Eur Respir J 2003; 21: 706–712
DOI: 10.1183/09031936.03.00113303
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European Respiratory Journal
ISSN 0903-1936

SERIES "CONTROVERSIES IN OCCUPATIONAL ASTHMA"
Edited by O. Vandenplas and J-L. Malo
Number 1 in this Series

Definitions and types of work-related asthma: a nosological approach

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Definitions and types of work-related asthma: a nosological approach. O. Vandenplas, J-L. Malo. ©ERS Journals Ltd 2003.

ABSTRACT: The workplace can trigger or induce asthma and cause the onset of different types of work-related asthma. Analysis of previous definitions of occupational asthma (OA) led to the conclusion that evidence of a direct causal relationship between workplace exposure and the development of asthma remains the key element for defining OA.

Based on clinical features and pathophysiological mechanisms, the following conditions should be distinguished in the spectrum of work-related asthma: 1) immunological OA characterised by a latency period necessary to acquire immunologically induced sensitisation; 2) nonimmunological OA characterised by the rapid onset of asthma following single or multiple exposures to high concentrations of irritant compounds; 3) work-related asthma defined by exacerbation of symptoms in workers with pre-existing or coincident asthma; and 4) variant syndromes including eosinophilic bronchitis, potroom asthma, and asthma-like disorders caused by organic dusts.

The issues and controversies relating to this approach are critically reviewed in order to stimulate the consensus development of operational definitions of work-related asthma.

Eur Respir J 2003; 21: 706–712.

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Keywords: Asthma, bronchial hyperresponsiveness, irritant-induced asthma, occupational disease, reactive airways dysfunction syndrome

Received: December 8 2002
Accepted after revision: December 13 2002

O. Vandenplas is supported by the Services Fédéraux des Affaires Scientifiques, Techniques et Culturelles (grant SSTC PS/10/44).

There is no uniformly accepted definition of occupational asthma (OA), probably because various forms of work-related asthma can result from different pathophysiological mechanisms. In addition, definitions of OA have varied according to the purposes for which they were needed, including epidemiological investigation, workplace surveillance programmes, clinical diagnosis, and medico-legal assessment. Nevertheless, in the same way as the existence of a consensus definition of asthma [1] has improved its recognition and management in recent years, precise and workable definitions of OA and other types of work-related asthma are required to improve the investigation and management of these common conditions.

Historical considerations

PEPYS [2] who made such an important contribution to the field of OA with his pioneered works in the 1960s and 1970s suggested the following: "Having made a diagnosis of asthma ('widespread airways obstruction reversible over short periods of time, either spontaneously or as a result of treatment') it is then necessary in occupational asthma to establish a relationship to the work as recommended by Ramazzini in 1713". Subsequent to this suggestion, several expert investigators have proposed definitions of OA including: "Occupational asthma is variable airways narrowing causally related to exposure in the working environment to airborne dust, gases, vapours or fumes. …Such findings fulfil the classical clinical criteria of hypersensitivity…" [3]; "Occupational asthma, therefore, is caused by some specific agent or agents in the form of dust, fumes or vapours in an industrial environment" [4]; "Occupational asthma is a disorder in which there is generalised obstruction of the airways, usually reversible, caused by inhalation of a substance or material that a worker manufactures or uses directly or is incidentally present at the worksite" [5]; "Occupational asthma is caused by exposure at a place of work to a sensitising bronchoconstrictor substance" [6]; "Occupational asthma will be defined as asthma caused by specific agents in the workplace. This will exclude bronchoconstrictions induced by irritants at work, exercise and cold air" [7]; "Occupational asthma is asthma which is due in whole or in part to agents met at work. Once occupational sensitisation has occurred…" [8]; and "Occupational asthma is a disease characterised by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace" [9].

All of these definitions stipulate that there should be a causal relationship between workplace exposure and asthma and/or that the causal agent (identified or not) should be specific to the workplace [3–9]. Some of them focus on the mechanisms leading to asthma and specify that OA should result from a sensitising mechanism [3, 6, 8]. The relevance of these two elements is examined hereafter in order to identify the concepts that should underlie the process of defining OA.

Causal relationship between the workplace and asthma

A causal relationship between workplace exposure and asthma implies that agents causing OA should be able to induce the development of the characteristic features of asthma, including variable airflow limitation, nonspecific

bronchial hyperresponsiveness (NSBH), and airway inflammation [1]. However, advances in the pathophysiological mechanisms of asthma in recent years have clearly indicated the various outcomes for agents that cause airway inflammation and NSBH, described as "inducers", and for those that trigger airway narrowing in subjects with NSBH, without inducing airway inflammation, labelled "inciters" [10]. Conceptually, only inducers can be considered to be causal agents, since they induce not only airflow obstruction but also changes in airway inflammation and NSBH, whereas inciters increase the frequency of asthma symptoms in those with pre-existing or coincidental asthma. The "prototypes" of asthma inducers are common aeroallergens acting through an immunoglobulin (Ig)E-mediated mechanism. Acute exposure to these agents in the laboratory can provoke immediate and nonimmediate (late) asthmatic reactions. Although it is not invariably the case, late reactions are associated with an increase in NSBH and in airway inflammation, more often than immediate reactions [11–14]. Furthermore, exposure to inducers at doses that do not elicit airflow obstruction can provoke an increase in NSBH and airway inflammation, which can be assumed to result in a worsening of the asthma condition [15, 16]. Viral infections, particularly in children, can induce asthma in a similar way to that of allergens [17]. By contrast, inciters, such as exercise or exposure to cold air, can trigger short-lasting asthma symptoms and transient airflow obstruction, but these stimuli do not generally cause changes in NSBH or airway inflammation [18].

Establishing the causal relationship between asthma and the workplace should therefore take into account the distinction between inciters and inducers. Numerous agents present in the workplace can be considered to be asthma inducers, since they have been documented as causing asthmatic reactions, airway inflammation, and NSBH. These agents encompass a wide variety of high molecular weight protein allergens, as well as low molecular weight substances. In subjects with OA, exposure to these agents can cause an increase in NSBH and airway inflammation, even in the absence of airway obstruction [19, 20]. Irritant materials, though only at high concentrations [21], can also lead to the development of NSBH and airway inflammation. They can cause what has been labelled reactive airways dysfunction syndrome (RADS). In contrast, exposure of asthmatic subjects to lower concentrations of irritants does not generally induce changes in NSBH or airway inflammation [22–26] (with the noticeable exception of ozone [27]), although some individuals may show minimal changes in airway calibre [23, 28].

Categorising various forms of asthma related to work exposure according to the strength of their causal relationship with the workplace environment is relevant not only for scientific reasons, but also for medical, preventive, and medico-legal purposes. Asthma caused by inducers may require complete removal from workplace exposure, since persistence of exposure to these agents can result in the progressive worsening of the characteristic features of asthma and long-term functional impairment. Such therapeutic and preventive options are associated with tremendous professional, financial, and social consequences. In contrast, asthma symptoms triggered by physical stimuli or irritants at work could be managed at a lower societal cost by reducing the levels of irritants at work to within acceptable limits at work and/or by optimising antiasthma treatment. Accepting exacerbation of asthma symptoms at work as an occupationally induced disease would have a considerable financial and psychosocial impact: the prevalence of asthma in the general population is high, and nearly all asthmatics could theoretically apply for compensation if they experience worsening of their symptoms on exposure to triggering factors at work, not to mention the considerable social impact of excluding asthmatic subjects from workplaces in which agents causing irritation of the airways could conceivably be encountered.

Sensitising nature of the process

A broad spectrum of occupational agents have been identified as causing a form of asthma that meets the clinical criteria of hypersensitivity: 1) work-related asthma symptoms develop only after an initial symptom-free period of exposure; 2) asthmatic reactions tend to recur on re-exposure to the causal agent at concentrations not affecting others that are similarly exposed; and 3) asthma affects only a proportion (usually a minority) of those exposed to the agent [3]. Accordingly, some definitions of OA have specified that the agent causing OA should exert its effects through "sensitisation" [6, 8]. The use of the term "sensitisation" may suggest that the immunological mechanism has been characterised precisely. However, the mechanisms leading to the development of asthma caused by most low molecular weight substances remain largely unknown, although there is evidence that immunological processes mediated by T-lymphocytes (CD8+) are involved independently from the production of specific IgE antibodies.

Irrespective of the underlying pathophysiological mechanisms, the presence of a latency period is a key feature that differentiates OA characterised clinically by bronchial hyperresponsiveness to occupational agents from asthma caused by acute exposure to high concentrations of irritants (RADS). Indeed, immunological mechanisms may well be involved in the development of RADS, although the original insult is purely an acute toxic injury of the airways. The presence of some cell types like lymphocytes suggests that an immunologically mediated mechanism may play a role. Whereas the functional and pathological features of OA that occur after a latency period are indistinguishable from those of common asthma, whether allergic or nonallergic, the features of RADS differ somewhat. After the initial event, the reversibility of airway obstruction is not as constant and as marked in subjects with RADS as in those with OA or nonoccupational asthma. Moreover, the chronic pathological features point to more airway remodelling than for standard asthma [29, 30]. That said, there is still sufficient clinical and functional evidence for accepting RADS as a category of asthma causally related to workplace exposure.

Proposed avenues for defining occupational asthma

The workplace can trigger or induce asthma, leading to what can be labelled "work-related asthma" (or "work-attributable asthma"). Within this broad spectrum of asthma conditions related to the workplace, several entities can be identified based on the strength of the causal relationship, clinical features, and/or pathophysiological mechanisms (table 1). Considering the above critical review of previous definitions, the keystone for defining OA is the causal relationship between workplace exposure and the development of asthma. It therefore seems logical to limit the definition of OA to those conditions in which the asthma is induced or caused by occupation in the same way as proposed recently by a panel of experts [9, 31, 32].

Occupational asthma

OA is a disease characterised by airway inflammation, variable airflow limitation, and airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered

Table 1. – Categorisation of work-related asthma

	Occupational asthma		Work-aggravated asthma	Variant syndromes
	Immunological	Nonimmunological (acute irritant-induced asthma)		
Mechanisms	IgE-mediated (HMW agents and some LMW agents) Unknown (most LMW agents)	Acute toxic injury from single (RADS) or multiple high-level irritant exposure(s)	Unknown	Endotoxins? (ALD) Unknown (EB, PA)
Clinical features	Latency period	Sudden onset No latency period (RADS)	Work-related asthma symptoms	EB: work-related cough+ sputum eosinophilia ALD: systemic symptoms
Evidence of causal relationship	Observational ascertainment in individuals (inhalation challenges)	Inference from temporal relationship between acute exposure and onset of asthma	No specific tests (exclusion of occupational asthma)	EB and ALD can be ascertained by *e.g.* objective tests (inhalation challenges)

HMW: high molecular weight; LMW: low molecular weight; RADS: reactive airways dysfunction syndrome; ALD: asthma-like disorders induced by vegetable dusts (cotton, textile fibres, grain, *etc.*); EB: eosinophilic bronchitis; PA: potroom asthma; Ig: immunoglobulin.

outside the workplace. This type of work-related asthma should be more appropriately labelled "occupation-induced asthma" to emphasise the determining causal relationship between asthma and the workplace. Two types of OA are distinguished by whether they appear after a latency period.

Immunological occupational asthma. Characterised by work-related asthma appearing after a latency period of exposure necessary to acquire immunologically mediated sensitisation to the causal agent. This category encompasses: 1) OA caused by most high and certain low molecular weight agents for which an immunological (IgE-mediated) mechanism has been proven; and 2) OA induced by low molecular weight occupational agents, such as isocyanates, Western red cedar, or acrylates, for which an IgE-mediated immunological mechanism has not been identified consistently.

Nonimmunological occupational asthma. Characterised by the absence of a latency period, as asthma develops within hours following a single exposure to inhaled irritants at very high concentrations in the workplace. This clinical entity has been described under the label "reactive airways dysfunction syndrome (RADS)" or "irritant-induced asthma". The diagnosis of RADS requires all of the following criteria [31]: 1) documented absence of preceding respiratory complaints; 2) onset of symptoms after a single exposure incident or accident; 3) exposure to a gas, smoke, fume or vapour with irritant properties present in a very high concentration; 4) onset of symptoms within 24 h of exposure with persistence of symptoms for at least 3 months; 5) asthma-like symptoms; 6) presence of airflow obstruction on pulmonary function tests; 7) presence of NSBH; and 8) exclusion of other pulmonary disease.

According to the revised nomenclature recently proposed by the European Academy of Allergy and Clinical Immunology [33], OA mediated by immunological mechanisms (whatever their precise nature) that results in clinical "allergic hypersensitivity" should be termed "allergic OA". When there is evidence of IgE-mediated mechanisms, the term should be "IgE-mediated (allergic) OA". Other nonimmunological types of asthma causally related to the workplace should be labelled "nonallergic OA".

Work-aggravated asthma

Work-aggravated asthma is defined as pre-existing or concurrent asthma that is exacerbated by workplace exposures.

Variant syndromes

Eosinophilic bronchitis. Eosinophilic bronchitis has been described increasingly as a cause of chronic cough, which is characterised by sputum eosinophilia in the absence of demonstrable variable airflow obstruction or NSBH [34]. At present, only two published case reports have shown that eosinophilic bronchitis can be causally related to occupational agents [35, 36]. In these cases, challenge exposure to occupational agents (acrylates in one subject and latex gloves in the other) resulted in a marked increase in sputum eosinophilia in the absence of airflow obstruction and NSBH. Although eosinophilic bronchitis does not meet the current definition of asthma, it should be considered as an occupationally induced condition when work-related changes in sputum eosinophils are significant and reproducible. The outcome of work-related eosinophilic bronchitis remains unknown and it should be determined whether this syndrome can progress to typical OA.

Potroom asthma. The term "potroom asthma" refers to the occurrence of work-related asthma symptoms among those employed in the production of aluminium from alumina into electrolytic cells ("pot") [37]. Different mechanisms could be involved in the development of these symptoms, including an irritant effect resulting from exposure to pollutants (*i.e.* hydrogen fluoride, sulphur dioxide) and an immunologically mediated reaction directed against trace amounts of metals. Work-related changes in peak expiratory flow have been described in symptomatic potroom workers, although most of these workers failed to demonstrate significant NSBH during workplace exposure. Only one report documented the development of a biphasic asthmatic reaction associated with an increase in NSBH on exposure to the potroom environment [38].

Asthma-like disorders. Exposure to vegetable dusts (grain, cotton and other textile fibres) and dust from animal confinement buildings can induce asthma-like and systemic symptoms associated with acute decrement in expiratory flows, transient increase in NSBH, and neutrophilic airway inflammation [39, 40]. These endotoxin-related conditions share common features that differentiate them from OA: 1) there are systemic symptoms, which are not generally present in OA; 2) the severity of the symptoms typically decreases over the working week (tolerance); 3) cross-shift changes in expiratory flows are less pronounced; and 4) NSBH is neither a prominent nor a persistent feature.

Issues and controversies

Immunological occupational asthma (with a latency period)

In contrast with most other occupational lung diseases, the causal role of occupational agents in the development of immunological OA can be investigated experimentally in individual cases using inhalation challenges in the laboratory or in the workplace. Showing that a particular agent or process provokes an asthmatic reaction or an increase in NSBH and/or airway inflammation but does not elicit such effects in other asthmatic subjects, provides strong evidence that the agent is an inducer rather than an inciter of asthma. There are, however, several issues of concern related to documenting the causal relationship between a specific workplace and asthma. In most individuals suffering from immunological OA, it cannot be proven that occupational environment caused asthma *de novo* after entering a particular workplace. The inception of the characteristic features of asthma can be formally demonstrated only *a posteriori* when inhalation challenges are performed in subjects in whom NSBH has returned to a normal level after cessation of exposure to the causal agent [41]. Conversely, pre-existing asthma does not exclude the development of a true immunologically mediated OA. A non-negligible proportion of subjects with ascertained OA report a history of asthma before employment [42]. This proportion is at least equal to the prevalence of asthma in the general population and it could be even higher considering that atopy and a measurable NSBH are associated with an increased risk for the development of OA caused by some high molecular weight agents [43].

Another question is which of the characteristic features of asthma should be required for establishing causality. Thus, it may be difficult to differentiate immediate bronchial responses to inducers from those triggered by irritant substances, although the latter are usually less reproducible and resolve faster than the former. An increase in NSBH provides strong evidence for OA induced by occupational agents acting through an immunological mechanism, although this is not a consistent finding [11]. Furthermore, occasionally there are cases in which subjects fail to exhibit NSBH both before and after asthmatic reactions induced by occupational agents [44–46]. Examination of induced sputum could provide a relatively noninvasive method for assessing changes in airway inflammation caused by exposure to occupational agents during inhalation challenges or exposure at work [47, 48]. However, there is some suggestion that different occupational exposures could induce different inflammatory responses of the airways [49, 50].

Nonimmunological occupational asthma (without a latency period)

In the case of RADS, documentation of the causal relationship is based on the strong temporal association between an inhalation accident and the rapid onset of asthma [31]. On the basis of these stringent criteria, a diagnosis of RADS should never be made in subjects with pre-existing asthma. It is, however, conceivable that high-level exposure to irritants would induce similar adverse effects in asthmatic and healthy subjects. Reactivation of asthma in remission or persistent worsening of pre-existing stable asthma should be considered as possible consequences of acute inhalation injury [51–53], although causation cannot be ascertained with the highest degree of confidence. Whether worsening of pre-existing asthma induced by high-level inhalation of irritants should be categorised as "acute irritant-induced OA" or as a subcategory (*e.g.* "accidental aggravation of asthma") [53] of "work-aggravated asthma" remains controversial.

The development of asthma has also been attributed to multiple exposures rather than a single exposure to high levels of irritants. TARLO and BRODER [54] introduced the term "irritant-induced asthma" to characterise workers who develop asthma after both single and multiple irritant exposures. In their series, five of 10 subjects with irritant-induced asthma did not identify an unusually high exposure before the onset of asthma symptoms. Among these five subjects with asthma attributed to multiple irritant exposures, three subjects demonstrated significant work-related changes in NSBH or in expiratory peak flow values, which are usually regarded as diagnostic criteria of immunologically induced OA [55]. CHAN-YEUNG *et al.* [56] described three pulp mill workers in whom asthma and NSBH occurred after multiple "gassing" episodes. However, their asthma symptoms developed immediately after an episode of heavier exposure requiring emergency-room treatment. Actually, these case series did not formally demonstrate that multiple exposures to an irritant substance can cause asthma, since data only confirmed that initiation of asthma required a single high-level exposure, which is consistent with classical RADS. This was further supported by longitudinal surveys of workers who had been exposed repeatedly to high levels of chlorine [57, 58]. In these studies, the persistence of NSBH was unrelated to the number of gassing episodes but was associated with a severe accidental exposure requiring a visit to the emergency room or the first-aid unit. Asthma resulting from multiple high-level exposures to irritant substances can be categorised as OA, provided that the onset of persistent asthma symptoms is temporally related to one documented severe inhalation accident requiring medical care. It should be underlined that in such conditions of multiple exposures, the absence of a latency period should no longer be regarded as a distinctive feature.

Several investigators have proposed to extend the spectrum of irritant-induced asthma to include new-onset asthma and reactivation of quiescent asthma in individuals who are repeatedly exposed to "moderate" or "excessive", although poorly documented, concentrations of irritant substances in the workplace [59, 60]. Evidence supporting such concepts of "low-dose RADS" or "not-so-sudden RADS" is still very weak. Only one survey has documented a relationship between the level of NSBH and the occurrence of gassing episodes with mild symptoms [61]. Accordingly, delayed-onset asthma following repeated exposures to moderate or excessive concentrations of irritants cannot be considered as OA, because the causal relationship between workplace exposure and the development of asthma cannot be ascertained with a sufficient level of confidence. Although widely used, the term "RADS" is not indicative of the nature and mechanisms of the disorder, and it might be better replaced in future nomenclature by "acute irritant-induced asthma" or "sudden-onset irritant-induced asthma" to avoid further confusion with delayed or progressive forms of asthma associated with irritant exposures at work.

Work-aggravated asthma

The term "work-aggravated asthma" is used to describe the worsening of pre-existing or coincident (new-onset) asthma as a result of workplace environmental exposure [31, 62–64]. Aggravation of asthma in the workplace can manifest as an increase in frequency or severity of asthma symptoms and/or an increase in medication required to control symptoms on working days. These clinical features are similar to those of immunological OA, which may lead to misclassification of OA as work-aggravated asthma when appropriate investigations are not carried out. Conceptually, worsening of asthma at work could be documented by work-related changes in

airway calibre, level of NSBH, or airway inflammation. However, these tests are not able to differentiate work-aggravated asthma from true OA, so that subjects who demonstrate work-related changes in airway obstruction, NSBH, or airway inflammation are currently diagnosed as having OA. In addition, several studies have shown that a substantial proportion of subjects who experience exacerbation of asthma symptoms at work, fail to demonstrate objective evidence of asthma worsening when they are exposed in their workplace or to the suspected agent in the laboratory [47, 65, 66]. Actually, the term "work-aggravated asthma" refers to self-reported symptoms but not to aggravation of any one of the physiological or pathological features of asthma. Accordingly, work-aggravated asthma would be more appropriately labelled as "work-aggravated asthma symptoms".

Work-related worsening of asthma symptoms appears to be a common condition [66], although little has been published on its pathophysiological mechanisms, management, and outcome. There is accumulating evidence that even in the documented absence of immunological OA, work-aggravated asthma may cause a substantial and potentially preventable burden of disability and socioeconomic consequences [42, 67]. Focusing on a global preventive approach, some authors have proposed to expand the definition of OA to include work-aggravated asthma [62, 63], a proposal with which the authors of this article totally disagree. The latter condition does indeed need to be distinguished clearly from immunological OA through objective evaluation, since its pathophysiological consequences are completely different from those of OA as reviewed above, and because their medical and preventive management differ dramatically.

Purposes and practical applications of the definition

The definition of OA can be adapted for different purposes and circumstances. For instance, establishing a clinical diagnosis of OA requires the highest level of evidence, as it is associated with considerable medical and socioeconomic consequences. The requirements for identifying OA in workplace surveillance programmes and epidemiological investigation are less stringent than for medical evaluation, although the validity of the inferences that can be drawn from the findings depends largely on the accuracy of the criteria used for case identification. The National Institute for Occupational Safety and Health has developed a surveillance case definition of OA (table 2) [68, 69]. Operational criteria for both medical and surveillance case identification have been derived by a consensus panel of experts from the American College of Chest Physicians (table 3) [31]. Several limitations of these definitions should, however, be considered. The association between documented (new-onset) asthma, work-related symptoms, and workplace exposure to agents known to cause asthma (criteria A+B+C3 in table 2 or A+B+C+D1 in table 3) provides only a low predictive value for the presence of OA [65], and may lead to gross overestimation of the true prevalence of the condition. On the other hand, the criterion new-onset asthma (criterion B in table 3) may result

Table 2. – Surveillance case definition of occupational asthma proposed by the Sentinel Event Notification Systems for Occupational Risks (SENSOR)

A. Healthcare professional's diagnosis of asthma
B. An association between symptoms of asthma and work
C. One or more of the following criteria
  1. Increased asthma symptoms or increased use of asthma medication (upon entering an occupational exposure setting) experienced by a person with pre-existing asthma who was symptomatic or treated with asthma medication within the 2 yrs prior to entering that new occupational setting (work-aggravated asthma)
  2. New asthma symptoms that develop within 24 h after a one-time high-level inhalation exposure (at work) to an irritant gas, fume, smoke, or vapour and that persist for at least 3 months (reactive airways dysfunction syndrome)
  3. Workplace exposure to an agent or process previously associated with occupational asthma.
  4. Work-related changes in serially measured FEV1 or peak expiratory flow rate
  5. Work-related changes in bronchial responsiveness as measured by serial nonspecific inhalation challenge testing
  6. Positive response to specific inhalation challenge testing with an agent to which the patient has been exposed at work

FEV1: forced expiratory volume in one second. Adapted from [69].

Table 3. – Criteria for defining occupational asthma proposed by the American College of Chest Physicians

Diagnostic criteria
  A. Diagnosis of asthma
  B. Onset of symptoms after entering the workplace
  C. Association between symptoms of asthma and work
  D. One or more of the following criteria
    1. Workplace exposure to an agent or process known to give rise to occupational asthma
    2. Significant work-related changes in FEV1 or peak expiratory flow rate
    3. Significant work-related changes in nonspecific airway responsiveness
    4. Positive response to specific inhalation challenge tests with an agent to which the patient is exposed at work
    5. Onset of asthma with a clear association with a symptomatic exposure to an irritant agent in the workplace (reactive airways dysfunction syndrome)
Requirements
  Occupational asthma
    Surveillance case definition: A+B+C+D1 or D2 or D3 or D4 or D5
    Medical case definition: A+B+C+D2 or D3 or D4 or D5
  Likely occupational asthma: A+B+C+D1
    Work-aggravated asthma: A+C (*i.e.* the subject was symptomatic or required medication before and had increase in symptoms or medication requirement after entering a new occupational exposure setting)

FEV1: forced expiratory volume in one second; RADS: reactive airways dysfunction syndrome. Adapted from [31].

in underestimating the occurrence of true immunological OA in subjects with pre-existing asthma.

Conclusion

The clinical and medico-legal definition of occupational asthma should be limited to include only those cases in which a causal relationship can be established objectively between exposure to a workplace or a substance in the workplace and the inception of asthma. Other types of asthma related to the workplace environment require further investigation in order to identify their characteristics and to develop evidence-based definitions.

Acknowledgements. The authors would like to express their thanks to L. Schubert for reviewing the manuscript.

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