

POSITION PAPER

## EAACI Position Paper on assessment of cough in the workplace

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### Abstract

Cough is a nonspecific and relatively common symptom that can present difficulties in diagnosis and management, particularly when it is reported to be associated with the workplace. The present consensus document, prepared by a taskforce of the Interest Group on Occupational Allergy of the European Academy of Allergy and Clinical Immunology by means of a nonsystematic review of the current literature, is intended to provide a definition and classification of work-related chronic cough (WRCC) to assist the daily practice of physicians facing with this symptom. The review demonstrates that several upper and lower airway work-related diseases may present with chronic cough; hence, the possible link with the workplace should always be considered. Due to the broad spectrum of underlying diseases, a multidisciplinary approach is necessary to achieve a definite diagnosis. Nevertheless, more epidemiological studies are necessary to estimate the real prevalence and risk factors for WRCC, the role of exposure to environmental and occupational sensitizers and irritants in its pathogenesis and the interaction with both upper and lower airways. Finally, the best management option should be evaluated in order to achieve the best outcome without adverse social and financial consequences for the worker.

### Abbreviations

GERD, gastroesophageal reflux disease; HP, hypersensitivity pneumonitis; ILS, irritable larynx syndrome; IVCD, irritant vocal cord dysfunction; MIF, maximal inspiratory flow; NAEB, nonasthmatic eosinophilic bronchitis; NSBH, nonspecific bronchial hyper-responsiveness; OA, occupational asthma; OCC, occupational chronic cough; OR, occupational rhinitis; PEF, peak expiratory flow; RARs, rapidly adapting receptors; SARs, slow-adapting receptors; TRPV-1, transient receptor potential vanilloid type 1; VAS, visual analogue scale; VCD, vocal cord dysfunction; WEA, work-exacerbated asthma; WECC, work-exacerbated chronic cough; WILS, work-related irritable larynx syndrome; WRA, work-related asthma; WRCC, work-related chronic cough.

Cough is a nonspecific and relatively common disruptive symptom (1) that serves as a crucial protective reflex for upper airways (1) but can also be a warning sign of disease (2). When cough is chronic (i.e. persisting for more than 8 weeks) (1, 3), it can present difficulties in diagnosis and management (2), particularly when reported to be associated with the workplace. Several guidelines and reviews on work-related chronic cough (WRCC) have recently been published (4–6), but an operative protocol intended to assist the daily practice of allergologists and a consensus definition and classification of WRCC are lacking.

The objectives of the present document are:

- 1 To summarize current scientific evidence on WRCC
- 2 To propose a definition and classification of WRCC
- 3 To elaborate a protocol for assessment, differential diagnosis and management of WRCC in clinical practice.

The present paper is primarily targeted at allergologists, and hence, causes of WRCC such as pneumoconiosis (asbestosis, silicosis, berylliosis, hard metal diseases, etc.), interstitial diseases and lung cancer will not be addressed.

## Methods

This consensus document was prepared by an EAACI Task Force consisting of an expert panel of allergologists, pneumologists and occupational physicians and was reviewed and accepted by the EAACI Executive Committee.

The mechanisms, epidemiology, clinical presentations, diagnostic tools and management are based on current literature using a Medline search. A meeting was held to review the findings and reach informal consensus. Further consensus was reached by an informal iterative process with inputs of all panel members into the drafts of the document and 'key messages' or 'suggestions' are provided based on consensus of the expert panel members, because the quality of evidence of published studies in this area would be graded as low, based on case series and unmatched cohort studies.

In April 2012, the expert panel discussed the first written draft version of the document. Key messages, suggestions and changes were included in the draft, and the revised draft was discussed in June 2012 during a dedicated meeting and

then discussed via e-mail communications, to achieve group consensus. All issues that received the agreement of all members were included in the final draft.

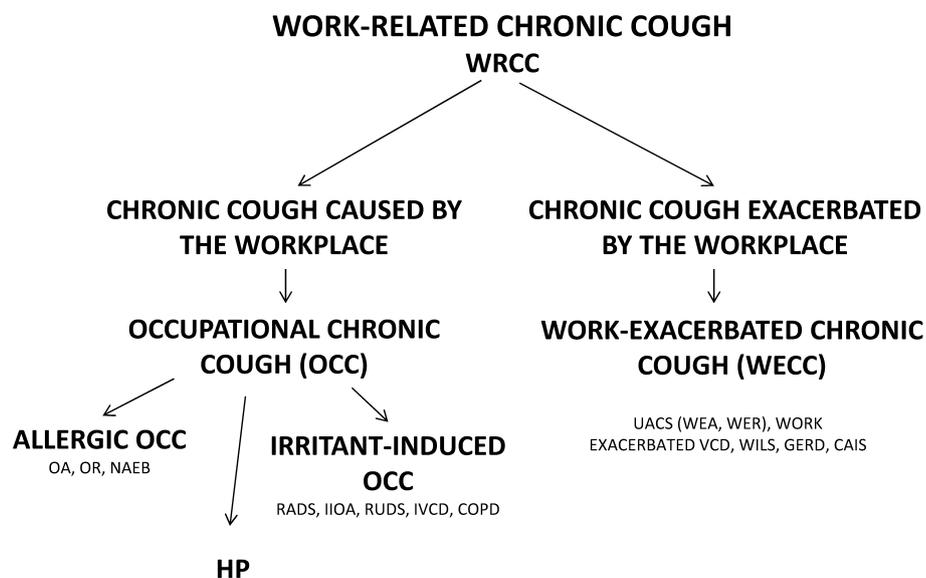
## Definition and classification of work-related chronic cough

The definition of 'cough' has been a matter of debate (7). For the purpose of this paper, we adopt the following consensus clinical definition: 'cough is a forced expulsive manoeuvre, usually against a closed glottis, which is associated with a characteristic sound' (5, 8).

According to symptom duration, cough lasting <3 weeks is termed acute, 3–8 weeks subacute and longer than 8 weeks chronic (3).

Starting from this definition and considering that chronic cough (CC) cannot be considered a disease, but rather a pathologic condition caused by several disorders of both the lower and the upper respiratory tract, we propose the following definition of WRCC, tailored on that of work-related asthma (9):

Work-related chronic cough (WRCC) is one that is present solely or mostly at the workplace, persisting for more than 8 weeks, representing the sole or the main manifestation of a work-related disease (occupational CC – OCC) or of the exacerbation of a pre-existent disease (work-exacerbated CC – WECC), due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace.



**Figure 1** Classification of WRCC. CAIS, cough and airways irritancy syndrome; COPD, chronic obstructive pulmonary disease; ERD, gastroesophageal reflux disease; HP, hypersensitivity pneumonitis; IIOA, irritant-induced asthma; NAEB, nonasthmatic eosinophilic bronchitis; OA, allergic occupational asthma; OR, allergic occupational rhinitis; RADS, reactive airways dysfunction syndrome; RUDS, reactive

upper airways dysfunction syndrome; UACS, upper airway cough syndrome; VCD, vocal cord dysfunction; WEA, work-exacerbated asthma; WER, work-exacerbated rhinitis; WILS, work-associated irritable larynx syndrome; work-exacerbated VCD, work-exacerbated vocal cord dysfunction.

According to the underlying disease, WRCC should be distinguished as follows (Fig. 1):

**Occupational chronic cough (OCC):** CC as the sole or main manifestation of a truly occupational disease, which may be induced by sensitizers (allergic OCC) or by irritants (irritant-induced OCC) or by chemicals or dusts contaminated by microorganisms (hypersensitivity pneumonitis).

**Work-exacerbated chronic cough (WECC):** CC as the only or main manifestation of a pre-existing or concurrent (allergic or nonallergic) disease that is *worsened* by workplace exposures while the disease has not been caused by the work environment.

## Epidemiology

The prevalence of cough in the general population, reported in surveillance studies in many countries in Europe and USA, ranged from 9% to 33%, and it is often related to cigarette smoking (2). Work-related chronic cough has seldom been directly measured in epidemiologic or experimental studies. However, cough is included in many questionnaires used to investigate occupational respiratory diseases, such as asthma and COPD, providing data on cough as a work-related symptom. Studies on WRCC have been reviewed (6, 10), and the principal agents and occupations associated with WRCC are summarized in Table 1.

The population attributable risk of WRCC was estimated at 4–18% (10).

A new risk of WRCC was shown for exposure to dust due to the World Trade Center collapse that caused CC in 8% of fire-fighters and other survivors present during the fall (11).

**Table 1** Causal agents of work-related chronic cough

<i>Occupation</i>
Miners
Cement and glass bottle production
Construction workers
Farming workers
Food industry
Mushroom factory
Wood industry
Dental technicians
Fire-fighters
Bakery
Mechanic and repair jobs
Spice factory
Greenhouse
Cleaners
<i>Agents</i>
Methyl methacrylate
Aliphatic polyamines
Grain and flour mills
Spices
Dust due to World Trade Center collapse
Vapour, gases, dusts, fumes
Cattle and swine confinement farms
Cleaning products
Second-hand smoking

A few studies analysed the risk factors for WRCC. Farming and smoking were found synergistic for CC (12). After adjusting for smoking, age and duration of employment, CC was found to be more common in males (13). Mechanic and repair jobs as well as cleaning and building service occupations were associated with increased incidence of respiratory symptoms, particularly new-onset CC and chronic phlegm (14). A population-based study showed an association between occupational exposure to vapours, gases, dusts and fumes and chronic cough, mostly in female (15).

**Key message:** the population attributable risk of WRCC is estimated to be 4–18%.

## Pathogenesis

Chronic cough may arise from exposure to work-related agents acting through immunological mechanisms, nonimmunological irritant mechanisms or both. The pathogenesis of CC will depend on the underlying disease, the causal agents and the involvement and activation of immune inflammatory or irritant pathways.

A cough reflex can be triggered by several inflammatory and mechanical changes in the airways and by inhalation of chemical and mechanical irritants, usually from upper airway sites (16, 17). Cigarette smoking is the most important risk factor for cough and sputum production (18), and cough is also commonly associated with exposure to environmental pollution, especially PM10 particulates (19).

Sensory nerve receptors involved in cough pathways are defined by their conductive properties as rapidly adapting receptors (RARs), slow-adapting receptors (SARs) or C-fibre receptors, which can be selectively activated by different physical and chemical stimuli (2). Chronic cough is often associated with an increased response to tussive agents such as capsaicin or citric acid. This cough hyper-reactive response could result either from an increased sensitivity of cough receptors or from changes in the cough centre (2). In individuals exposed to organic solvents during work, the cough sensitivity was associated with changes in the levels of nerve growth factor in nasal lavage (20). The transient receptor potential vanilloid type 1 (TRPV1) is the capsaicin receptor present in the plasma membrane of sensory neurons innervating both the upper and lower airways, while TRPA1 channels, co-expressed with TRPV1 in sensory neurons, are stimulated by acrolein, crotonaldehyde and other aldehydes known to stimulate cough reflex during occupational exposure. Furthermore, TRPA1 channels play a pivotal role in response to pollutants, both originated from cigarette smoke or oxidizing agents and from other irritants in the air (21, 22). In occupational CC, the stimulation of cough receptors mainly occurs via environmental irritant stimuli and afterwards by endogenously produced irritants such as reactive oxygen species (ROS). The duration of the irritant exposure leads to the chronicity of cough. In nonoccupational conditions, oxidative stress, endogenous irritants and inflammation are mainly responsible for CC.

### The role of inflammation

Inflammation is one of the most common conditions associated with CC. Most of these conditions, like asthma, cough variant asthma and nonasthmatic eosinophilic bronchitis (NAEB), are associated with eosinophilic inflammation (23). Eosinophils are likely to lead to an up-regulation of the cough reflex sensitivity via either indirect mechanism (disruption of airway epithelium) or direct interactions with airway nerves. However, the results of clinical trials with anti-IL-5 suggest that eosinophilic inflammation is unlikely to be crucial for the development of cough and the importance of other mechanisms such as mast cell interactions with superficial nerves should be investigated (14, 24).

In patients with nonasthmatic chronic cough, an increase in mast cells, eosinophils and histamine, as well as increase in neutrophils, lymphocytes, interleukin (IL)-8 and tumour necrosis factor (TNF)- $\alpha$ , has been reported (25–27) in BAL.

Remodelling features, such as sub-basement membrane thickening, found both in asthmatic and in nonasthmatic cough, seem to be linked to CC, rather than to asthma (28). The interaction between inflammation and structural changes in the airways of patients with CC may be a vicious cycle of cough persistence, because the remodelling changes may enhance cough reflex at sensory (afferent) levels through interaction with inflammation (e.g. increase in histamine or prostanoids, substance P, calcitonin gene-related peptide (CGRP), reduced pH or chloride levels), whereas cough itself may induce remodelling (23).

Airway inflammation can affect the cough reflex by increasing the mechanical sensitivity of the RAR fibres or by causing a switch to RAR neuron-synthesized neuropeptides (tachykinins and CGRP) in the airways or by activating C-fibre through the stimulation of transient receptor sensitive to vanilloid molecules (TRPV-1) like capsaicin (29).

Neurogenic inflammation, present in the airways and produced by neuropeptides released from peripheral ending of TRPV-1, seems to have a controversial role in the induction of cough, but a more evident role in exaggerating cough induced by other stimuli (30).

Airway inflammation can also be a direct cause of TRPV-1 stimulation because this receptor is activated by different stimuli including lipoxigenase metabolites of arachidonic acid and leukotriene B<sub>4</sub> (31). Bradykinin also sensitizes TRPV-1 by diverse intracellular mechanisms. Recently, single-nucleotide polymorphisms (SNPs) in transient receptor potential channels (TRP) were associated with cough among subjects without asthma, and they may enhance susceptibility to cough in subjects with workplace-irritant exposure (15).

Goblet cell hyperplasia, another effect induced by airway inflammation, may stimulate cough through the resultant mucous hypersecretion (32). Cigarette smoke can also induce conditions that may activate the afferent limb of the cough reflex and trigger cough airway inflammation and mucus hypersecretion and impair mucociliary clearance (33).

**Key message:** the pathogenesis of chronic cough depends on the underlying disease, the work-related agent and the involvement and activation of immune inflammatory or irritant pathways. Inflammation is one of the most common conditions associated with chronic cough, and most conditions associated with this symptom are associated with eosinophilic inflammation.

### Diseases causing WRCC

Exposure to workplace sensitizers and irritants may give rise to CC due to both new-onset and work-exacerbated diseases involving the lower and upper respiratory tract. Some of these diseases are common and widely studied, while others are less common and hence less investigated (Tables 2 and 3).

#### Common causes of WRCC

##### *Work-related asthma (WRA)*

Work-related asthma (WRA) encompasses two main conditions: (1) occupational asthma (OA): asthma caused by the workplace, either of the immunological (sensitizing) or of the nonimmunological (irritant-induced) types (9, 34), and (2) work-exacerbated asthma (WEA) for which pre- or co-existing 'personal' asthma is exacerbated by the workplace (34, 35).

In a series of more than 200 participants (36), it has been shown that wheezing was present in 88% of subjects with OA and coughing in 83%. However, wheezing, in contrast to coughing, was a symptom that was significantly predictive of the presence of OA, especially in subjects with OA due to high molecular weight agents. It is not known if coughing is more frequent in subjects with OA due to high as compared to low molecular weight agents. Cough is also common in subjects with WEA because exposure of subjects with asthma to nonspecific irritants like those present in many workplaces frequently induces coughing. Moreover, cough can also be present in subjects presenting with work-related respiratory symptoms without asthma, being reported by 63% of 69 subjects described in a series (37). In the same study, a similar proportion of subjects with WRA reported cough.

##### *Work-related rhinitis and upper airway cough*

Rhinitis and rhinosinusitis are recognized as diseases that may trigger CC. In a recent study among 372 patients with CC, perennial rhinitis and rhinosinusitis appeared to be the primary trigger for CC in 56% of the subjects (38). Upper airway disease was present in 95% of the asthmatics with cough and in 6% of the asthmatics without cough. In 76% of the subjects with CC and upper airway disease, laryngeal hyper-responsiveness (i.e. vocal cord adduction on histamine challenge) could be demonstrated. Probably, postnasal drip and inflammatory material stimulate pharyngolaryngeal receptors (39). Rhinitis appears to be an independent risk factor for the development of CC (OR: 1.8, 95% CI: 1.2–2.6) (40).

**Table 2** Clinical characteristics of occupational chronic cough (OCC) syndromes

Disease causing OCC	Associated symptoms & signs	Confirmatory procedures	Reference
Allergic occupational asthma (OA)	Cough, wheezing, chest tightness, shortness of breath related to work	Immunological tests, serial assessments of PEF/FEV <sub>1</sub> , NSBH and/or sputum eosinophils at work, SIC in the laboratory or at the workplace	9, 27, 76
Chronic obstructive pulmonary disease (COPD)	Chronic cough, dyspnoea, chronic sputum production	Spirometry: persistent airflow limitation (postbronchodilator FEV <sub>1</sub> /FVC < 0.70)	72
Occupational nonasthmatic eosinophilic bronchitis (NAEB)	Isolated cough related to work	Immunological tests, absence of variable airflow obstruction and NSBH, increase in bronchial eosinophilia during SIC or at the workplace	58, 60, 76
Reactive airways dysfunction syndrome (RADS), irritant-induced asthma (IIOA)	Acute onset of cough after a single or multiple high-level irritant exposures	Chronology of symptom onset and demonstration of NSBH	88, 89
Allergic occupational rhinitis (OR)	Sneezing, nasal pruritus, rhinorrhea, cough, conjunctivitis related to work	Immunological tests, specific nasal provocation test in the laboratory, workplace assessment of nasal patency, inflammation and/or nonspecific hyper-responsiveness	73
Irritant-induced vocal cord dysfunction (IVCD) syndrome (paradoxical vocal fold motion disorder).	Throat tightness, globus pharyngeus, cough, inspiratory wheezing/stridor, rather than expiratory as is usual in asthma, poor response to inhaled bronchodilator; onset of symptoms within 24 h after a single high-level exposure to irritating gas, smoke, fume, vapour, mist or dust. During an acute episode, the wheeze may be loudest over the neck and upper thorax, but transmitted to the chest wall. Hyperventilation during an episode may lead to symptoms such as tingling of the perioral area and digits, dizziness and light headedness. Frequently, episodes have a rapid onset and resolution	Spirometry: truncated inspiratory flow-volume loop during attack of symptoms Laryngoscopy: paradoxical adduction of the vocal folds with a 'posterior chink' (glottic opening) during inspiration	74, 90–92
Reactive upper airways dysfunction syndrome (RUDS)	Chronic rhinosinusitis (nasal and/or sinus inflammation) initiated by high-level exposure to inhaled irritants, with recurrence of symptoms after re-exposure to irritants, often associated with GERD and RADS	Diagnosis depends largely on history without quantifiable diagnostic tests.	65, 93
World Trade Center Cough (WTCC)	Onset of cough after massive, short-term exposure to respiratory irritants (inorganic dust, fumes, products of pyrolysis and other respirable materials frequently associated with GERD and UACS)	History of acute high-level exposure to chemicals or dusts; absence of NSBH	65, 94
Hypersensitivity pneumonitis (HP)	Recurrent influenza-like symptoms (chills, fever, sweating, myalgia, lassitude, headache and nausea); symptoms occurring 2–9 h after antigenic exposure in acute forms; inspiratory crackles	Evidence of exposure to appropriate antigen by history or by the detection of antigen-specific precipitating IgG antibodies in serum; consistent findings on chest radiograph and/or HRCT; decreased carbon monoxide diffusion capacity (Dlco); bronchoalveolar lavage fluid lymphocytosis; granulomas on lung biopsy (usually not required)	61, 95, 96

**Table 3** Clinical characteristics of work-exacerbated chronic cough (WECC) syndromes

Disease causing WECC	Associated symptoms & signs	Confirmatory procedures	References
Work-exacerbated asthma (WEA)	Work exacerbation of wheezing, chest tightness, shortness of breath and cough related to work in pre-existing or coincident asthma	Exclusion of allergic occupational asthma	97
Work-exacerbated upper airway cough syndrome (UACS) due to work-exacerbated rhinitis (WER) or chronic rhinosinusitis (WERS)	WEA: work exacerbation of sneezing, nasal pruritus, rhinorrhea, cough and conjunctivitis in pre-existing rhinitis WERS: work exacerbation of sensation of drainage into the posterior pharynx, tickle in the throat, throat clearing and cough; nasal congestion, nasal discharge, hoarseness, cobblestone appearance of the oropharyngeal mucosa	WER: exclusion of allergic occupational rhinitis. WERS: combination of symptoms, physical examination, radiographic/CT findings.	5, 39, 73, 98
Work-exacerbated vocal cord dysfunction VCD syndrome	Pre-existent VCD triggered by workplace exposure to odours and irritants, poor response to inhaled bronchodilator; frequent association with UACS, GERD and laryngopharyngeal reflux	Spirometry: truncated inspiratory flow-volume loop during attack of symptoms Laryngoscopy: paradoxical adduction of the vocal folds with a 'posterior chink' (glottic opening) during inspiration	52, 57
Work-associated irritable larynx syndrome (WILS)	Episodic laryngospasm and/or dysphonia, globus pharyngeus, visible or palpable evidence of tension or tenderness in laryngeal muscles, specific workplace trigger (e.g. odours, fumes, perfumes and cleaning agents); frequent association with GERD	Extrathoracic hyper-responsiveness (decrease in MIF50 equal or >20% or 25%) on histamine bronchoprovocation testing	38, 54, 55, 75
Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (laryngopharyngeal reflux)	Heartburn, acid regurgitation, postprandial cough, hoarseness, excess mucus, throat clearing, globus pharyngeus	Endoscopy, 24-h oesophageal pH and impedance monitoring	99

Therefore, it is plausible that occupational rhinitis (OR) may be a trigger for WRCC (4). However, very few studies addressed the relationship between WRCC and OR. Most studies describe nasal symptoms (if reported at all), cough, wheeze or dyspnoea as separate consequences of specific occupations such as hairdressers (41), bakers (42) or students of agricultural schools (43). In one study on a mushroom farm, 42 of 63 workers reported CC after work. The authors attempted to subdivide the subjects according to possible causes. In 18 of 42 workers, CC was attributed to a runny nose and postnasal drip (44), whereas in other subjects cough could be attributed to hypersensitivity pneumonitis, organic dust toxic syndrome, CVA and NAEB. Although conceivable, few data on work-related rhinitis as a trigger for WRCC are available. In spite of the lack of sufficient data, subjects with WRCC should be asked and examined for the presence of work-related rhinitis.

#### *Chronic bronchitis and chronic obstructive pulmonary disease*

Cough is a defining feature of chronic bronchitis and is commonly associated with chronic obstructive pulmonary disease (COPD), particularly in smokers. There is a coherent body of evidence that both conditions are associated with workplace exposures to respiratory irritants (45) although some doubt that the general associations are entirely causal (46). Thus, while there is strong evidence that prolonged exposure to coal mine dust can induce COPD, independently of smoking (47), and moderate evidence that the same is true for crystalline silica (48), grain dust (49), cotton dust (50) and welding fume (51), in each case, perhaps, modified by cigarette smoking, far less is known about the aetiological effects of occupational exposure to dusts and fumes more generally. In contrast, there seems little doubt that exposures to high concentrations of respiratory irritants in the workplace may exacerbate the cough of pre-existing chronic bronchitis or COPD.

**Key message:** WRA work-related rhinitis and COPD are the commonest causes of WRCC.

### Less common causes and diseases mimicking WRCC

#### *Work-related laryngeal syndromes*

Workplace exposures have been reported as precipitants for the development of nonorganic laryngeal dysfunction and also as triggers for recurrent symptoms. Laryngeal dysfunction may masquerade with symptoms suggestive of asthma and may coexist with asthma (52). Unfortunately, there is a lack of consensus regarding clinical features and terminology of laryngeal dysfunction (53).

*Irritable larynx syndrome.* The term 'irritable larynx syndrome' (ILS) has been used to describe laryngeal hyper-responsiveness masquerading as asthma, upper airway obstruction or voice disorders. A recent study showed that laryngeal hyper-responsiveness was highly prevalent in patients with CC due to various conditions (i.e. chronic rhinosinusitis, gastroesophageal reflux disease, unexplained CC and asthma), but was rare in asthmatic patients without CC (38). The term 'work-associated ILS' (WILS) has been proposed to describe a condition including other laryngeal symptoms such as acute dysphonia (muscular tension dysphonia), sensation of tension in the throat (globus pharyngeus), recurrent cough and sometime dysphagia, with a specific sensory trigger present at the workplace (54, 55).

*Vocal cord dysfunction (VCD).* Is probably the most well-known manifestation of nonorganic dysfunctional laryngeal behaviour which may mimic cough or more commonly accompany cough, and should be considered in differential diagnosis. Vocal cord dysfunction has a complex and multifactorial pathophysiology where the main feature is paradoxical adduction of the vocal cords causing dyspnoea attacks. The mechanism behind the vocal cord adduction is a hyperfunctional laryngeal reflex that protects lower airway from aspiration. The most common presentation of VCD mimics asthma (56, 57). This condition remains often underdiagnosed.

A lack of prospective cohort studies makes it difficult to evaluate the incidence of VCD. Also, the definition and diagnostic criteria vary from centre to centre, which makes it difficult to interpret the studies of prevalence (57).

Morris et al. (53) proposed a classification for laryngeal movement disorders into three forms: (1) psychogenic, (2) exercise VCD and (3) irritant VCD (IVCD). Occupational exposures to airborne irritants may result in inflammation of the upper respiratory tract and in IVCD. Finally, pre-existent VCD can be exacerbated by workplace exposure to odours and irritants, leading to a condition of work-exacerbated VCD.

#### *Others*

*Nonasthmatic eosinophilic bronchitis.* Nonasthmatic eosinophilic bronchitis is a condition characterized by CC in patients without symptoms or objective evidence of variable airflow obstruction, normal nonspecific bronchial responsiveness

(NSBH) and sputum eosinophilia (58, 59). When it develops as a consequence of work exposure, it is considered a variant syndrome of OA.

Nonasthmatic eosinophilic bronchitis has been recognized as an important cause of CC, because it is present in 10–30% of patients referred to specialists. However, the burden of occupational factors to this specific condition has not been specifically investigated.

The occurrence of neutrophilic bronchial inflammation without the functional characteristics of OA has also been described (60).

*Hypersensitivity pneumonitis (HP).* Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, is a granulomatous disease of the lung due to immune reactions following repeated inhalation of organic dust, chemicals or metal-working fluid contaminated by microorganisms especially encountered in the occupational environment (61).

Hypersensitivity pneumonitis presents in three overlapping clinical forms: acute, subacute and chronic or insidious (61). Cough is a common symptom of HP in addition to dyspnoea, chills and fever (4).

*Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux.* Gastroesophageal reflux disease is a common disorder in the general population. A range of symptoms other than heartburn and acid regurgitation can be associated with GERD, including CC (62). The causal relationship between GERD and work remains controversial. Although GERD symptoms can be aggravated by intense physical activity and high exposure to irritant substances, there is no evidence that work exposures can induce the development of GERD, with the exception of some specific occupations (i.e. professional singers, wind players and glass blowers) (62, 63). Gastroesophageal reflux disease has been found to be one of the most frequently reported conditions among rescue and recovery workers of the World Trade Center, and high-level irritant exposures might also trigger reflux as a cause of cough in this patient population (4, 64, 65).

*World Trade Center Cough Syndrome.* The World Trade Center Cough Syndrome is a chronic cough syndrome firstly described in fire-fighters who were exposed to a variety of inhaled materials during and after the collapse of the World Trade Center (11). Due to the exceptionality of that event, it is simply reported in this context as an historical phenomenon.

*Cough and airways irritancy syndrome.* Some patients report WRCC in the absence of any demonstrable explanation. Some studies have suggested that WRCC in workers exposed to high levels of respiratory irritants (e.g. sulphur oxides, ozone and hydrochloric acid in glass bottle workers (66, 67) and chilli-exposed workers (68)) is associated with an enhanced cough reflex response to capsaicin, which has been termed 'cough and airways irritancy syndrome'.

**Key message:** less common diseases that may present as WRCC have been described and include the laryngeal

syndromes, the nonasthmatic eosinophilic bronchitis, the hypersensitivity pneumonitis, the gastroesophageal and laryngopharyngeal reflux, the vocal cord dysfunction, the cough and airways irritancy syndrome and the World Trade Center Cough Syndrome.

### Diagnostic approaches to WRCC

The major challenge in patients with WRCC is to distinguish OCC (i.e. resulting from an occupational disease) from WECC (i.e. cough worsened at work, but resulting from a condition unrelated to the work environment). A consensus diagnostic algorithm has been elaborated (Fig. 2) based on currently available scientific evidence and the expert panel's clinical expertise. This section will also address specific diagnostic tools for the assessment of CC.

### Diagnostic algorithm

The first step of the diagnostic investigation (Fig. 2) includes a detailed clinical and occupational history and physical examination (4). The occupational history should inquire about direct and indirect exposures at the workplace at the time of symptom onset. Key issues of clinical history are summarized in Table 4. Nevertheless, studies have shown that the clinical characteristics and timing of cough and associated symptoms have a low predictive value for identifying the aetiologic mechanism (69, 70). The physical examination aims at identifying conditions that may cause or aggravate cough (e.g. wheeze, nasal inflammation, postnasal drip or cobblestone appearance of the posterior pharyngeal mucosa) (Tables 2 and 3).

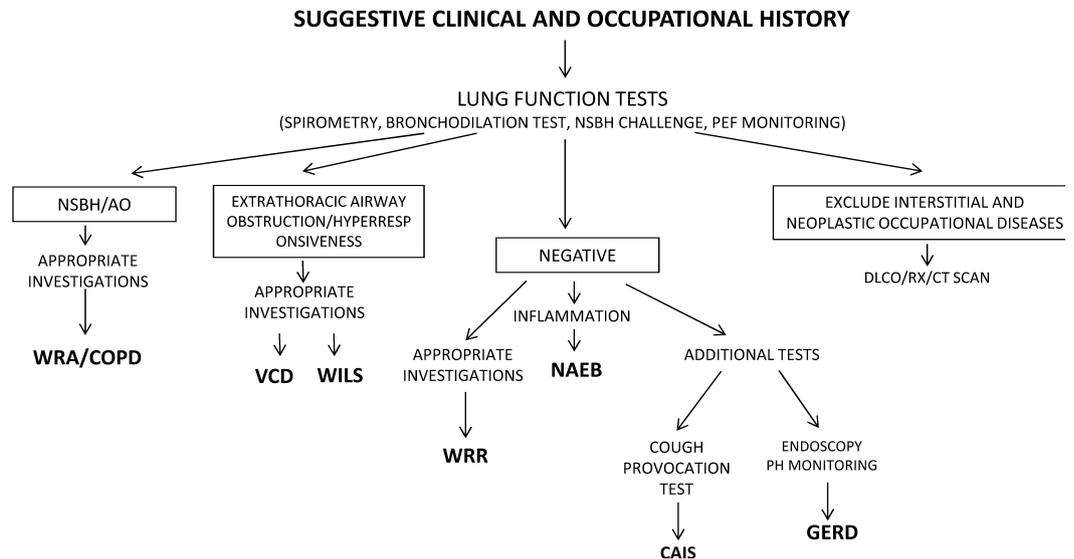
The possibility of exposure to agents able to induce interstitial lung diseases and lung cancer should always carefully

**Table 4** Key issues of clinical history for the investigation of WRCC

Duration of the cough (more or <8 weeks)
Time elapsed between start of exposure and symptom onset (i.e. latency period)
Temporal relationship between cough and work (i.e. improvement on holidays or weekends and rest days; exacerbation by specific exposure to substances or tasks at the workplace)
Any history of accidental high-level exposures to irritants at work
Pre-existing conditions that may cause or contribute to chronic cough (i.e. smoking, atopic diseases, gastroesophageal reflux disease, rhinosinusitis, treatment with angiotensin-converting enzyme inhibitors)
Other symptoms that may suggest a potential cause of chronic cough

be taken into account, and radiological examination (X-ray and/or CT scan) as well as carbon monoxide diffusion capacity (DLCO) measurement should be performed to exclude such diseases. Once the latter have been excluded, the diagnostic workup should firstly deal with the most common causes of WRCC, namely WRA, rhinitis and COPD; only afterwards should the less common causes of WRCC be considered.

Evaluation of WRA includes spirometry and bronchodilation test, measurement of NSBH by means of nonspecific bronchial challenge, and serial peak expiratory flow (PEF) monitoring, according to the current guidelines (9, 71). Nonspecific bronchial hyper-responsiveness should be assessed preferably within 24 h of exposure to the suspected workplace and at the end of a working week, because they may become rapidly normal after cessation of exposure to the causal agent. The presence of variable airflow obstruction



**Figure 2** Diagnostic algorithm. AO, airflow obstruction; CAIS, cough and airways irritancy syndrome; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; NAEB, nonasthmatic eosinophilic bronchitis; NSBH, nonspecific bronchial hyper-responsiveness; VCD, vocal cord dysfunction; WILS, work-associated irritable larynx syndrome; WRA, work-related asthma.

nonasthmatic eosinophilic bronchitis; NSBH, nonspecific bronchial hyper-responsiveness; VCD, vocal cord dysfunction; WILS, work-associated irritable larynx syndrome; WRA, work-related asthma.

and/or NSBH steers the investigation to the diagnosis of WRA (9) as the cause of WRCC.

Evaluation of COPD includes spirometry and bronchodilation test to demonstrate persistent airflow limitation (72).

If variable or persistent airflow obstruction and/or NSBH and/or PEF variability are absent, in the presence of nasal symptoms work-related rhinitis should be considered (73).

If diagnostic criteria for WRA and/or COPD and/or work-related rhinitis are not satisfied, the less common causes of WRCC should be carefully evaluated (Fig. 2).

#### *Irritant vocal cord dysfunction syndrome*

Features that suggest VCD are reported in Table 2. The diagnostic criteria for VCD include (1) suggestive clinical symptoms, (2) laryngoscopic evidence of vocal cord adduction during an acute episode and (3) confirmatory pulmonary function test findings of an abnormal flow-volume loop (53). Standard spirometry can demonstrate a flattened inspiratory loop on the flow-volume curve reflecting variable extrathoracic airway obstruction consistent with VCD (53, 57). Inspiratory flow limitation is defined by a maximal inspiratory flow (MIF) at 50% of forced vital capacity (MIF50)/maximal expiratory flow at 50% of forced vital capacity (MEF50) ratio of <1. To confirm the presence of VCD due to workplace irritants (IVCD), the criteria proposed by Perkner et al. (74) should be satisfied (Table 5). Pre-existing documented VCD and its symptoms exacerbation by exposure to workplace odours or irritants may satisfy the diagnostic criteria proposed for work-exacerbated VCD (Table 5).

**Table 5** Diagnostic criteria for irritant VCD and work-exacerbated VCD (from ref 74 mod)

Irritant VCD	Work-exacerbated VCD
Documented absence of preceding VCD or laryngeal disease	Documented pre-existing VCD or laryngeal disease
Onset of symptoms after a single specific exposure or accident	Onset of symptoms not related to workplace
Exposure to an irritating gas, smoke, fume, vapour, mist or dust	Exposure to an irritating gas, smoke, fume, vapour, mist or dust
Onset of symptoms within 24 h after exposure	Exacerbation of symptoms at workplace
Symptoms of wheezing, stridor, dyspnoea, cough or throat tightness	Symptoms of wheezing, stridor, dyspnoea, cough or throat tightness
Abnormal direct laryngoscopy for VCD either in the asymptomatic state, during symptoms, or with a provocative study	Abnormal direct laryngoscopy for VCD either in the asymptomatic state, during symptoms, or with a provocative study
Exclusion of other types of a significant vocal cord disease	Exclusion of other types of a significant vocal cord disease

#### *Work-associated irritable larynx syndrome*

According to Morrison et al. (54), criteria for diagnosing ILS should be (1) episodic laryngospasm and/or dysphonia with or without globus or CC (2) visible or palpable evidence of tension or tenderness in laryngeal muscles and (3) a definite symptom-triggering stimulus (Table 3). Changes in maximal inspiratory flow (MIF) during histamine challenge test have been used for the assessment of extrathoracic airway hyper-responsiveness (38, 75). A decrease in MIF50 equal or >20% (75) or 25% (38) at a concentration of histamine equal to 8 mg/ml or lower has been considered to reflect laryngeal hyper-responsiveness and an 'irritable larynx'. Diagnostic criteria for WILS have recently been proposed (Table 6).

#### *Nonasthmatic eosinophilic bronchitis*

In the absence of variable airflow obstruction and/or NSBH, when cough is the only symptom, the presence of eosinophilic airway inflammation should be investigated using the induced sputum technique or the measurement of exhaled NO (76, 77), to evaluate the possibility of NAEB as cause of WRCC (58, 59) (Fig. 2). The diagnostic criteria for occupational NAEB are reported in Table 2.

#### *Hypersensitivity pneumonitis*

Key steps for the diagnosis (4, 78) include (1) a careful history taking, (2) pulmonary function tests, (3) chest radiography and computed tomography, (4) BAL, (5) specific serum IgG antibodies to the suspected agent and (6) lung biopsy. Occasionally, a specific challenge may be needed to confirm the diagnosis and to identify the causative agent.

### Other causes

The evidence of a 'workplace' sensory trigger and cough provocation testing with capsaicin, citric acid and low-chloride solutions can be used to investigate the 'cough and airways irritancy syndrome', which is associated with an enhanced cough reflex response.

Endoscopy, multichannel impedance and pH monitoring should be used to confirm GERD/laryngopharyngeal reflux.

**Table 6** Diagnostic criteria for work-associated ILS (from ref. 55)

Episodic symptoms attributable to laryngeal and/or supraglottic tension:
Major symptoms
Dysphonia (muscular tension dysphonia)
Dyspnoea with sensation of airflow limitation at the level of throat
Minor symptoms
Globus (sensation of lump or constriction at the level of throat)
Chronic cough
Presence of a 'workplace' sensory trigger:
Airborne substance, odour
Confirmation of laryngeal tension and exclusion of organic laryngeal pathology by specialist voice disorders clinic.
'Probable' WILS = 1 (at least one major symptom) + 2
'Definite' WILS = 1 (at least one major symptom) + 2 + 3

### Specific diagnostic tools for assessing chronic cough

#### *Assessing the severity of cough*

Cough diaries and visual analogue scales (VASs) are simple, highly repeatable over short periods and responsive tools that are commonly used in clinical studies to evaluate cough severity (79, 80), but these instruments still lack thorough validation against objective parameters.

Ambulatory devices for cough recording still lack standardization, and adequately validated cough monitors are currently not commercially available (80).

These methods may be useful to suspect the work relatedness of cough (i.e. presence at work, improvement or disappearance off work, higher severity at work, lowest severity off work). Unfortunately, at present, no study has explored this approach.

#### *Rhinolaryngoscopy*

Flexible fiberoptic rhinolaryngoscopy may reveal evidence of chronic rhinitis, postnasal drip, chronic inflammation of the pharynx, with a cobblestone appearance of the posterior wall, and features suggestive of laryngopharyngeal reflux (i.e. aryepiglottic fold swelling and posterior commissure thickening (pachyderma)). These features are, however, nonspecific, and GERD/LPR should be confirmed using multichannel impedance and pH monitoring.

Laryngoscopy performed during a (provoked) attack of symptoms may be considered as the key procedure for identifying the paradoxical adduction of the vocal folds (81): early paradoxical adduction of the vocal folds with the formation of a posterior diamond-shaped gap ('posterior chink') during inspiration (53, 57).

#### *Cough provocation testing*

Cough reflex sensitivity has been assessed using diverse methods (i.e. single-breath and tidal breathing concentration-response challenges) and various tussigenic stimuli (i.e. capsaicin, citric acid and low-chloride solutions). Because there is wide interindividual variation in cough reflex sensitivity within the normal population, an individual cough challenge data have no clear diagnostic implication (8).

**Key message:** the diagnostic approach to a patient with WRCC should firstly consider the commonest diseases known to present as chronic cough and subsequently consider the less common diseases in the differential diagnosis.

**Key message:** a broad spectrum of diseases may present as chronic cough; hence, a multidisciplinary approach is necessary to achieve a definite diagnosis.

### Management

The key to successful management is the identification of one or more causative agents in the workplace. Where a single agent is indicted, such as in cases of OA, OR, HP or NAEB, then attention may be directed at it alone. In cases where the

aetiology is less well defined, such as those where a broadly irritant atmosphere is considered responsible for the induction or, more commonly, the persistence or aggravation of cough, then wider attention to exposure(s) may be necessary. In either instance, the main aim of management should be the elimination of further exposure(s). Where the underlying disease is allergic OA, there is reasonably strong evidence that a better symptomatic outcome is achieved by exposure elimination than by exposure reduction (82, 83). The same may not be true in HP or irritant-related disease (e.g. ILS, VCD) where exposure reduction may be an appropriate alternative to complete elimination (84, 85). If an individual strategy of exposure reduction is followed, then its success or otherwise should be monitored by regular clinical review.

Control of exposure is the duty of the employer and should broadly follow standard, hierarchical guidance. The first option to be considered is removal of the offending agent from the process; where this is not possible, subsequent options include containment of the process and similar engineering controls or, less satisfactorily, the provision or improvement of adequate exhaust ventilation. Only if these are impossible or inappropriate should consideration be given to the use of appropriate respiratory protection or, in the last resort, relocation of the employee. There is very limited evidence that the use of a face mask is effective in controlling the symptoms of OA, but it may be a valuable solution in cases of HP or irritant-related CC.

The relative effectiveness of different pharmaceutical approaches to chronic cough is usefully summarized elsewhere (86). While there is no published evidence on their value in the treatment for WRCC, it is likely that they will be relatively ineffective in the face of continuing workplace exposure(s). Nonetheless, they have an important role in some cases and in particular those where symptoms are relatively mild and nonprogressing and major adjustments to exposure are considered disproportionate.

Work-related chronic cough can be a cause of impairment of body function or patient's activity and participation, which are dimensions of disability. The level of limitations is usually too low to fulfil criteria of disability required for compensation; thus, in most countries, chronic cough is not compensated. Nevertheless, in some cases, WRCC may interfere with work activity, leading affected workers to leave the job, with possible unemployment. In such cases, compensation may be considered.

**Key message:** the first step to successful management of WRCC is the identification of the causative agents, followed by its removal or containment and in the last resort by the use of appropriate respiratory protection or relocation of the employee.

### Conclusions, unmet needs and research areas

Several upper and lower airway work-related diseases may present with chronic cough; thus, the assessment of patients with CC should include the evaluation of a possible link with the workplace.

Some diseases underlying WRCC, like WRA, are frequently encountered in clinical practice, other are less common, and should always be considered in the differential diagnosis. Due to the broad spectrum of underlying diseases, a multidisciplinary approach, including allergologists, pneumologists, ENT specialists and occupational physicians, is necessary to achieve a definite diagnosis. The present document may be an incentive for further investigations in the comprehension of this common symptom that may be the presentation of a work-related disease.

Certainly, more epidemiological data and studies are necessary to estimate the real prevalence and risk factors for WRCC, the role of exposure to environmental and occupational sensitizers and irritants in its pathogenesis and the interaction with both upper and lower airways. It is necessary to determine the cost and effectiveness of diagnostic algorithms for WRCC and the usefulness of specific diagnostic

tools (e.g. cough diaries and visual analogue scales) in suspecting the work relatedness of cough. Finally, the best management option should be evaluated (i.e. cessation vs reduction in exposure) in order to achieve the best outcome without adverse social and financial consequences for the worker (87).

### Author contributions

This Position Paper is the result of the collaboration of a panel of experts who contributed to the document according to their different experiences and competences, coordinated by Gianna Moscato.

### Conflicts of interest

All authors have no conflicts of interest to declare.

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