Guidelines for the Management of Work-related Asthma

Final Report of the ERS Task Force: "Management of work-related asthma."

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PART I

1. HISTORY OF TASK FORCE ACTIVITES

The kick off meeting of the task force in the current form took place September 19th during the ERS congress in Stockholm 2007. Members present were: Tor Aasen (TA), Xaver Baur (XB), Sherwood Burge (SB), Piero Maestrelli (PM), Torben Sigsgaard (TS), Olivier Vandenplas (OV), Dennis Wilken (DW), Guests/collaborators from ATS present: Carrie Redlich (CR), Paul Henneberger (PH). During this meeting key questions and sub questions for the guideline were appointed, each handled by a small working group of 2-4 of the before mentioned members and some additional ERS members. It was decided that for key questions 2-5 (see below) evidence-based literature evaluation search should be performed via PubMed search terms including the relevant Mesh-terms by the task force members from Hamburg. The results were compared with the literature references from other current guidelines on similar topics and delivered to the concerning working groups. The working groups scanned the retrieved literature search results and selected the relevant papers for their key questions. Team Hamburg organized full text versions of the selected papers and delivered them to the working groups who have used the results as basis to answer their key questions. Telephone and internet conferences were held to coordinate the work of the individual groups.

The 2nd task force meeting took place in Berlin during the ERS congress 2008, where the first results of the literature evaluation were presented. Further, the structure of the final guidelines was discussed. It was decided that a final draft of the literature evaluation including evidence-based statements, filled in evidence tables and a draft of recommendations should be prepared for a task force meeting in spring 2009. Due to over commitment and other responsibilities the initial team for key question 5 left the task force and other members needed additional assistance. By inviting Vivi Schlünssen (VS), Jos Rooijackers (JR), Evert Meijer (EM) and Holger Dressel (HD) as new task force members the teams for the individual key questions were modified. This led to a delay in the time table. Although further telephone and internet conferences were held in a weekly rhythm to accelerate the orientation of the new members, the finalization of the guideline until 2009 was no longer realistic.

A next task force meeting was scheduled for the time of the ATS international conference San Diego California May 18th 2009. The focus of the meeting was to bring the data together, to clarify

disagreements with regard to the content of the key questions and to avoid overlap between the individual groups. Consensus was reached that key question 4 on medical screening and key question 5 on medical surveillance have a strong conjunction and should be connected to one key question. September 13th 2009 as the date for the next and final task force meeting was set as new deadline for the final summarisation of the literature evaluation with the evidence tables, the evidence-based statements, the recommendations and the reflection of the findings in the light of the already existing guidelines and consensus papers. During this task force meeting at the ERS congress in Vienna the final results of the literature evaluation were presented and the drafts of the statements and recommendations by the individual working groups were discussed. Consensus was reached for several critical statements. It was agreed that each working group prepares a synopsis chapter comparing their findings with existing guidelines and consensus statements.

In order to accelerate the task force progress and solving still persistent problems and disagreements a short-dated conference was held at the Institute for Occupational and Maritime Medicine in Hamburg, Germany February 26th 2010 focusing on general aspects of the guidelines, e.g. form of publication and how to condense the extensive manuscript. Further, the final formulation of the evidence statements and recommendations was finished. It was agreed to perform an update of the literature search to make sure that new publications are considered. Due to the relatively autonomous work of the different working groups a substantial lack of uniformity between the different chapters was recognizable and all groups were asked to adapt the structure of their chapters and the evidence tables. It was decided that a small editing group should finalize the draft manuscript after the final meeting at the ERS congress in Barcelona 2010.

The essential topic of this meeting was the presentation and the discussion of the final drafts from each working group. In cases of disagreements consensus was found. All manuscripts were accepted by all members of the task force. Another main aspect was the publication strategy of the guidelines. According to the proceedings of the ERS we initially intended to publish the guidelines in ERJ together with an editorial and online supplements. After communicating this aspects with ERS officials especially the ERS guideline coordinator and taking into consideration the extensiveness of the existing manuscript, it was decided to publish one summary chapter in the ERJ and separate adjacent chapter for each key question in the ERR together with one chapter presenting the guidelines in a broader perspective.

In addition two papers that are based on the task force results going beyond the aims of the guideline are in preparation, i.e. exposure reduction vs. exposure avoidance by Olivier Vandenplas and one publication one diagnostics in work-related asthma.

The major activity since the last meeting was the editing of the exiting chapters in order to have a uniform style (layout, references etc.) for all publications and to fulfil the ERJ / ERR requirements. Even though every key question should become a separate publication, relevant shortenings became necessary for every manuscript. To guarantee the uniform style and in order to avoid incompatibilities, an editorial team was formed. This team was meant to be responsible for the final editing of all chapters.
Meanwhile all guideline chapters are published or in print. We have initiated a symposium at the ERS congress in Amsterdam in order to present the guidelines to a broad public and to begin a lively discussion about the management of occupational asthma between all medical and paramedical participants in this field.

The formal guideline project was reached after final publication of the submitted manuscripts and after the Amsterdam meeting. To make sure that the guideline will keep its initial high level of quality, regular updates and ongoing evaluation of the field of occupations asthma are important.

A further remaining task is to enhance the translation of the guidelines content from theory into daily practical work. Therefore, we have to promote the implementation of the guidelines recommendations into national regulations / legislations. To make sure these attempted goals can be reached, a further promotion of the guidelines at national and international congresses / conferences is essential. A joined strategy by the whole task force and a close cooperation beyond the first publication has to be established and additional publications on separate aspects in the light of local / national conditions could became necessary.

PUBLICATIONS

- Summary chapter “Overview of the Guidelines Management of Work-related Asthma” (ERJ 2012;39:529-545) http://erj.ersjournals.com/content/39/3/529.full.pdf+html, and the corresponding “Editorial” (ERJ 2012;39:518-519)

http://erj.ersjournals.com/content/39/3/518.full.pdf+html

- Chapter 1 by Maestrelli et al.: “Contribution of Host Factors and Workplace Exposure to the Outcome of Occupational Asthma” (ERR 2012, 21 :124, 88-96) http://err.ersjournals.com/content/21/124/88.full.pdf+html
- Chapter 2 by Vandenplas et al.: “What is the optimal Management for Occupational Asthma?” (ERR 2012, 21 :124, 97-104) http://err.ersjournals.com/content/21/124/97.full.pdf+html
- Chapter 3 by Wilken et al.: “What are the Benefits of Medical Screening and Surveillance?” (ERR 2012, 21 :124, 105-111) http://err.ersjournals.com/content/21/124/105.full.pdf+html
- Chapter 4 by Heederik et al.: “Primary Prevention of Occupational Asthma: Exposure Reduction, Skin Exposure and respiratory Protection” (ERR 2012, 21 :124, 112-124) http://err.ersjournals.com/content/21/124/112.full.pdf+html
- Chapter 5 by Baur et al.: The “Management of Work-related Asthma - Guidelines in a broader Perspective” (ERR 2012, 21 :124, 125-139) http://err.ersjournals.com/content/21/124/125.full.pdf+html

Part II - Appendix

1. Background

1.1. What is work-related asthma (WRA)?

W*ork-related asthma (WRA)* refers to occupational asthma and work-aggravated asthma (Fig. 1). *Occupational asthma* is a disease characterized by variable airflow limitation and/or hyperresponsiveness associated with inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace [1]. Occupational asthma involves IgE-mediated asthma after a latency period, irritant asthma with or without a latency period, including reactive airways dysfunction syndrome (RADS), that results from high-exposure(s), and asthma due to specific occupational agents with unknown pathomechanisms which frequently also show a latency period (Fig. 1) [2].

Work-aggravated asthma is characterized by worsening of pre-existing asthma (e.g. shown by a decrease of forced expiratory volume in one second (FEV_1) or dose of pharmacological agent inducing a 20% fall in FEV_1 (PD_{20}), or increases in airway resistance, asthma medications or frequency and/or severity of asthma attacks) due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace. The worker has a concurrent history of asthma that was not induced by an exposure in the workplace. Aggravation is typically due to an occupational irritant (e.g. non-sensitizing fumes) [3].

There are also workers with pre-existing asthma who after a latent interval have a worsening of their pre-existing non-occupational asthma with regular daily exposures to agents which can cause IgE-mediated allergies in others. These workers are included in the group of occupational asthma or in that of work aggravated asthma, depending on national regulations and related case definitions.

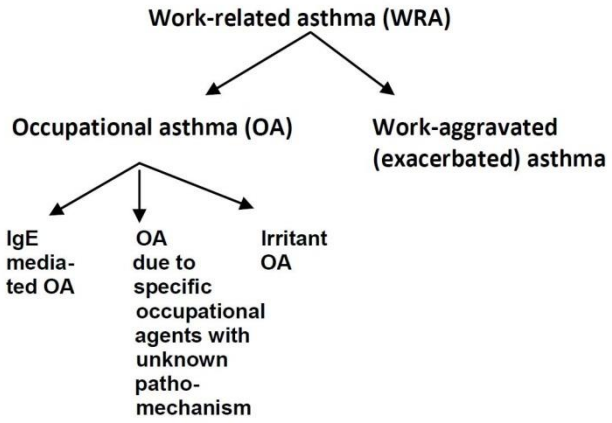

FIGURE 1. Work-related asthma with its subgroups

Some occupational exposures which are potential causes of occupational asthma, particularly high concentrations of welding fumes, isocyanates, potroom and a range of other occupational noxae (e.g. aluminium, cadmium, metals, ammonia, environmental tobacco smoke, wood dust, cotton, endotoxin) may also cause COPD, without any acute symptoms to suggest asthma [4-11].

Furthermore, symptoms in asthmatics that do not improve over weekends or during holidays may indicate a progressive course and may coincide with symptoms typical for COPD patients. This observation also applies to occupational asthma [6, 12]; so, there is evidence for a group with

changing diagnoses as well as with some overlap between occupational asthma and occupational COPD [5, 6, 13-16].

Recently, Blanc and Torén [17] reviewing the literature estimated the population attributable risk of the latter to be 15 % which indicates that the occupational causes of these disorders are mostly overlooked in routine diagnostics. Misdiagnoses result mainly due to the lack of specific diagnostic tests, the absence of attacks of shortness of breath and the frequent concomitant smoking habits as a confounder. Salvi and Barnes [18] reported similar figures in their review which was mainly based on the papers of Behrendt [19], Lamprecht et al. [20], Ulvestadt et al. 2001 [21], Bergdahl et al. 2004 [10], Hnizdo et al. 2002 [8], Weinmann et al. 2008 [22].

Several other conditions with some overlap represent risk factors for occupational asthma including eosinophilic bronchitis, asthma-like symptoms and work-related rhinitis [2].

Since the before mentioned overlapping occupational disorders have not been subjected to detailed scientific investigations these guidelines will focus on WRA .

Adverse consequences for the affected workers

Follow-up studies of workers with occupational asthma have consistently documented that the condition is associated with a high rate of prolonged work disruption or even permanent unemployment (14–69%) and loss of income (44–74%) [23-25]. The financial consequences of occupational asthma are more pronounced in workers who avoid further exposure to the causal agent. Notably, the lowest rates of unemployment (14–25%) have been reported in countries (i.e. Finland and Canada) where a high proportion of workers with occupational asthma actually do benefit from effective job retraining programs. A lower level of education and being older are also associated with a worse socioeconomic outcome. Retraining possibilities for a new occupation are often ineffectual, especially in older workers [23, 24]. The severity of asthma does not appear to be an important determinant for the socioeconomic outcome in subjects with occupational asthma, with the exception of one cohort of Finnish workers with isocyanate-induced occupational asthma [26]. The disease-related loss of income is only offset by the financial compensation awarded in a minority of affected workers. Recent data indicate that subjects with work-related asthma show higher healthcare resource utilisation than asthmatic subjects without work-related symptoms [27].

There is evidence that occupational asthma is associated with an adverse impact on healthcare resource utilisation [27], quality of life [26, 28, 29] and mental well-being [29, 30].

There are only scarce data available for workers suffering from work-aggravated asthma [86] and none for those suffering from occupational COPD. It can be assumed that their outcome does not differ substantially from that already described for the occupational asthma sufferers.

1.2. Objectives and audiences of these guidelines

WRA is a preventable diseases. The same is true for occupational COPD. Relevant legal definitions, regulations as well as measures on prevention, diagnosis, compensation, and rehabilitation differ considerably between countries, some having lower standards than others.

The objective of this task force is the development of European guidelines for the management of work-related asthma in order to standardize and optimize the management of patients with WRA. Addressing also legislative authorities in the sector of public health, it is hoped this work could help to assimilate the different European compensation systems.

A further task was to propose evidence-based recommendations in order to extend and if necessary modify the available national guidelines regarding these topics.

Another objective is to compile useful information, such as legal framework for the prevention of occupational asthma in individual countries, in order to describe the basis for improving primary and secondary prevention. It is intended to focus on this issue in a future publication, also preparing a set of cases with the aim to compare management and compensation systems for WRA in different countries, and providing content for leaflets to help guide different audiences.These guidelines cover both primary and secondary prevention. Tertiary prevention, rehabilitation and compensation issues are addressed but not in detail.

These evidence-based guidelines take into consideration already existing guidelines and reports for the prevention of occupational asthma [2] including the British Occupational Health Research Foundation (BOHRF) [31], American College of Chest Physicians (ACCP) [3], Agency for Healthcare Research and Quality (AHRQ) [32] (Table 1).

Table 1: Existing Guidelines and statement papers on WRA.

• Nicholson PJ. British Occupational Health Research Foundation London 2010, BOHRF guidelines for occupational asthma OEM 62:290
• Systematic Review of the Diagnosis of Occupational Asthma Chest 2007;131:569
• Work-related asthma, ACCP statement. Chest , 2008 ; 134 : 1S-41S
• Work-exacerbated asthma. Am J Respir Crit Care Med , 2011;184:368
• BTS Standards of care Thorax 2008;63:240
• Standards of care for occupational asthma, an update, Thorax 2012;67:278

These guidelines are intended to supplement those other guidelines. In particular, management issues specific to WRA, in contrast to asthma in general, were considered.

An initial step was to summarize the available knowledge with evidence-based findings. This comprised recommendations on the frequency and causes of occupational asthma in order to show the urgent necessity for intensified prevention efforts. Evidence regarding prevention, diagnostic tools and management was critically reviewed.

Our main focus was on the articles retrieved from extensive systematic searches of the literature in order to answer the five key questions and their ancillary questions. These guidelines have two primary audiences: 1) workers in all industrial and occupational sectors; and 2) health care providers and practitioners, such as occupational physicians and primary care physicians involved in diagnosis, treatment, and/or education. In addition, political parties, policy makers, industrial physicians, workers' and employers' representatives with responsibility for the safety and health of workers may benefit from the guideline. The knowledge summarized in this document might help them to improvement company policies and legal regulations related to WRA. However, the guidelines do not focus on management tools for governmental authorities.

For more detailed information see the summary chapter "Overview of the Guidelines Management of Work-related Asthma" [33] http://erj.ersjournals.com/content/39/3/529.full.pdf+html, and the corresponding "Editorial" (ERJ 2012;39:518-519)
and the background chapter 5 "Management of Work-related Asthma - Guidelines in a broader Perspective" [2]

http://err.ersjournals.com/content/21/124/125.full.pdf+html

2. METHODS

2.1 Formulation of research questions

An international panel of experts was convened to develop these guidelines as a Task Force of the European Respiratory Society (ERS). An initial meeting of the Task Force took place at the 2007 ERS Congress in Stockholm. A consensus was reached at this meeting on five key questions (Table 3). Specific questions arising at subsequent Task Force meetings were included as ancillary questions.

2.2 Literature review

Appropriate terms were used to search Medline via PubMed (www.ncbi.nlm.nih.gov/pubmed; see Table sO1 (http://erj.ersjournals.com/content/39/3/529/suppl/DC1)[1] for search terms used and number of retrieved results). The database was searched by tracking the most sentinel articles forward in time. Initial searches were performed for each key question and their ancillary questions. The searches were completed and included references of papers published until the end of April 2010. Case reports and non-systematic review articles were excluded; each retrieved title and, when available, abstract was independently screened by two occupational respiratory medicine specialists of each working group. Papers obviously not addressing the topic of interest were excluded. The full text versions of remaining papers were independently assessed by the two occupational respiratory medicine specialists of each working group for each question. Members of the working groups for the different key questions and ancillary questions made supplementary literature searches using Medline and their own archives of published literature. Further publications

from the reference lists of the reviewed papers and of review articles were added if considered useful by the individual working group, and assessed according to the method already described. For these additional searches, the same selection criteria were applied, as described above (see Table sO2 for the deepening search results).

[1] refers to all Tables sOx which are available as supplementary material online

2.3 Quality review of the literature

The methodological quality of each selected study was assessed independently by two reviewers and rated according to the Scottish Intercollegiate Guidelines Network (SIGN) classification [34] (Table 1).

Table 1: SIGN Grading System for the individual papers

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs or RCTs 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 with 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 with a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and with a significant risk that the relationship is not causal
3	Non-analytic studies, such as case reports and case series
4	Expert opinion

Disagreements were resolved by discussion and/or consulting the whole Task Force. The evidence relevant to the two working groups on prognostic factors, surveillance and primary prevention often consisted of observational study designs. The studies were assessed for potential biases (selection, confounding, information bias), considering the sources of bias and bias minimisation strategies in either the design or analysis phase, specific to each study design. For primary prevention studies, where measurement of exposure to occupational agents plays a crucial role, the exposure assessment component was specifically considered, using criteria described in a World Health Organization working document [35] for exposure assessment studies in epidemiological surveys, and applied by LENTERS et al. [36] in a meta-analysis for asbestos.

2.4 Synthesis

The heterogeneity of the studies in the following areas prevented the use of sophisticated methods of meta-analysis for the majority of questions. This refers to study designs (cross-sectional, case–control, longitudinal), measurement methods for disease end-points or intermediate end-points such as sensitisation, and epidemiological end-points; (repeated measurements in longitidudinal studies versus incidence data), measurement methods for the determinants considered, and the statistical methods applied. Narrative summaries were written in these cases. The available evidence often consisted of a crosssectional survey with relatively low SIGN scores. The combined power (study size or number of patients) answering a specific question was considered to give an impression of the discriminatory power of the study by providing an intuitive estimate of precision. For key question 3, study design and measurement methods of the included intervention studies were comparable and a meta-analysis could be conducted. The pooled odds ratio (based on available individual studies) was calculated for each outcome after reduction or cessation of exposure using a random-effect model because heterogeneity between studies was observed. Full details about the methodology used are given elsewhere [37].

Figure 1: Nature of the available information

Source: SUNY Downstate Medical Center. Medical Research Library of Brooklyn. Evidence Based Medicine Course. A Guide to Research Methods: The Evidence Pyramid: http://servers.medlib.hscbklyn.edu/ebm/2100.htm]

Search results and a list of articles considered have been included in the evidence tables presented in Table sO3.

2.5 Strength of evidence and grading of recommendation

The strength of the evidence for each question was graded according to the three-star system of the Royal College of General Practitioners (RCGP), which includes the quality and the quantity of the evidence [38].

Table 2: The Royal College of General Practitioners' Three Star System

***	Strong evidence – provided by generally consistent findings in multiple, high quality scientific studies
**	Moderate evidence – provided by generally consistent findings in fewer, smaller, or lower quality scientific studies
*	Limited or contradictory evidence – provided by one scientific study or inconsistent findings in multiple scientific studies
-	No scientific evidence – based on clinical studies, theoretical considerations, and/or clinical consensus

The strength and clinical relevance of the recommendation was classified according to the system of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [39], which was adapted by the American Thoracic Society (ATS) [40]. Draft statements and recommendations were presented and discussed during Task Force meetings. Final statements and grades of recommendations were the result of consensus among Task Force members.

4. Results

For further details see individual publications listed above.

Table 3: Recommendations for key question 1: How are work-related asthma cases diagnosed and how should they be diagnosed?

Recommendations	Strength of recommendation	Level of evidence
• Occupational asthma should be confirmed by objective physiological and in case of allergic pathogenesis by immunological tests.	Strong	High
• All adults with new or recurrent or deteriorating symptoms of asthma, COPD, or rhinitis should be asked about their job, materials with which they work and whether they improve when away from work.	Strong	High
• In case of non-allergic (irritant) asthma, physicians should consider possible high exposure to irritants in the workplace as relevant pathogenetic factors.	Strong	Low
• If after full investigation the diagnosis is still equivocal, follow up evaluation is required by a specialist, including monitoring of spirometry, serial measurements of PEF or spirometry , NSBHR and allergological testing.	Strong	Low
• Specific bronchial challenge testing is recommended when the diagnosis is not clear beforehand, when the cause is new, or is necessary for the management of the individual worker. If done it should be performed in a centre with expertise in specific occupational challenge testing.	Strong	Low
• We recommend a supervised workplace challenge if specific challenge testing is equivocal or not possible.	Strong	Low

Table 4: Recommendations for key question 2: what are the risk factors (host and exposure) for a bad outcome?

Recommendations	Strength of recommendation	Level of evidence
• Health practitioners should consider that an early recognition and diagnosis of work-related asthma is recommended since shorter symptomatic period after diagnosis is associated with a better outcome.	Strong	High
• Smoking habit and atopy should not be taken into account in assessing prognosis for medical legal purposes	Strong	Moderate
• More research is needed in order to assess the effects of gender, type of asthmatic response to specific bronchial challenge, on the outcome of occupational asthma.	Strong	Moderate

Table 5: Recommendations for key question 3: what is the outcome of different management options in subjects who are already affected?

Recommendation	Strength of recommendation	Quality of evidence
• Patients, physicians, and employers should be informed that persistence of exposure to the causal agent is likely to result in a deterioration of asthma symptoms and airway obstruction.	Strong	Moderate

• Patients and their attending physicians should be aware that complete avoidance of exposure is associated with the highest probability of improvement, but may not lead to a complete recovery from asthma.	Strong	Moderate
• Reducing exposure to the causal agent can be considered an alternative to complete avoidance in order to minimize the adverse socio-economic consequences, but available evidence is insufficient to recommend this option as a first-choice therapeutic strategy. This approach requires careful medical monitoring in order to ensure an early identification of asthma worsening	Weak	Low
• The use of respiratory protective devices (RPD) should not be regarded as a safe approach, especially on the long-term and in patients with severe asthma	Strong	Low
• Anti-asthma medications should not be regarded as a reasonable alternative to environmental interventions	Strong	Very low
• The pharmacological treatment of work-related asthma should follow the general recommendations for asthma	Strong	Moderate

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Table 6: Recommendations for key question 4: what are the benefits of medical screening and surveillance?

Recommendations	**Strength of recommendation**	**Level of evidence**
Questionnaire-based identification of all workers at risk of developing work-related asthma is recommended as basis for surveillance.	Strong	High

A pre-placement screening for specific cross-reacting work-associated sensitisation among potentially HMW allergen-exposed subjects is recommended in order to identify those at higher risk for WRA.	Strong	Moderate
Detection of sensitization either by specific IgE or SPT should be included in surveillance *(not only pre-placement)* for identification of subjects at risk of WRA with foreseeable regular exposure to high molecular weight agents (such as laboratory animals, bakery dust, enzymes or latex).	Strong	Moderate
In atopics and subjects with pre-existing asthma or sensitization pre-employment investigation should be performed in order to inform them about their increased WRA risk. Because of the low positive predictive value, exclusion of asymptomatic atopics or sensitized subjects from exposures to potential occupational allergens or irritative agents cannot be recommended.	weak	Moderate
In all workers with confirmed occupational rhinitis and/or NSBHR medical surveillance programs should be performed. They should include periodic administration of a questionnaire, detection of sensitization by standardized skin prick tests or serum specific IgE antibodies, early referral of symptomatic and/or sensitized subjects for specialized medical assessment and assessment of asthma. Surveillance programs should be already implemented during vocational training of individuals at risk.	Strong	Moderate
Identification of symptoms or sensitization during surveillance should result into an investigation to confirm or exclude occupational asthma, work-related asthma,	Strong	High

rhinitis and COPD, respectively.		
Risk stratification by diagnostic models can be used in medical surveillance to select exposed workers for further medical evaluation.	Strong	Moderate
A comprehensive medical surveillance program as a secondary prevention measure should – in addition to early detection of sensitization, allergic symptoms, and occupational asthma – comprise exposure assessment and intervention targeted both at workers and exposure.	Strong	Moderate

Table 7: Recommendations for key question 5: what is the impact of controlling work-related exposure to prevent asthma?

Recommendations	**Strength of recommendation**	**Level of evidence**
Exposure elimination is the strongest preventive approach to reduce the disease burden of work-related asthma and is the preferred primary prevention approach.	Strong	High
If elimination is not possible, reduction is the second best option for primary prevention for WRA based on exposure response relationships.	Strong	Moderate
The evidence for the effectiveness of respirators in preventing occupational asthma is limited, and other options higher in the hierarchy of controls for occupational exposures, notably eliminating or minimizing exposures at the source or in the environment, should be used preferentially.	Strong	Moderate

Stop using powdered allergen-rich natural rubber latex gloves.	Strong	High

5. DISCUSSION

The Global Initiative for Asthma (GINA) has revised its guidelines and changed its focus from asthma severity to asthma control, with an emphasis on carefully titrating drug doses, according to the level of control [41, 42]. This new understanding is also relevant for management of work-related asthma. However, in terms of work-related asthma, the benefits from avoiding exposure far exceed those of drug treatment.

In clinical decision-making for work-related asthma, physicians must be able to i) identify whether a patient is adequately controlled ii) understand how increments of control can be achieved by adjusting exposure levels and/or the regimen iii) evaluate the resulting improvements or lack thereof.

A recent paper evaluated and compared existing instruments for measuring asthma control [42, 43]. Five validated instruments that were designed to measure asthma control demonstrated validity and responsiveness, with some measure of reliability, and all had evidence to support their use in clinical decision-making. The individual GINA characteristics of asthma control to be checked were i) daytime symptoms ii) limitations of activities iii) noctural symptoms/awakening iv) need for reliever/rescue treatment v) lung function (PEF or FEV1) vi) exacerbations. Other characteristics that were not included in GINA but were considered by some investigators were airway inflammation, patients' perception of asthma control, overall asthma severity, and specific asthma symptoms (i.e. shortness of breath, wheezing or cough, or chest pain). For the measurement of work-related asthma control, the following characteristics were added: work-related symptoms and work-related lung function impairment (PEF or FEV1). To maintain clinical control, which is challenging and the most important aim, the following additional factors should be taken into account: intensity and variability of exposure to causative occupational agent(s), individual exposure–response relations, the underlying pathogenetic mechanisms (i.e. allergic or irritative effects at high, medium or low concentrations),

impairment of lung function and degree of NSBHR, and realistic secondary and tertiary preventive measures in the particular case.

Evaluating the outcome of work-related asthma is not only based on clinical aspects but includes physiological as well as social variables. The relevant literature was recently summarised in systematic reviews [44-46]. RACHIOTIS et al. [44] summarised as follows: ‘‘one third of patients with occupational asthma will recover fully from their disease following avoidance of exposure to the initiating agent. This proportion seems not to be related to the duration of avoidance. In most cases, non-specific bronchial responsiveness detected at diagnosis persists. There was evidence that symptomatic outcomes worsened with increasing age and with duration of symptomatic exposure, although the latter was not significant.’’

For results of our literature search on the clinical outcome of work-related asthma, see online supplementary text sO5.

In conclusion, we suggest to orientate on existing recommendations from GINA when the effect of interventions on clinical and physiological indices of work-related asthma is assessed and tried to be improved as well as to control the consequences on employment and income. Work-related symptoms, lung function deterioration and sensitisation are major parameters for decision-making in work-related asthma management. The combination of a questionnaire, with results of SPT and/or IgE tests, increases the predictive value significantly [47]. Screening as well as surveillance results and NSBHR were found to be informative prognostic parameters in high-risk workers. Since the level of exposure to allergenic or irritative airborne agents is the dominant risk factor for work-related asthma, exposure avoidance or at least reduction as primary preventive measures are the most effective approaches. This is obviously also true for occupational COPD [17, 19, 48]. There is less evidence for the effectiveness of secondary prevention, in which sensitisation or early symptoms are identified during health surveillance programmes, with the aim of a substantial reduction in and, if possible, avoidance of further causative exposures. Tertiary prevention of occupational airway diseases involves a therapeutic and general asthma or COPD management plan, and may include a change of workplace or even job for individuals who continue to have work-related symptoms, despite efforts to control exposures and optimise management. Pharmacological treatment and respirators are of limited effect. The limited amount of data about the relationship of work-related

asthma with sex, age, smoking and type of agent does not allow recommendations to be made about these factors.

The aforementioned management options refer to new-onset occupational asthma as well as work-aggravated asthma. The latter can be differentiated from occupational asthma by the temporally work-associated worsening of pre-existing or concurrent work-independent asthma (see Chapter introduction). Although there are only a few studies on the management of work-aggravated asthma [3, 49], there is general agreement that reduction of causative exposures and intensified surveillance and treatment are urgent measures for management. If this approach is not successful, a change in jobs should be considered [50].

Increased suspicion of an occupational cause in all cases of asthma and COPD by all involved is required. On the basis of the key and ancillary questions and evidence-based statements, our recommendations for the effective prevention and management of work-related asthma are: i) avoidance of causative exposures or, if that is not possible, exposure reduction ii) screening and monitoring (surveillance) of endangered workers (those with high-risk work sites or with individual susceptibility iii) comprehensive assessment of disease in suspected cases (diagnostics) iv) pharmacological treatment of subjects with obstructive ventilation patterns, NSBHR or work-related asthma symptoms.

Furthermore, there is a need for patient health education, in an effort to improve the individual's ability to cope with unplanned harmful exposures, exacerbation episodes, avoidance of risk factors and smoking cessation. We also recommend providing detailed information to employees, employers and medical personnel, which should lead to increased awareness and earlier detection of work-related asthma and occupational COPD. We recommend notification to accessible registers and systematic surveys that may detect increased occurrence of asthma and COPD in populations. Since many epidemiological studies are hypothesis-generating, this may lead to more focused investigations, which in turn may form a basis for prevention.

Future research aspects

Given the limited evidence available, additional research is required to demonstrate the effectiveness of primary preventive measures on: allergen exposure; and the occurrence of allergy and asthma for most allergens. In general, studies that make use of strong analytical designs, such as

randomised controlled trials and controlled intervention studies, have the potential for allergen exposure. Observational studies, which focus on disease occurrence in relation to exposure, have further limitations. Exposure studies focusing on evaluation of allergen exposure and exposure interventions are strongly encouraged. Further evidence is required for all types of preventive actions, including improved ventilation, education of workers, changes in work organisation, and use of personal protective equipment. There is also a clear need to further explore the role of skin exposure in relation to development of sensitisation and disease occurrence.

Given earlier information, it is important to evaluate the independent and additional predictive value of diagnostic tests. Prediction research provides an appropriate solution by using a multivariate approach in design and analysis that accounts for mutual dependence between different test results. The information from these tests can then be translated into a predicted probability of the chosen outcome. Prediction models applied in occupational health practice may therefore enable an occupational physician to deal with uncertainties in considering workers at risk of having occupational diseases.

Research is needed to assess the prognostic value of sex, type of asthmatic response to specific agents, and other determinants at diagnosis. Furthermore, most research on risk factors for a bad outcome is performed on a limited number of exposures, i.e. isocyanates and western red cedar. So it is crucial to include other exposures in the research field as well.

Although its role in disease management is not disputed, there are important questions that are still awaiting answers: when and how to set up medical surveillance; and which tests, test frequency and outcome parameters should be used in different occupational groups. As direct evidence for the benefit of medical surveillance is scarcely available, there is a need for prospective studies using clearly defined instruments and outcomes.

Large-scale, standardised studies on the prognosis of occupational asthma and its determinants after environmental interventions are required in order to provide evidence-based recommendations to affected workers, employers and policy makers. Prospective studies of the prognosis of occupational asthma should use the outcomes that have been validated for asthma in general.

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STATEMENT OF INTEREST

None declared.

All mentioned sOx Tables are available as supplementary material online by (http://erj.ersjournals.com/content/39/3/529/suppl/DC1)[1]

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