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An Official American Thoracic Society Workshop Report: Presentations and Discussion of the Sixth Jack Pepys Workshop on Asthma in the Workplace

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Abstract

The Sixth Jack Pepys Workshop on Asthma in the Workplace focused on six key themes regarding the recognition and assessment of work-related asthma and airway diseases: (*1*) cleaning agents and disinfectants (including in swimming pools) as irritants and sensitizers: how to evaluate types of bronchial reactions and reduce risks; (*2*) population-based studies of occupational obstructive diseases: use of databanks, advantages and pitfalls, what strategies to deal with biases and confounding?; (*3*) damp environments, dilapidated buildings, recycling processes, and molds, an increasing problem: mechanisms, how to assess causality and diagnosis; (*4*) diagnosis of occupational asthma and rhinitis: how useful are recombinant allergens (component-resolved diagnosis), metabolomics, and other new tests?; (*5*) how does exposure to gas, dust, and fumes enhance sensitization and asthma?; and (*6*) how to determine probability of occupational causality in chronic obstructive pulmonary disease: epidemiological and clinical, confirmation, and compensation aspects. A summary of the presentations and discussion is provided in this proceedings document. Increased knowledge has been gained in each topic over the past few years, but there remain aspects of controversy and uncertainty requiring further research.

Overview

Work-related asthma (WRA; encompasses two conditions: occupational asthma [OA; i.e., asthma that is caused by an occupational exposure] and work-exacerbated asthma) is a global issue and is a term that includes OA and work-exacerbated asthma (i.e., asthma that is worsened by an occupational exposure, but not caused by an occupational exposure) (1).

The Jack Pepys Workshop is held every 3 years to discuss WRA and airway diseases (2). The sixth workshop was held in May 2016 and focused on six areas of controversy or

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uncertainty that are considered currently important pertaining to WRA and airway diseases: (*1*) cleaning agents and disinfectants (including in swimming pools) can be irritants and/or sensitizers: how should bronchial reactions be evaluated and risks reduced? (presenter, F. De Blay; discussion leaders, R. M. Agius, and A. Cartier); (*2*) population-based studies of occupational obstructive diseases: what are advantages and pitfalls of databank use, and strategies to adjust for biases and confounding? (presenters, N. Le Moual and P. Henneberger; discussion leaders, J. Beach and R. Hoy); (*3*) damp environments, dilapidated buildings, recycling processes, and molds are an increasing problem: what are the mechanisms and how should causality be established and diagnosis reached? (presenter, D. Heederik; discussion leaders, T. Sigsgaard, I. Folletti, and S. Quirce); (*4*) how useful are recombinant allergens (component-resolved diagnosis [CRD]), metabolomics, and others (presenter, M. Raulf; discussion leaders, J. Sastre, D. Bernstein, and G. Moscato); (*5*) how does exposure to gas, dust, and fumes enhance sensitization and asthma? (presenter, C. Carlsten; discussion leaders, P. Maestrelli, D. Heederik, X. Munoz, and M. Akpinar); (*6*) how should probability of occupational causality in chronic obstructive pulmonary disease (COPD) be determined?—epidemiological and clinical confirmation, objective markers, and compensation aspects (presenters, S. Tarlo and A. Cartier; discussion leaders, P. Harber and R. Merget). Key conclusions were:

- **A.** Cleaning agents and damp, moldy environments both continue to be important causes of respiratory symptoms and asthma among workers and others with exposure, requiring further understanding of mechanisms and appropriate control measures.
- **B.** High mold exposures are related to asthma symptoms and respiratory inflammation, often in the absence of allergic responses, and the relationships are difficult to assess, especially in environments such as offices and schools.
- **C.** There are new methods of identifying specific allergic responses to occupational allergens up to the point of the single molecule, but there is a need for better availability of standardized commercial skin prick test extracts for occupational allergens (ideally standardized), which provide a simple and useful investigation.
- **D.** Controlled human exposure studies have allowed improved understanding of the mechanisms of airway irritant exposures.
- **E.** Occupational COPD is underrecognized and undercompensated at present, despite convincing epidemiologic evidence for the role of occupational exposure to vapors, gases, dusts, and fumes (VGDF).
- **F.** Epidemiologic studies continue to provide important information on risks and risk factors for occupational airways disease, but phenotyping is important, as is good characterization of exposures.

WRA is a term that includes OA and work-exacerbated asthma (1). It has been estimated that at least 15% of adult asthma and of COPD is work related. Some studies have reported that more than 25% of adult working individuals with asthma have exacerbations of asthma at work. The Sixth Jack Pepys Workshop on work-related airway diseases was held in Toronto (ON, Canada) in 2016 and focused on six areas of controversy/uncertainty that were

selected by an organizing committee for their relevance and importance to the scientific and health care community. The workshop format was to have short, formal presentations on each topic, followed by extensive discussions among the invited participants, including aspects of research in progress, allowing informal exchange of current views, recent research, and areas of uncertainty. This proceedings document summarizes aspects of the workshop, including relevant published studies.

Methods

A total of 48 international experts from various disciplines were invited to the workshop, as well as a small number of self-registered participants. Invitees were selected on the basis of publications or other expertise in the area of WRA. Represented specialties included occupational medicine, pulmonary medicine, and allied health workers. Participants disclosed any potential conflicts of interest to the American Thoracic Society (ATS), and were managed in accordance with the policies and procedures of the ATS.

Topics for discussion at the workshop were selected by an International Scientific Committee (J.-L.M., S.M.T., G. Moscato, M.D., University of Pavia, Italy, D. Bernstein, M.D., University of Cincinnatti, OH, J. Beach, M.D., University of Alberta, Alberta, Canada). The program was approved by the ATS' Environmental and Occupational Health Assembly Planning Committee.

After a tribute to Professor Jack Pepys, short presentations were given by internationally acknowledged experts, who briefly reviewed the evidence. Each presentation was followed by brief comments from discussion leaders and then general, extensive discussion. The content of each presentation is available on the Government of Quebec Commission des normes, de l'équité, de la santé et de la sécurité du travail Web site (http://www.csst.qc.ca/en/prevention/reptox/occupational-asthma/jack-pepys-workshop-asthma-workplace/pages/jack-pepys-2016.aspx).

Summaries for this proceedings document were prepared by the co-chairs (J.-L.M. and S.M.T.) who composed the writing committee. The full committee of primary speakers and discussion leaders reviewed and approved the final workshop report.

Theme 1: Cleaning Agents and Disinfectants as Irritants and Sensitizers: How to Evaluate Types of Bronchial Reactions and Reduce Risks

Discussion of this session focused on: (*1*) the distinct types of inflammation caused by irritants and sensitizers; (*2*) the various effects on airways that can be better identified by specific inhalation challenges; (*3*) the propensity of a substance to have an irritant or a sensitizing effect as assessed by using a structure–activity analysis; and (*4*) the modification of the working environment that is essential in the management of affected workers.

Mechanism—Cleaning agents and disinfectants can be either irritants or sensitizers (or both) (3). A definition from the U.S. Occupational Safety and Health Association states: "Irritants are noncorrosive substances that cause temporary inflammation on direct contact with the skin, eyes, nose, or respiratory system by a chemical action at the point of contact"

(3). Irritants can cause epithelial damage, proinflammatory and Th2 responses, neurogenic inflammation, and increased permeability and remodeling of the airway epithelium (4). By assessing, in lymph nodes of mice, the increase of B cells, including B22 and in B220 or IgG^+/IgM B cells, after allergenic and irritant stimulations, a ratio of cells that distinguished the two reactions has been proposed (5). As an interesting example of a product that can be both a specific sensitizer and an irritant, benzalkonium chloride, a quaternary ammonium compound, can induce total IgE and eosinophilic infiltration responses (6), cause bronchoconstriction through mast cell activation and stimulation of neural pathways (7), and also cause specific IgE-mediated sensitization (8).

Human Effects—Occupational exposure to chemicals from cleaning agents can cause several airway effects including sensitizer-induced OA (9), irritant-induced asthma (IIA) (10), work-exacerbated asthma (11), particularly in workers with increased nonspecific bronchial responsiveness (12), and work-associated irritable larynx syndrome, that describes recurrent laryngeal symptoms triggered by sensory stimuli (13, 14).

Specific inhalation challenges can identify sensitizer-induced OA and may clarify the nature of the symptoms presented by the worker (15, 16). If there is suspicion of work-associated irritable larynx syndrome, laryngoscopy at the time of inhalation challenges is justified. Nasal provocation testing may confirm occupational rhinitis, as shown in the case of amines (17). Increased risk of respiratory infection has been reported in children exposed to bleach at home (18).

Public Health—A study in Ontario suggested an increased frequency of complaints related to exposure to cleaning products and odors/scents in recent years (2008–2015) (19). Conversely, in the United Kingdom Surveillance of Work-Related and Occupational Respiratory Disease (SWORD), from 1992 to 2014, an annual decline of 4.5% (95% confidence interval = 6.9–2.0) in the frequency of work-related respiratory diseases due to cleaning agents has been shown, comparable to the decline noted for other agents. The highest incidence rates were in nurses (20), cleaners, and sports and leisure assistants. A third of suspected causative cleaning agents contained aldehydes, another third include chlorine-related agents, whereas the remaining third comprised a variety of other agents (acids and alkalis) (20).

One predictive model is the quantitative structure activity relationship developed to ascertain the likelihood that a chemical can cause OA through a sensitizing mechanism that has a sensitivity of 90% and a specificity of 96%, with an area under receiver operating characteristic curve of 0.95 (21).

Among other strategies, primary prevention includes avoiding: mixing bleach with nitrogen-containing compounds; mixing bleach inadvertently with acid; using bleach in nonventilated rooms; using sprays that may oversaturate the processed material (rather than “wipes” that do not); and avoiding glutaraldehyde by using a less-volatile compound, orthophthalaldehyde. Educational programs and behavioral interventions should be conducted in high-risk workplaces (22, 23).

Management—Workers with OA should be withdrawn from exposure to improve their outcome. If no objective diagnosis can be made, then management is difficult, because symptoms may prevent ongoing work with cleaning products even after various interventions (change in work process, voice therapist, behavioral and pharmacological treatment). Whatever the diagnosis, it is often most practical to modify the working environment and/or changing either the formulation or the content of the cleaning products used. A change to “green products” can also be considered, as these have been associated with less dermal and respiratory health hazards (24). Selecting a process control (such as avoiding spray products) rather than an agent-specific control may be more generalizable, although not always helpful (25). Both the “killing capability” of a cleaning product and possible adverse health effects in health workers need to be considered (26). In some jurisdictions (Ontario and Quebec, Canada), monetary compensation offered by medicolegal agencies may be different if the causal mechanism is judged to be irritant or allergic, further emphasizing need for definitive diagnosis when possible.

Theme 2: Population-based Studies of Occupational Obstructive Diseases by Using Databanks—Advantages and Pitfalls: Are There Strategies to Deal with Biases and Confounding?

After a review on population-based studies of asthma in the workplace, a proposal was made to improve asthma phenotypes and characterization of exposure. In addition, ways to examine the impact of low participation and assess representativeness were presented.

Population-based Surveys—Population-based surveys: (*1*) evaluate the burden of the disease; (*2*) take into account confounding factors; and (*3*) are less affected by a healthy worker effect than workplace-based studies (27), although previous asthma or atopic history have been generally observed to influence job selection. Follow-up of birth cohorts may limit healthy worker effect and yield information on exposure before onset of disease, avoiding estimation of biased associations (28). Specificity should be favored over sensitivity for both the definitions of asthma and exposure (29). A large Estonian databank, besides showing associations between occupational exposure and asthma, showed that the strengths were increased by using more specific asthma definitions (30). One pitfall is that such studies identify WRA and not OA, partly due to lack of information linking ages of onsets of asthma and exposure.

Asthma Phenotypes—Characterization of asthma phenotypes should be improved by including biological markers (e.g., skin prick tests, IgE levels, blood eosinophils, and fractional exhaled nitric oxide, especially for allergic asthma), lung function, and medication prescription, to allow a better understanding of mechanisms. Diagnosis based on asthma drug reimbursement databases has been used in Scandinavia (31). In a French longitudinal study, the number of positive responses about asthma (“have you ever had asthma?”) was positively associated with the number of corticosteroid inhalers dispensed (32). In the American Agricultural Health Study, allergic asthma was defined as adult onset, doctor diagnosed, and allergic status was based on doctor-diagnosed eczema or hay fever (33).

OA may develop in workers who suffered from childhood asthma and experienced remission (34). Asthma recurred in adulthood in over one-third of participants (35, 36). This recurrent asthma phenotype seems to be associated with atopy and airway obstruction (37), but its association with occupational exposure is unknown.

Exposure—Assessment of exposure, especially for specific hazards, is mostly based on self-report, but can be underreported (38), and associations based on this are likely to be biased (39, 40). There has been increased use of job-exposure matrices (JEMs) to evaluate exposure, but this approach should be improved by adding new asthmagens and validating exposure by environmental sampling. A generic, as compared with specific, JEM may not capture exposure to some agents (e.g., latex), and a job–task–exposure matrix may be more appropriate (41). A large birth cohort study in the United Kingdom that used a JEM found that the population attributable fraction of lifetime occupational exposures for adult onset asthma by age 42 years was 16% (95% confidence interval = 3.8–22.0) (42). To improve exposure assessment, more precise and objective tools should be developed. Administrative data may include insufficient details on occupation and workplace. The use of brand names and bar code (43) to identify occupational agents has been proposed. Those seeking to use of geolocation data to assess exposure, as obtained from cell phones, should consider the potential loss of privacy.

Participation and Representativeness—Response rates and representativeness (44) have been examined by social scientists (45). The concern is that low response rates cause biases in the assessment of frequency (e.g., prevalence), variance, and association of outcome with exposure (called selection bias in epidemiology). Popular scientific wisdom suggests that a response rate of at least 60–70% reduces biases. However, response rates are poor indicators of nonresponse bias, explaining only about 11% of the latter based on a meta-analysis of nonresponse bias studies in household surveys (46). A strategy to deal with the impact of nonresponse is to conduct a short survey in subjects who do not participate to obtain data on demographics, risk factors, and health outcome. With data available from nonparticipants, inverse probability of participation weights can be calculated at several steps, with the subsequent up-weighting of responses in those less likely to participate and down-weighting of responses in those more likely to participate (47, 48). The final inverse probability of participation weights can be used to adjust estimates of frequency and association for nonresponse. It is important to note that this and similar strategies have limitations, and implementing them does not guarantee that all bias has been controlled.

Public health surveillance has two functions: (*1*) to discover new potential causes of disease; and (*2*) to estimate prevalence or impact. Whereas the latter is based on “hard data,” the former can rely on simple methods.

Theme 3: Damp Environments, Dilapidated Buildings, Recycling Processes, and Molds: An Increasing Problem—Mechanisms and How to Assess Causality and Diagnosis

In this session, the effects of chronic and acute exposures to molds, as well as working in recycling processes, were reviewed. The mechanisms of these effects are still not fully unraveled.

Chronic Exposure—A meta-analysis showed an increase of 30–50% for several asthma-related symptoms or diagnoses in subjects living in damp or moldy homes (odds ratio 1.53 [95% confidence interval = 1.39–1.68] for wheezing) (49). In the ECRHS (European Community Respiratory Health Survey) study, a relationship was documented between reported indoor mold exposure and asthma in individuals sensitized to *Cladosporium* and *Alternaria*, molds that are more commonly found outdoors (50). Work disability is associated with asthma related to workplace dampness (51).

Few studies have observed causal associations between measured mold exposure and asthma or asthma symptoms, like wheezing (52). There is a correlation between measured fungi in the air of homes and mold damage in schools on the one hand, and some respiratory endpoints on the other (52, 53). In schools, there is no association between moisture and lung function (54), but total viable molds and fungal DNA are associated with more respiratory symptoms (55). However, increased microbial and mold exposure is associated with lower prevalence of atopy, whereas shortness of breath is increased (56). Being exposed to a biodiverse (total and not only fungal) home microbiome, at “acceptable” levels, keeps people healthy, according to a current opinion shared by bacteriologists and mycologists (57, 58). Coexposure to contaminants (pollution, agricultural) should also be considered in models predicting onset and exacerbations of asthma. The future lies in molecular analysis of dust samples that can reveal a whole spectrum of species and their relative abundance (microbiome studies). Cheap sampling approaches exist that can be sent back and forth by mail, reducing logistic costs. Metagenomic analysis of dust samples can assess the complete spectrum of bacterial or mold exposure.

Acute High Exposure—A high proportion (35–40%) of the requests made to the National Institute for Occupational Safety and Health relates to indoor environment quality secondary to dampness and mold. Spores of all species induce inflammation in experimental studies (59), and exposure to high concentrations of spores, such as can occur in dairy farms, is associated with symptoms (60). Accidental exposures to a damp and moldy environment can cause acute respiratory and general health symptoms. In addition, moisture damage in schools may be associated with respiratory symptoms, but with no effects on lung function tests in pupils, according to the HITEA (Health Effects of Indoor Pollutants: Integrating Microbial, Toxicological, and Epidemiological Approaches) study performed in three European countries (53).

Mechanism—Among hypothetical mechanisms, allergic responses, mycotoxin-induced and Toll-like process effects, as well as CD14 polymorphism can be considered. The quality of antigenic preparations used for immunological tests is generally unsatisfactory (61), except for *Alternaria* and *Cladosporium*, which makes identification of specific mold allergy difficult. Around 20% of patients with respiratory symptoms visiting a specialist are allergic to one or another of the limited number of molds tested, so they may be allergic to others that are not tested. There is not a satisfactory correlation between the presence of identified specific IgE and symptoms. In a cohort of children seen from 8 months to 7 years of age, a high Environmental Relative Mouldiness Index and the summation of levels of three mold

genera (including *Aspergillus* and *Penicillium*) in infancy were associated with the development of asthma at age 7 years (62).

Management of Workers and Environment—Many problems are encountered not only in confirming sensitization and in assessing exposure to molds, but also in management. A two-step questionnaire can identify workers for whom an environmental assessment should be performed (61). From a practical standpoint, repairing mold-damaged houses and offices decreases asthma-related symptoms and respiratory infections compared with no intervention (63).

Recycling Process—Several European countries have been concerned with health effects of collecting waste in the 1990s (64). A review of more than 50 studies shows that the prevalence of respiratory symptoms is generally elevated (65). Elevated levels of endotoxin and glucan are found in some cases (66), and normal IgG antibody titres to fungi and increased specific IgE antibodies are reported in a few instances (67). A neutrophilic response and a small cross-week change in total cells in nasal lavage have been reported (68).

Theme 4: Diagnosis of OA and Rhinitis: How Useful Are Recombinant Allergens Component Resolved Diagnosis, Metabolomics, and Other New Aspects?

In this session, there was discussion of advantages and disadvantages of new techniques that may be used in diagnosis of IgE antibody responses to occupational sensitizers to improve sensitivity and specificity of skin tests and *in vitro* specific IgE determinations. Although testing with allergen extract is the standard procedure, for selected allergens, purified and recombinant allergens can be used for *in vitro* assays to determine specific IgE antibodies. Basophil activation tests, when feasible, may be useful when serum specific IgE antibodies cannot be identified, and nasal secretion, tryptase, was discussed as a possible “point-of-care” test.

Allergy skin prick tests have been the most common clinical test indicating the presence of specific IgE antibodies to high–molecular weight allergens, but there are limited available commercial extracts of occupational allergens, and some have low sensitivity (69). For high–molecular weight agents, if standardized extracts are not available, the actual material is potentially useful to test (using a slurry of a material or pricking a plant or food, then pricking the skin [a “prick-by-prick test]) (69). Nevertheless, skin tests are usually not feasible for low–molecular weight sensitizers. The alternative, specific serum IgE assays, are generally less sensitive, but newer tests are being assessed, as detailed subsequently here.

Extracts used for specific IgE assessment are mixtures of allergenic and nonallergenic molecules solubilized from a defined source, and an allergen molecule that comprises proteins or glycoproteins that can be identified with serum IgE of sensitized patients. Purified allergens and recombinant allergens can be used for CRD in immunologic assays as single agents (the singleplex method), or combined in a microarray (multiplex method). They can also be used to spike extracts for testing, and, in the future, may be used as surrogate extracts (70). Use of allergen molecules in an assay can: (*1*) improve the sensitivity by increasing components that are very low in a mixture; (*2*) increase analytical

specificity when there is a defined clinical role of an allergen; and (*3*) act as a marker for cross-reactivity or for specific reactivity with primary sensitization (71). Examples of allergens associated with greater risk of severe responses include wheat Ω 5-gliadin (Tri a 19) in the case of wheat-dependent, exercise-induced anaphylaxis and various storage proteins. Those associated with lower risk include profilin and some PR-10 proteins (71).

CRD and use of cross-reactive carbohydrate determinants can help distinguish natural rubber latex (NRL) allergy that is relevant to the occupational setting (with specific IgE to Hev b 5 and Hev b 6.01), with or without potential cross-reacting clinical allergy to fruits, from sensitization that may be relevant only to food ingestion (due to glycan-associated cross-reactivity) or sensitization that may not be clinically relevant. A total of 15 NRL allergens are characterized (Hev b 1–15), and several are available as recombinant allergens (rHev b 1, 3, 5, 6.01, 6.02, 7, 8, and 11) (72). Spiking of the latex extract with stable rHev b 5 improves *in vitro* diagnostic ability (73). Importance of individual allergens differs in those sensitized due to multiple surgical procedures (e.g., patients with spina bifida) compared with those occupationally sensitized by use of powdered latex gloves. Specific IgE antibodies to Hev b and Hev b 6.01 are strongly associated with positive specific inhalation challenge testing for latex, with a positive predictive value of 96% and a negative predictive value of 56%. Similar results are found for latex k82 (74), whereas reactivity only to Hev b 8 is not relevant for clinical NRL allergy, and isolated Hev b 11 responses may be relevant for allergy to cross-reacting fruits.

In contrast to the potential usefulness of some allergen components in diagnosis of NRL allergy, for bakers' asthma, proteomic approaches with two-dimensional electrophoresis and two-dimensional immunoblotting (75–77) identified no major wheat allergens, although over 35 wheat flour allergens were detected. Limitations to these studies include: (*1*) subjects from different countries, with potentially different exposures; (*2*) different methods; and (*3*) testing with a single or only a few purified proteins in natural or recombinant forms. Use of a wide panel of identified wheat flour major allergens showed differences between grass-allergic patients and bakers (78). Conclusions are that, for routine diagnosis, allergen-specific IgE tests with whole wheat flour extracts have the best diagnostic sensitivity (78). However, CRD might help in future to differentiate between bakers' asthma, grass pollen allergy, and wheat-induced food allergy (e.g., Tri a 19 [Ω 5-gliadin] is not relevant for baker‘s asthma).

Blood basophil activation tests, reflecting a specific IgE-mediated response, require a fresh blood sample, but have been reported to be positive in several allergic occupational airway studies, and correlate with specific inhalation challenge, even when skin tests have been negative (79–86). They have also been used to investigate local nasal allergic responses (87), although there is a need for additional studies to evaluate the sensitivity and specificity of the test.

Nasal secretion tryptase (to identify a mast cell–mediated response) also needs further investigation as a potential "point-of-care" test that could also be useful for local allergic rhinitis (88).

Theme 5: How Does Exposure to Gas, Dust, and Fumes Enhance Sensitization and Asthma?

Mechanisms by which allergic responses and asthma may be induced or worsened by these exposures were the focus of this session. Although common in work environments, most relevant research on mechanisms on these reactions has come from cellular or animal studies with limited human exposure studies. Recent controlled human exposure studies with diesel exhaust particles (DEPs) may reflect effects in occupational settings.

Multiple population studies have shown an association between exposure to air pollutants and increased risk of asthma (89–92). An increased risk of developing asthma associated with self-reported or assumed “low-level or moderate irritant exposures” has also been suggested from epidemiologic studies, and has been listed as possible IIA in the European Academy of Allergy and Clinical Immunology Task Force statement on IIA (4), with examples given as work as cleaners or work with pesticides, and in the wood industry. Although some of these can cause sensitization or IIA (4), low- or moderate-level irritant exposures might have direct effect causing asthma or may enhance an allergic response. Exposures may be expected to be higher in developing countries if there is less adherence to occupational hygiene control measures.

Possible pathways for an enhanced response to allergens with VGDF exposures include: (*1*) VGDF acting as a carrier of allergens; (*2*) increasing epithelial permeability; (*3*) modifying allergens; (*4*) enhancing the host response to allergens by affecting adaptive or innate immunity; (*5*) causing epigenetic changes; or (*6*) neuroimmune effects.

CCR2 chemokine receptor dependence for the monocyte-derived dendritic cell recruitment and allergic Th2 responses after exposure to DEPs has been reported in mice (93).

Potentially not only allergic airway responses, but also irritant airway responses, may trigger eosinophilic inflammation: bronchoalveolar lavage fluid analysis showed increased eosinophils in 30% of subjects with IIA, and increased eosinophil cationic protein compared with other subjects with asthma (94). The importance of understanding mechanisms of irritant effects in WRA include the potential to target prevention and treatment and inform regulations and compensation claims.

A combined effect with allergen exposure is suggested by the finding of an increased risk of childhood asthma at age 8 years among children with early-life coexposure to allergen and nitrogen dioxide or second-hand smoke compared with allergen alone (95). DEP plus ragweed directly instilled into the nose led to greater specific IgE compared with ragweed alone (96, 97). Possible mechanisms for the effects of DEP on nasal responses have been reviewed (98). DEP plus allergen (*Aspergillus fumigatus*), increases specific IgE in rat blood at 4 days after exposure (99), and induces reduction in DNA methylation in promoter of IL-4 and increase in IFN-γ. An increase in bronchoalveolar lavage eosinophils was found in a human exposure study with diesel exhaust (DE) plus a relevant allergen, with a nonsignificant trend to increase in specific IgE (100).

Epithelial damage is reported with human DE exposure (including particles and gases) versus clean air (100, 101). The same authors showed an interaction with glutathione-*S*-transferase theta-1 and DE in the activation of cytotoxic T cells in lung lavage, and in the development of airflow limitation (with glutathione-*S*-transferase theta-1-null plus DE exposure) (100). An epithelial epigenetic effect has been shown: acute exposure to DE and/or allergen alters expression of microRNA and genes, with effects on inflammatory markers associated with asthma (101, 102). There are methylation changes in airway epithelium after acute DE exposure, and exposure–exposure epigenetic interactions caused by DE with allergen exposure. DNA methylation may lead to protein formation via mRNA, resulting in cytokine release and cell recruitment, causing inflammation and asthma exacerbation. However, full details of the mechanisms need further studies separately evaluating the particles and gases.

Preliminary human exposure studies of DE with allergen versus allergen alone were presented. Differences from those reported in a mouse model have been suggested, emphasizing needs for such studies with both animal models and human exposures (103, 104).

Theme 6: How Can the Probability of Occupational Causality in Individuals with COPD Be Determined? Epidemiological and Clinical, Confirmation, and Compensation Aspects

Some issues presented for discussion included: (*1*) difficulties in developing a clinical case definition of work-related COPD; (*2*) causes and the range of individuals and populations at increased risk (should risks be assessed from specific occupations or from self-reported or JEM exposures to VGDF?) (105); (*3*) difficulties in clinical etiological attribution of COPD raised by confounding factors/contributing or underlying risk factors, such as smoking, atopy, α_1-antitrypsin deficiency, and other factors; and (*4*) difficulties in clinical diagnosis in the presence of overlap syndromes, such as asthma/COPD overlap or overlap with bronchiolitis or bronchiectasis.

The 2016 GOLD (Global Initiative for Chronic Obstructive Lung Disease) includes exposure to particles as a risk factor for COPD, including occupational dusts, organic and inorganic, as well as exposure to tobacco smoke and indoor and outdoor pollution (106). In addition, many epidemiologic studies consistently show an increased risk of COPD not only from dust exposures (such as among miners and grain handlers), but also in those with self-reported or with JEM-identified exposure to VGDF (107). This association persists even after adjustment for smoking history, and the risks of developing COPD among smokers are magnified by VGDF exposure with an effect that is synergistic (108, 109). Smoking rates are reduced in recent years, but smoking is relatively more common in at-risk working populations (the highest rates of smoking are in those between ages 20 and 44 yr in North America [110, 111]). Work-related COPD can be considered as COPD caused or aggravated in whole or in part by occupational exposures. Due to greater-than-additive effects of smoking with VGDF exposure, for the individual patient, smoking should be considered as a potential synergistic factor in the development of work-related COPD. Despite the good epidemiologic evidence for work-related COPD, decisions on imputation in an individual

patient are difficult and usually based on estimation of the likelihood that the work environment has caused COPD, and there is no clear clinical case definition.

The 2003 ATS statement concluded from epidemiologic evidence that “a value of 15% is a reasonable estimate of the occupational contribution to the population burden of COPD” (112). A subsequent estimate based on six additional studies, including over 18,000 subjects and a mortality study of over 300,000 subjects, concluded that the population attributable risk of occupation was 0–37%, with a median estimate of 15% (113). Among nonsmokers (five estimates), the range was 27–53%, with a median of 31%. Thus, the occupational attributable risk is greater in nonsmokers, but the odds ratio of developing COPD is greater in those with a heavy smoking history plus VGDF exposure compared with a heavy smoking history alone (108). Ongoing exposure has also been associated with more rapid decline in FEV_1 (114).

Given the high prevalence of COPD in the population, it would be expected that a diagnosis of work-related COPD would be reached in a large number of individuals, and that appropriate workers’ compensation would result. Nevertheless, workshop participants indicated that only a small number of claims each year are accepted for workers’ compensation in Ontario, Quebec, and in Germany. In Germany, claim acceptance may occur for obstructive airway disease that includes asthma and COPD due to irritants. Most of these accepted claims are among hard coal miners with a much smaller proportion of those submitted for other high-irritant exposures (exposure at least 10 yr with a lag time before symptoms of <3 yr), such as welding, lubricants, and farming. Acceptance requires exclusion of dominant, nonoccupational contributing factors, such as smoking or atopy (personal communication, R. Merget, M.D., Ruhr University, Bochum, Germany). Criteria reported in different countries for compensation vary, and there are few published data on the basis for compensation decisions (Table 1). The limited information does not appear to have included more recent understanding from epidemiologic evidence regarding VGDF and magnification of smoking effects. Lack of published criteria for COPD claims leads to difficulty for clinicians in advising their patients regarding likely compensation support.

Difficulties in individual patient’s occupational imputation were discussed, including current frequent lack of clinical ability to objectively assess extent of exposures to VGDF, and objectively validate the extent of a reported smoking history. Although the attribution is based on individual details, the likely basis of a diagnosis derived from epidemiological studies has shown relative risks from occupational exposures that are generally smaller than 2, making it difficult to infer from these “probable” causation from a particular exposure/occupation in an individual. Besides occupations, such as mining or work with grain dust, there is a wide range of exposures reported at some increased risk in epidemiologic studies (28, 115). In some individuals, exposures associated with increased risk of obstructive airways disease (such as nitrogen oxides [116]), or dust from the World Trade Center collapse (117), may have caused airway diseases, such as bronchiolitis obliterans, bronchiectasis, or asthma, that may not have been identified in epidemiologic studies, such as reported by De Matteis and colleagues (28).

Needs for medical surveillance in occupations at high risk of VGDF exposure have been reviewed in the ATS statement on spirometry in the occupational setting (118). Additional research questions were identified (Table 2).

Conclusions

The topics discussed in this workshop are important and relevant to occupational airways diseases.

Cleaning agents and damp, moldy environments both continue to be important causes of respiratory symptoms and asthma among workers and others with exposure, requiring further understanding of mechanisms and appropriate control measures.

High mold exposures are associated with asthma symptoms and respiratory inflammation, often in the absence of allergic responses, but the relationships are often difficult to assess, especially in environments such as offices and schools.

The new methods of identifying specific allergic responses to occupational allergens need to be further investigated for clinical application. There is also need for characterization of occupational allergens to the molecular level. There is an immediate requirement for better availability of high-quality, standardized commercial skin prick test extracts for occupational allergens that provide a simple and useful investigational method.

Controlled human exposure studies will increase understanding of the mechanisms of airway irritant exposures.

Occupational COPD is underrecognized and undercompensated at present. Despite convincing epidemiologic evidence for the role of occupational exposure to VGDF, there is difficulty in developing a clear case definition that would facilitate workers' compensation decisions, and the synergistic role of smoking with occupational exposures needs to be better recognized.

Epidemiologic studies continue to provide important information on risks and risk factors for occupational airways disease, but more specific phenotyping and improved characterization of exposures are needed.

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Table 1

Examples of criteria reported used or recommended for acceptance of occupational chronic obstructive pulmonary disease in different workers' compensation systems

Country or System	Criteria
Canada	Workers' compensation systems have recognized only a few cases of occupational COPD Assessed on a case-by-case basis based on medical "experts" or committees. Ontario: criteria based on age (average loss of FEV_1 with age: 33.6 ml/yr), estimated mg/m^3 respirable dust × number of years (average loss of FEV_1 with dust: 5.8 ml/mg/m^3-yr) estimated as a percentage of causation by reduction for smoking pack-years (average loss of FEV_1 with smoking: 8.5 ml/pack-year) *. The WSIB's standard for allowing COPD is based on doubling of the risk of developing COPD after a cumulative dust exposure of approximately 50 mg/m^3-yr †. No reported estimate for VGDF. Quebec: agreed relationship to work if <20 pack-years and >20 yr exposure to high level of VGDF.
Korea	Compensation is limited to workers exposed to high concentrations of coal mine dust, silica, or cadmium fumes for prolonged periods (119)
France	Accepted if listed in tables (coal and iron mines, cotton, Ar), FEV_1 < 40% predicted and sufficient duration of exposure or if recognized by a committee of three medical experts (when exposures are not listed in the tables and if disability is >25% or death) (120)
Germany	High occupational exposure to irritants, usually for several years Occurrence of symptoms during exposure without or small lag Symptoms with relation to work (not a prerequisite for particulate exposures) No dominant, nonoccupational confounders (atopy, smoking) Phenotype of disease should not be considered (121)
United Kingdom	Recognized if >20 yr exposure of coal face work or cadmium fume exposure

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; VGDF = vapor, gas, dusts, and fume; WSIB = Workplace Safety and Insurance Board.

*Criteria quoted from Ontario WSIB COPD binder as reported in Workplace Safety and Insurance Appeal Tribunal (WSIAT) decision no. 484/06 (2009); dust type unspecified (http://www.ibew353.org/wsib/new_doc/Case%20Law/WSIAT%20484%2006%20COPD%20&%20Smoking%20Athey%20Divisible%20Injury.pdf).

†Criterion quoted from WSIAT decision no. 1,923/14 (2014; http://wsiat.on.ca/decisions/2014/1923%2014.pdf).

Table 2

Additional proposed questions regarding occupational chronic obstructive pulmonary disease

1	Should compensation systems consider all obstructive occupational airway diseases (including asthma) in the same way when evaluating impairment or should they divide by mechanisms and physiological changes?
2	Do early-life events modulate the action of risk factors for COPD later in life (122)?
3	How can acute or subacute nonreversible decline in lung function related to events, such as the WTC disaster, be explained?
4	Should studies of occupational COPD take phenotype into consideration? Is emphysema indicative of smoking as the etiology?
5	When evaluating the extent of an occupational component, how much importance should be given to pre-exposure lung function status (whether from actual measurement or imputed from activity level)?

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; WTC = World Trade Center.