	34.9		x**		nd		x**		nd					Workers of PVC industry. * Trend of increasing prevalence over a 5-day week: Monday 16.2% and Friday 34.9%; sign. increase of chronic wheeze in non-smoking workers (3.54-fold higher than community population prevalence); **pre and post shift spirometry with reduction of FEV1/FVC across-shift, ns
"	Andrasch, Bardana et al., 1976 [27]		**3+**; Survey with case series	96		3	33/96*			14/ 14		nd		nd		3/ 11			3		Meatwrappers. *33/96 with brochospasm at work
"	Muñoz, Cruz et al., 2003 [366]		**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1			1		Fish-processing factory worker
", (resin dust)	Lee, Yap et al., 1989 [367]		**3**; Case report	1		1	1/1			nd		1/1		1/1*		1/1			1		Bottle caps factory worker. SIC with PVC dust; *SFT for 3 weeks
", (fume and dust)	Sokol, Aelony et al., 1973 [368]		**3**; Case reports	3		3	3/3			2/3		nd		nd		3/3*		2	1		Meatwrappers; *SIC at workplace; BD+ 2/2
Potassium dichromate, 7778-50-9 (see also chromium;cement)	Bright, Burge et al., 1997 [369]	**(*)**	**3+**; Case series	7	**7**	7	7/7			4/7		nd		4/4		7/7		2	1	4	Electroplating industry workers. 2/7 SPT+; in 2 subjecs co-sensitization to nickel chloride proven
Potassium aluminum tetrafluoride, 14484-69-6	Hjortsberg, Nise et al., 1986 [370]	**(*)**	**3+**; Case series	7	**5***	5	5/7			nd		5/7*		nd		2/2*					Soldering workers. More spec. data not given
Potroom aluminum smelting	Musk, de Klerk et al., 2000 [458]	***[*]**	**2-; cross-sectional**	2388	**≥ 470**	*	x**			x**		nd		nd		nd					Alumina refinery workers. **sign. higher prevalence of WRS (wheeze) in digestion, precipitation and calcification workers, PR 2.2 -2.9,sign. WRS sign. associated with decline of FEV1,FVC and FEV1/FVC ratio.
″	Kongerud, Grønnesby et al., 1990 [26]		**2-**; Longitudinal study	641		122 (19.1)	122/641	19.1		x*		nd		nd		nd					Employees with > 10 yrs of exposure. *FEV1 sign. negatively related to duration of exposure
″	Saric, Godnic-Cvar et al. 1986 [460]		**3+**; Survey	227		7 (3.1)	7/227*	3.1		20/ 227	8.8	5/7		nd		nd					Workers of aluminum smelter; *7/227 wheezing and dyspnea; 54/227 chronic bronchitis;
"	Chan-Yeung, Wong et al., 1983 [456]		**3+**; Comparative survey	797		126 (15.1)	126/ 797*	15.1		x***		nd		x**		nd					Workers of aluminum smelter. *Wheezing (15.1% vs. 10.5% of controls); **SFT not sign. vs. controls; resp. symptoms sign. higher and ***FEV1 decreased in workers with >50% working time in potroom. Evidence for healthy worker effect
"	Sorgdrager, de Looff et al., 1998 [461]; Sorgdrager, de Looff et al., 2001 [462]		**3+**; Case series with follow up	179		179	x**			x*,**		x**		nd		nd					179 cases in 1970-1990 (during 2845 person years); incidence density 6.1/1000 workers; 122/179 workers at follow up 5 years later ; *sign. FEV1 decline after more than 1 year of exposure; **individual data not given
″	O'Donnell, Welford et al., 1989 [459]		**3+**; Case series	57		34	57/ 57			7/ 57		34/ 57		x**		nd					Workers of aluminium smelter ; *7/7 BD+; **individual data not given.
″	Burge, Scott et al., 2000 [455]		**3**; Case report	1		1	1/1			1/1		1/1		0/1*		1/1				1	Caster of molten aluminium. SIC with aluminum chloride; *SFT with positive occupational effect (OASYS-2 score 2.67)
″	Desjardins, Bergeron et al., 1994 [457]		**3**; Case report	1		1	1/1			0/1		1/1		1/1*		nd					Worker of aluminum plant. SFT for 3 weeks
″	Bernstein and Merget, 2006 [14]		**4**; Review				x*			x*						x*					First asthma symptoms between 1 week and 10 years after first exposure. *Individual data not given; about 40% of former workers continue to have asthma; association to RADS possible. The causative agent(s) are unknown

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Poultry confinement	Rylander and Carvalheiro 2006 [506]	*[*]	**2-**; Cross-sectional	42	**54**	x*	x*,**			x**,***		x**,****		nd		nd					Poultry workers.*Asthma and asthma symptoms were not a spec. target. **Individual data not given; ***sign. FEV1-decline in exposed group; ****sign. FEV1 decline in exposed group after methacholine-challenge; endotoxin range between 10 - 1003ng/m³ in poultry house
"	Hagmar, Schütz et al., 1990 [507]		**3+**; Cross-sectional	23		2 (8.6)	2/ 23	8.6		0/23		nd		x*		nd					Shacklers of poultry slaughter houses. 2/23 chest symptoms; *sign. VC and FEV1 declines across-shift
"	Danuser, Wyss et al., 1988 [508]		**3+**; Survey	26		10 (38.0)	14/ 26	53.8		10/26	38.0	nd		nd		nd					Swiss poultry farm workers. FEV1 decline sign. related to duration of occupation
"	Danuser, Weber et al., 2001 [146]		**3+**; Case series (representative sample)	37		37	37/ 37			nd		nd		nd		nd					Swiss poultry farm workers. Asthma OR 2.87, ns
", (slaughtery house)	King, Page et al.,2006 [509]	*	**2-**; cross-sectional	68	**5**	0	18/68*	26.0		nd		nd		0/34		nd					Poultry processing workers of evisceration department. *Asthma symptoms ns different vs. controls. At follow-up (n=34) upper resp. symptoms sign. associated to trichloramine/soluble chlorine mean TWA concentration
","	Borghetti, Magarolas et al., 2002 [510]		**2-**; Cross-sectional	15		1 (7.1)	5/14	35.7		2/5	40.0	nd		nd		1/5*	20.0			1	Spanish poultry farmers who participated in the European Farmers' Project. *Subject with SIC+ also allergic to storage mite
","	Perfetti, Cartier et al., 1997 [511]		**3**; Case reports	4		4	4/4			0/4		nd		4/4		nd					Slaughterhouse workers. 4/4 SPT+ to chicken feathers
Powder paints	Blomqvist, Düzakin-Nystedt et al., 2005 [463]	(*)	**2-**; Cross-sectional	118	**23**	23 (21.9)	23/105*	30.5		x**		nd		nd		nd					Employees of powder paint shops. *WR asthmatic symptoms (according to physician) sign. exposure-related;IgE-; co-exposure to various organic acid anhydrides and to triglycidyl isocyanurate; **LFT declines ns; 32/119 asthmatic symptoms (according to questionnaire)
Pyrazolone (s.reactive dye)	Nakano, Tsuchiya et al, 2000 [464]	-	**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1*		1			Chemical manufacturing worker, making silver halide photographic paper . SIC done with pyrazolone-derivative.
Reactive dyes	Nilsson, Nordlinder et al., 1993 [466]	*	**3**; Survey	162		4* (2.5)	6/162	3.7		2/15	13.3	3/6	50.0	0/2		nd					Workers of textile plants in dye houses. *4 workers with asthma symptoms and LFT+ or NSBHR+
"	Park, Lee et al., 1991 [468]		**3**; Survey	309		13 (4.2)	78/ 309			nd		38/ 78		nd		13/78		5	1	7	Korean workers in dye-industry. 55 SPT+(5 with SIC+ had SPT-); 53/309 spec.IgE+ (23/53 also SIC+ were asymptomatic)
	Romano, Sulotto et al., 1992 [469]		**3**; Case report	1		1	1/1			0/1		0/1		nd		1/1*		1			Worker of textile manufacturing; *SIC with lanasal yellow 4G and anaphylactic reaction; SPT+
"	Park, Lee, et al. 1990 [467]		**3**; Case reports	3		3	3/3			0/3		1/3				3/3*		3			Workers of dye industries. Exposure to "Black GR"with 3/3 SPT+ and spec.IgE+. SIC done with "Black GR"
"	Alanko, Keskinen et al., 1978 [465]		**3**; Case reports	4		4	4/4			nd		3/4		nd		4/4*		4			Workers of dye industry. *SIC with levafix brilliant yellow E-36, drimaren brilliant yellow K-GL, cibachrome brilliant scarlet 3 R, drimaren brilliant blue K-BL; 3/4 spec.IgE+; 4/4 SPT+

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Refractory ceramic fibers [RCF]	Lemasters,Lockey et al., 1998 [471]	*	**2-**; Cross-sectional and longitudinal study	742	**≥ 1**	x*	x**			x**		nd		nd		nd					Refractory ceramic fibers industry workers. *Asthma was not a spec. target. **Individual data not given. sign. resp symptoms: dyspnea 1° in males (15.7% vs. 2.5% of controls), dyspnea 2° in females (10.5% vs. 0.0% of controls). sign. FEV1 and FVC declines in exposed male smokers per 10 years of work
", **phosphoric acid binder mixture**	Forrester, 1997 [470]		**3**; Case report	1		1	1/1		+	1/1		nd		nd		nd					Millwright in steel mill exposed to spill (dust). Asthma symptoms persistent for > 4 years
Rosin core solder, (thermal decomposition) **[colophony],** 8050-09-7		*			**≥ 178**																
"	Burge, Edge et al., 1981 [371]		**2-**; cross-sectional	45		5 (11.1)	5/45	11.1		x		nd		nd		nd					Solder manufacturers. Prevalence of asthma dose-related (4% in lowest exposure group, 21% in highest and intermediate exposure group)
"	Burge, Harries et al., 1980 [372]		**3+**; Case series	51		34	51/51*			nd		16/ 31		nd		34/51**		34			Electric industry workers. *34/51 with OA and 17/51 with asthmatic symptoms before survey, **only sensitized with SIC+; SIC also with abietic acid (5/6 immediate)
"	Ross, Keynes et al., 1997 [86]		**3+**; Occupational disease statistics (SWORD)	94		94	x*			x*		x*		x*		x*					*94/1765 physician-diagnosed asthma cases in 1996; *Individual data not given
"	Gannon and Burge, 1993 [58]		**3+**; Occupational diseases statistics (SHIELD)	41		41	41/ 41			nd		nd		x		x					41/500 OA cases in 1989-1991
"	Maestrelli, Alessandri et al. 1985 [373]		**3**; Case reports	4		4	4/4			4/4		4/4				3/4		2		1	Female electronic factory workers. Persisting resp symptoms after avoidance
"	Malo, 2006 [14]		**4;** Review	237			x			x						x					
Smoke (fires, pyrolysis products)	Almeida, Duarte et al., 2007 [472]	*	**2-**; Cross-sectional	203	**62**	24*	x**			24/203	11.8	nd		nd		nd					Firefighters. *11/24 non-smoking; **individual data not given
"	Reinisch, Harrison et al., 2001 [20]		**3+**; Occupational diseases statistics (SENSOR), survey	34		34	34/34			x*		nd		nd		nd					23/430 new-onset asthma in 1993-1996; *individual data not given
"	Moisan, 1991 [473]		**3**; Case reports	3		3	3/3		+	1/3		1/1		nd		nd					1 fire fighter,2 accidental exposures. Persistent asthma symptoms
"	Brooks, Weiss et al., 1985 [5]		**3**; Case reports	1		1	1/1		+	nd		1/1		nd		nd					Accidental smoke exposure in burning book store. RADS for 13 months
", (oil fire and dust storm)	Kelsall, Sim et al., 2004 [474]	*	**2-**; Cross-sectional	1424		141* (10.2)	171	12.4		68/ 1341**	6.4	nd		nd		nd					Australian Gulf War veterans.*Asthma by ECRHS definition; **lung function decline ns compared to controls
", (biomass, indoor)	Ekici, Ekici et al.,2005 [475]	(*)	**3+**; Cross-sectional	397	**113**	113 (28.5)	113/397			x		nd		nd		nd					Stove smoke-exposed non-smoking women. COPD prevalence 28.5% vs. 13.6% of controls
Sodium azide (powder dust), 26628-22-8	Weiss 1996 [374]	-	**3**; Case reports	2	**2**	2	2/2		+	2/2		2/2		nd		nd					Material handlers exposed to massive spill. Asthmatic symptoms > 2 years
Sodium iso-nonanoyl oxybenzene sulphonate [SINOS], 123354-92-7	Stenton, Dennis et al., 1990 [375]	(*)	**3**; Case reports	3	**5**	3	3/3			0/3		2/3		nd		3/3			3		Development technicians
"	Hendrick, Connolly et al., 1988 [376]		**3**; Case report	1		1	1/1			nd		1/1		0/1		1/1			1		Laboratory technician
"	Ferguson, Thomas et al., 1990 [377]		**3**; Case report	1		1	1/1			nd		nd		nd		1/1			1		Research worker with high exposure over 18 months

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Sodium metabisulfite [metabisulfite sodium], 7681-57-4	Merget and Korn, 2005 [378]	-	**3**; Case report	1	**4**	1	1/1			0/1		1/1		1/1		1/1		1			Radiographer
"	Madsen, Sherson et al., 2004 [379]		**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1		1			Fisherman
"	Malo, Cartier et al., 1995 [380]		**3**; Case report	1		1	1/1			0/1		0/1		nd		1/1		1			Agricultural producer
"	Valero, Bescos et al. 1993 [93]		**3**; Case report	1		1	1/1			1/1		nd		1/1		1/1		1			Factory worker. Work-exacerbated asthma
Soldering flux (fumes)	Lee, Koh et al. 1994 [477]	*	**2-**; Cross-sectional	150	**19**	0*	5/144	3,5		x**		nd		9/134**		nd					Solderers of electronic factory manufacturing computers.*OA cases were not found; **FEV1/FVC sign. lower in workers with exposure duration > 5 years; all other pulmonary function tests ns
"	Burge, Perks et al. 1979 [476]		**2-**; Cross-sectional survey	106		16	58			x*		nd		16/48**	33,0	9/9***					Workers of electronic factory. OA cases defined by symptoms(30), taking asthma medication for at least 12 months(13) and asthma symptoms over the week (all); *FEV1 sign. reduced before exposure on Monday mornings compared to controls; **SFT with FEV1 decline more than 10% compared to controls (5%); ***individual data not given.
"	Weir, Robertson et al.1989 [175] **s.amm.chloride, s. zinc chloride**		**3**; Case reports	2		2	2/2			2/2		2/2		2/2		2/2		1	1		1 tin maker and 1 car radiator repair man. Use of soft corrosive soldering fluxes; co-exposure to zinc chloride, see also zinc chloride;1/1 SIC+ (ammonium chloride): immediate
	Stevens, 1976 [478]		**3**; Case report	1		1	1/1			0/1		nd		nd		1/1		1			Electronic assembler developing resp. symptoms within days after exposure
Solvents (not specified)	Toren, Balder et al., 1999 [21]	*	**2-**; Case control study	294	**≥ 46**	38	x*			x*		x*		nd		nd					38/294 OA cases in 1996. OR 2.1, sign.; *individual data not given
", "	Cakmak, Ekici et al., 2004 [479]		**3+**; Cross-sectional	411		*	202/ 411*	49,1		x*		nd		nd		nd					Gun factory workers.*Group with definite asthma not mentioned, asthma-related symptoms not specified.
", "	Henneberger, Derk et al., 2003 [432]		**3+**; Case series	8		8	8/8		+	x		x		nd		nd					8/424 OA cases in 1993-1995. 8/131 RADS cases
", (glue)	Chatkin, Tarlo et al., 1999 [157]	(*)	**3+**; Occupational diseases statistics (WCB)	5	**5**	5	5/5		(+)**	nd		x*		nd		nd					5/469 asthma claims between mid 1984 and mid 1988 identified by retrospective review: 4 cases with work-exacerbated asthma; *5/5 BD+ and /or NSBHR+;**1/5 RADS
Spray paint	Brooks, Weiss et al., 1985 [5]	-	**3**; Case reports	3	**3**	3	3/3		+	3/3		3/3		nd		nd					Painters. 2 RADS for 4 months, 1 RADS for 56 months
Styrene monomer, 100-42-5	Lorimer, Lilis et al. 1976 [123]	*	**3+**; Survey	488	**≥ 3**	x*	56/488*	11.0		163/ 451*	36.1	nd		nd		nd					Production workers. Sign. correlation of dose-response relationship and recurrent episodes or severity of WRS. *No specified information if workers with LFT+ also had asthma symptoms.
"	Hayes, Lambourn et al, 1991 [381]		**3**; Case report	1		1	1/1			0/1		1/1		1/1		1/1				1	RAF air frame technician
"	Moscato, Biscaldi et al., 1987 [382]		**3**; Case reports	2		2	2/2			0/2		2/2		nd		2/2		2			Plastic factory workers
Sulfur dioxide, 7446-09-5	Andersson, Knutsson et al., 2006 [383]	*[*]	**2-**; Cross-sectional	674	**86**	35 (5.2)	35/ 674	5.2		nd		nd		nd		nd					Sulfite mill workers. Asthma incidence rate sign. increased; attributable fraction of incident asthma due to SO2 exposure 63%, and 75% due to SO2 gassing
"	Koksal, Hasanoglu et al., 2003 [384]		**3+**; Survey	69		10 (14.5)	55/ 69*	79.7		nd		nd		10/ 69**		nd					Workers of apricot farms. *55/69 dyspnea; **SFT+ with sign. declines also as a group in FVC, FEV1, FEV1/VC

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Andersson, Nilsson et al., 1998 [147]		**3+**; Case reference study	186		33**	x*			x*		x*		x*		x*					Sulfite mill workers. Mortality study of deceased workers aged 40-75 years. * physician diagnosed with individual data not given; **sign. increased mortality from asthma (n=13) and COPD (n=20), OR1.6; other sign. increased causes of death were brain tumors (n=5), OR 3.3
"	Härkönen, Nordman et al. 1983 [385]; Piirilä, Nordman et al., 1996 [567]		**3+**; Case series with follow-up	9		7	9/9		(+)*	6/9		4/7		nd		nd					Men accidently exposed to SO2 in pyrite mine in 1977. *7/9 with RADS; 6/7 re-examined after 4 and 13 years; 1 subject died hours post exposure due to pulmonary edema; 4 subjects with persisting NSBHR; 2/6 with persistent obstr.
"	Tarlo and Broder, 1989 [9]		**3**; Case report	1		1	1/1			x*		1/1		x*		nd					Profession not mentioned; persistent asthma symptoms; co-exposure to sulphuric acid and chlorine; *individual data not given..
Sulfathiazole 72-14-0	Rosberg, 1946 [386]	-	**3**; Case reports	2		2	2/2			nd		nd		nd		2/2*					Nurses; *individual reaction type not given.
Swine confinement		**			**≥ 371**																
"	Vogelzang, v.d.Gulden et al., 2000 [512]		**2-**; Cohort study with 3-years follow-up.	171		12*	82/171			x**		12/82	15	x**		nd					Pig farmers. *Asthma or COPD cases; **individual data not given; long term average exposure to dust: 2.63mg/m³, to endotoxin 105ng/m3, to ammonia 150mg/m3
"	Reynolds, Donham et al. 1996 [513]		**2-**; Longitudinal study with 5years follow-up	151			x*			x*		nd		x*		nd					Swine production workers. *Individual data not given; **sign. across-shift change in FEV1 for 46 workers with exposure of 10-13 years; levels of 2.5 mg/m³ for total dust and 7.5 ppm for ammonia are associated with sign. across-shift decrease in FEV1.
"	Schwartz, Donham et al., 1995 [514]		**2-**; Population based longitudinal cohort study	168			x*,**			x*,**		nd		x*,**		nd					Pig farmers. *sign. longitudinal declines in FEV1, FVC, and FEF25-75 related to across-shift declines, additionally sign. relationship of FEV1 and FEF25-75 decline to endotoxin exposure; **individual data not given
"	Preller, Heederik et al., 1995 [148]		**2-**; Cross-sectional	194		x*	94/194	48.4		x*		nd		nd		nd					Pig farmers.*Sign. decline of baseline lung function (FVC,FEV1, PEF, FEF25-75) vs. controls. Sign. and positive association between resp. symptoms and duration (OR 4.2 for >10min) of desinfection procedure (medium and high pressure: OR 7.1); average exposure to dust: 2.7 mg/m³; endotoxins: 112 ng/m³; ammonia: 1.7mg/m³
"	Radon, Büsching et al., 2002 [133]		**2-**; Cross-sectional	2278		554 (24.3)*	x			x**		nd		nd		nd					Pig farmers in the European Farmers' Project. *24.3% with WR resp. symptoms, sign. exposure-related; **individual data not given
"	Vogelzang, van der Gulden, 1998 [512]		**3+**; Longitudinal study with follow-up	171			82/ 171			x*		nd		nd		nd					Pig farmers. *sign. FEV1 decline 73 mL/yr, sign. related to endotoxin exposure
"	Dosman, Lawson et al., 2004 [18]		**3**; Case reports	4		4	4/4			0/4		3/4		nd		nd					Intensive swine facility workers. Onset of first resp symptoms between 4.5 and 48 months; 1/1 BD+
"	Cormier, Coll et al., 1996 [17]		**3**; Case report	1		1	1/1		+	1/1		1/1		nd		nd					Profession not mentioned. Massive exposure
Tall oil	Tarlo, 1992 [480]	-	**3**; Case report	1	**1**	1	1/1			0/1		1/1		1/1**		1/1*		1			Rubber tyre industry worker. SIC with Pamtac 1500 (heated); **SFT for 2 weeks
Tear gas	Hill, Silverberg et al., 2000 [482]	-	**3**; Case report	1	**4**	1	1/1		+	1/1		nd		nd		nd					Prisoner. Massive exposure with generalized symptoms (spongiotic lichenoid dermatitis, fever); SPT+; general and resp symptoms over > 6 months

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Bayeux-Dunglas, Deparis et al., 1999 [481]		**3**; Case report	1		1	1/1			nd		1/1		nd		nd					Teacher with repeated exposure. "Low level RADS"; duration of symptoms over 6 months
"	Roth and Franzblau, 1996 [484]		**3**; Case report	1		1	1/1		+	1/1		nd		nd		nd					Prison guard. Agent 'Deep Freeze' containing 1% orthochlorobenzalmalonitrile. Persistent symptoms >3 years
"	Hu and Christiani, 1992 [483]		**3**; Case report	1		1	1/1		+	1/1		1/1		nd		nd					Massive spill in nightclub; resp symptoms > 2 years
Terpene [3-carene], 13466-78-9	Eriksson, Levin et al., 1997 [387]	-	**3**; cross-sectional	38	**1**	0	0*			x**		nd		x***		nd					Joinery workers. *Only occurence of upper resp symptoms. **Sign. lower FEV1 and FEV1/VC ratio in joinery workers, compared to controls.***No sign. change of LFT across working shift. Total terpene exposure between 19 - 123mg/m³ during a work shift.
"	Seaton, Cherrie et al., 1988 [388]		**3**; Case report	1		1	1/1			nd		nd		0/1		1/1		1			Laboratory technician for about 10 years. Asthma provoked by rubber glove vapors
Tetrachloroisophthalonitrile (fungicide)	Honda, Kohrogi et al., 1992 [389]	-	**3**; Case report	1	**1**	1	1/1			0/1		1/1		1/1		1/1				1	Farmer
Tetrahydrothiopene, 110-01-0	Baur and Bittner, 2009 [568]	-	**3**; Case reports	2	**2**	2	2/2			2/2*		nd		nd		nd					Workers engaged in odorizing natural gas; *2/2 BD+
Tetramethrin [1-(5-tretrazoly)- 4-guanyl-tetrazene hydrate], 7696-12-0	Vandenplas, Delwiche et al., 2000 [391]	-	**3**; Case report	1	**2**	1	1/1			0/1		1/1		nd		1/1				1	Worker of insect pest extermination firm
"	Burge and Richardson, 1994 [328]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1			1		Hospital pharmacist
Tributyl tin oxide (carpet fungicide)	Shelton, Urch et al., 1992 [392]	-	**3**; Case report	1	**1**	1	1/1			0/1		1/1		nd		1/1		1			Venipuncture technician
Triethanolamine, 102-71-6	Savonius, Keskinen et al., 1994 [167]	-	**3**; Case report	2	**2**	2	2/2			0/2		1/2		2/2		2/2		1		1	Metal workers
Tungsten carbide, 11130-73-7	Bruckner, 1967 [393]	-	**3**; Case report	1	**1**	1	1/1			nd		nd		nd		nd					Tungsten carbide worker
Uranium hexafluoride, 7783-81-5	Brooks, Weiss et al., 1985 [5]	-	**3**; Case report	1	**2**	1	1/1		+	nd		1/1		nd		nd					Chemical worker with accidental exposure
"	Frigas, Filley et al., 1981 [395]		**3**; Case report	1		1	1/1			0/1		nd		nd		1/1		1			UF foam exposure
Urea (fume), 57-13-6	Cockcroft, Hoeppner et al., 1982 [94]	-	**3**; Case reports	2	**2**	2	2/2			0/2		2/2		nd		2/2*		1		1	Carpenters. Exposure to dust from western red cedar chips with urea formaldehyde; *SIC with cedar urea formaldehyde sawdust with 1/2 borderline immediate (FEV1 decline – 14%)
Urea formaldehyde foam, 64869-57-4 **Phenol-formaldehyde resin,** 9003-35-4	Bertrand, Simon et al. 2007 [396]	-	**3**; cross-sectional	89	**0**	0	3/80	3,7		0/89		nd		nd		nd					Coal miners exposed to ureaformol and also formophenolic-based resins; *sign. increase of resp. symptoms, e.g. chronic bronchitis and wheezing, compared to workers exposed to MDI-based resins
Vanadium 7440-62-2		*			**90**																
", **divanadium pentoxide** 1314-62-1	Irsigler, Visser et al., 1999 [397]		**2-**; Case control study	375		12	40/ 375			3/ 40		12/ 40		nd		nd					40 open cast miners with persistent resp. symptoms
", "	Pistelli, Pupp et al., 1991 [398]		**3+**; Survey	11		7	x*			0/11		7/11		nd		nd					Workers exposed during removal of ashes and clinker in oil-fired power station. NSBHR sign. increased; *individual data not given
", "	Esterhuizen, Hnizdo et al., 2001 [87]		**3+**; Occupational diseases statistics (SORDSA)	8		8	x*			x*		x*		nd		x*					8/324 OA cases due to vanadium in 1997-1999; *individual data not given.
", "	Kielkowski and Rees, 1997 [399]		**3+**; Occupational diseases statistics	333		59	59/ 333			52/ 326		nd		nd		nd					Employees of vanadium plant. WRA sign. increased (17.7% vs. 5.1% of controls); 22/333 chronic bronchitis
", "	Musk and Tees, 1982 [400]		**3**; Case reports	4		4	4/4			3/4		2/4		nd		nd					Refinery workers

Agents (specification) [synonyms], CAS No.	Publication [Reference]	Strength of evidence per agent (three star system of RCGP)	Evidence grading, applied to individual study (modified SIGN system); Study type	Occupationally exposed subjects studied, n	Total no. of irritant-induced occupational asthma/ occupational COPD cases per agent	Irritant-induced occupational asthma/ occupational COPD cases, n (prevalence, %)	EVIDENCE (pathological results)														Remarks
							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
Welding fumes	El-Zein, Malo et al., 2003 [485]	**	**2+**; Epidemiological prospective cohort study	194	**≥ 160**	5	14/ 193			22/ 194		46/ 194		nd		nd					5/194 new-onset asthma cases /incidence 3%) plus 1/6 exacerbated asthma; increase in incidence of NSBHR (11.9%); sign. FEV1 decline (- 8.4%)
"	Jafari, 2004 [486]		**2-**; Case control	63		4	4/ 63			x		nd		nd		nd					Manual steel arc welders. sign. asthma symptoms (6.3% vs. 1.3%) and sign. spirom. declines in VC, FVC, FEV1, FEF 25-75% as a group
"	Toren, Balder et al., 1999 [21]		**2-**; Case control	26		26	x*			x*		x*		nd		nd					26/294 OA cases in 1996. OR 2.0, sign.; *individual data not given
"	Nakadate, Aizawa et al., 1998 [487]		**2-**; Cross-sectional	143		x*	x*			x*		nd		nd		nd					Electric arc welders. Cumulative exposure sign. associated with chronic cough (11/143) and FEV1/VC decline; *individual data not given
"	Beach, Dennis et al., 1996 [488]		**2-**; Cross-sectional	682		x*	x*			x*		x*		nd		nd					Welders. NSBHR+ sign. exposure-related; *individual data not given
"	Hannu, Piipari et al., 2006 [489]		**3+**; Case series with follow-up	34		34	34/ 34			18/ 34		9/ 15		nd		34/ 34		9	16	9	Workers of metal industry
"	Latza and Baur, 2005 [31]		**3+**; Occupational diseases statistics	28		28	x*			x*		nd		nd		x*					28/835 OA cases in 2003 (28/210 irritant asthma cases); *individual data not given
"	Piipari and Keskinen, 2005 [272]		**3+**;Occupational diseases statistics (SORDSA)	6		6	6/6*			nd		nd		6/6*		6/6*					6/324 OA cases due to welding fumes in 1997-1999; *individual data not given
"	Karjalainen, Martikainen et al., 2002 [490]		**3+**; Occupational diseases statistics	14		14	14/ 14			14/ 14		nd		nd		nd					Construction workers
"	Reinisch, Harrison et al., 2001 [20]		**3+**; Occupational diseases statistics (SENSOR), survey	9		9	9/9			x*		nd		nd		nd					9/430 new onset asthma in 1993-1996. *individual data not given
"	Contreras and Chan-Yeung, 1997 [491]		**3+**; Case series	6		3	6/6			0/6		5/6		nd		3/6		3			Welders. SIC with mild steel, stainless steel and/or galvanised steel; conc. 3.4-150 mg/m³
"	Hannu, Piipari et al., 2005 [492]		**3**; Case reports	2		2	2/2			0/2		0/2		1/1*		2/2**			2		Metal arc welders on stainless steel. **SIC with SMO steel or duplex steel with an nickel/molybdenum electrode; *SFT for 1 week
", **aluminium**	Vandenplas, Delwiche et al., 1998 [493]		**3**; Case report	1		1	1/1			0/1		1/1		nd		1/1				1	Welder performing manual metal arc welding on aluminium
"	Ross, Keynes et al.,1997 [86]		**3+**;Occupational diseases statistics (SWORD)	22		22	x*			x*		x*		x*		x*					22/1765 physician-diagnosed asthma cases in 1996. *Individual data not given
"	Vandenplas, Dargent et al., 1995 [494]		**3**; Case report	1		1	1/1			1/1		1/1		nd		1/1*				1	Welder manufacturing automatic gates. *SIC with gas metal arc welding on mild steel
"	Keskinen, Kalliomäki et al., 1980 [495]		**3+**; Case series	7		5	5/7			0/7*		2/7		nd		2/3		1	1		Metal arc stainless steel welders. (2 years later, 3 subjects re-examinated, out of them 2/3 SIC+: 1 immediate, 1 late)
"	Bernstein and Merget, 2006 [569]		**4**; Review			[incidence about 3.0 - 5.0]															Stainless steel sign. stronger irritant than "mild steel"
World Trade Center desaster 2001	Wheeler, McKelvey et al., 2007 [149]	**	**2+**; prospektive cohort study	25748	**≥ 1355**	926 (3.6)**	x*			x*		x*		x*		x*					Workers and volunteers who were involved at the WTC site from 09/11/01 to 06/30/02. *Individual data not given; **new onset asthma, physician diagnosed after 09/11/01; sign. risk faktor for arrival date(OR 1.81-1.69) within the first week and >90 days of work at WTC site (OR 1.74); sign. elevated risk for new onset asthma for professionals compared to volunteers (unadjusted OR 1.88-1.66)

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							WORK-RELATED SYMPTOMS			LFT		NSBHR		SFT		SIC				
							Asthma		RADS									Reaction type		
							n/n	%	all affected cases: + or at least one out of several cases: (+)	n/n	%	n/n	%	n/n	%	n/n	%	i(n)	l(n)	d(n)	
"	Banauch, Hall et al., 2006 [518]		**2+**; Longitudinal study	11766		48 [incidence (0.4)]	x			x		nd		nd		nd					Exposed FDNY rescue workers. Resp. symptoms sign. time of arrival-related: Severity (i.e., greater number) early- > intermediate-> late-arrival; sign. loss of FEV1 after desaster in each group; FEV1< 60% in 45 exposed before, in 93 after desaster
"	Banauch, Alleyne et al., 2003 [516]; Banauch, Dhala et al., 2005 [517]		**2+**; Prospective cohort study / review	123		20 (16.3)	20/123*		+	27/ 151		24/ 112		nd		nd					17/83 of highly, 3/40 of moderately exposed fire-fighters developed RADS (diagnosed 6 months after disaster). NSBHR exposure-related (31%, 10%); after 6 mo. persistent NSBHR in 55%; *sign. declines of spirometric parameters post WTC
"	Herbstman, Frank et al., 2005 [519]		**3+**; Survey	119		22 (18.5)	22/ 119			x*		nd		nd		nd					Clean-up and recovery workers; 22/119 new-onset wheezing with *sign. decline of FEV1; prevalence of symptoms sign. exposure-related
"	Salzman, Moosavy, 2004 [520]		**3+**; Survey	240		55 (18.5)	55/ 240		+	37/ 240		nd		nd		nd					Emergency services police officers. Dyspnea and prevalence of abnormal spirometry sign. related to exposure intensity
"	Prezant, Weiden et al., 2002 [124]		**3+**; Survey with follow-up of exposed workers			332 (3.3)	332/ 9914		+	332/ 9914		332/ 9914		nd		nd					Firefighters. 332/9914 persistent cough; sign. FEV1 and FVC declines; 315 dyspnea; dose-related cough (8% of high, 3% of moderate, 1% of low exposure), and NSBHR (23% of high, 8% of moderate exposure)
Zinc (fume), 7440-66-6	Malo and Cartier, 1987 [401]	-	**3**; Case report	2	**4**	2	2/2			2/2		2/2		nd		2/2					Solderers exposed to fume of galvanized metal. 1 subject with metal fever
"	Malo and Cartier, 1993 [402]		**3**; Case report	1		1	1/1			0/1		1/1		1/1*		1/1**		1			Metal plant worker. *SFT+ (late); **SIC done with zinc sulfate; SPT+
"	Kawane, 1988 [403]		**3**; Case report	1		1	1/1			1/1		1/1		nd		nd					Welder. Presenting additionally metal fume fever.
Zinc chloride (fume), 7646-85-7	Weir, Robertson et al., 1989 [175]	-	**3**; Case reports	2	**2**	2	2/2			2/2		nd		2/2		2/2		2			1 worker of tin making industry and 1 car/truck repairer. Use of soldering fluxes, co-exposure to ammonium chloride (see also ammonium chloride)

*, **, ***: for details see column "Remarks"; + : positive test result; - : negative test result; BD: significant bronchodilator effect; conc.: concentration; LFT: lung function test showing obstructive ventilation pattern; n: number of subjects; n/n: number of subjects with work-related symptoms or positive test results / all investigated subjects; nd: not done; ns: not significant; NSBHR: non-specific bronchial hyperresponsiveness; OA: occupational asthma; obstr.: obstructive ventialation pattern(s); P: pathology; Reaction type: i: immediate, d: dual, l: late response type; resp.: respiratory; restr. = restrictive ventilation pattern; SFT: Serial peak flow, FEV1 or PEFR showing significant change in follow-up pre-, (during) and post shift; SIC: specific inhalative challenge test, ; spec.: specific; SPT: significant positive skin prick test result; sign.: significant/ significantly; vs.: versus; WR: work-related; WRS: work-related symptoms; x: test done, no individual results listed