Appendix 1: Irritant induced asthma

The focus of this BTS statement is occupational asthma (OA) due to sensitisation. Irritant induced asthma (IIA) is a separate entity but is included here for completeness and to highlight important differences between the two diseases. IIA refers to asthma that arises as a direct consequence of exposure to agents that irritate the respiratory tract once inhaled and is distinct from allergic OA in many ways, most notably by the absence of immunological sensitisation as the underlying mechanism.[1,2] In contrast to allergic OA, there is no period of latency and no clear associations with smoking or atopy have been identified for specific causal agents.

Acute IIA was previously known as reactive airways dysfunction syndrome (or RADS) and first described by Brooks in 1985[3], who set out strict diagnostic criteria in a series of ten cases:

- the absence of pre-existing asthma symptoms
- a rapid onset of asthma symptoms within the first 24 hours following a single exposure to very high levels of irritant vapour, gas, fume or smoke
- demonstrable airflow obstruction with bronchodilator reversibility or non-specific bronchial hyper-responsiveness
- exclusion of other diagnoses that might explain the symptoms.

Brooks originally described persistence of these symptoms for at least three months, but it is now recognised that, in some cases, they may resolve over a few weeks[2-4]. The exposure frequently occurs in, but is not limited to, the workplace; in cases of industrial accidents, more than one person may be affected. In the original Brooks paper[3], acute IIA was caused by exposure to uranium hexafluoride, floor sealant, spray paints, hydrazine, heated acid, fumigating fog, metal coat remover and fire/smoke. There is inconsistent reporting of acute IIA in the literature but, based on results of a recent review, the most commonly implicated agents are chlorine-containing compounds.[5] This is supported by unpublished data from SWORD (2010-2019), with the most common reported agents being cleaning products; dusts; cement, plaster and masonry; sterilising agents and disinfectants; and fuels, oils and diesel. [personal communication]

In almost all cases, there are no accurate measurements of the irritant compounds generated during inhalation accidents. Therefore, estimation of the intensity of exposure is generally qualitative (and may be affected by recall bias) and can be difficult to prove. This may be an important point to acknowledge with the patient. Management should be focused on objective assessment of the presence (or absence) of disease including the assessment of non-specific bronchial hyper-responsiveness or demonstration of significant bronchodilator reversibility of reproducible spirometry. Treatment of acute IIA is with standard asthma therapy including inhaled corticosteroids and bronchodilators. There is a paucity of data on the long-term prognosis of acute IIA but evidence suggests a range of responses from complete resolution to persistent respiratory disability.[6-8] Asthma medication should be reviewed regularly and withdrawn and stopped if possible. Because the underlying mechanism is not due to IgE mediated allergy, individuals can continue in their usual work environment so long as there are measures to prevent further high-level exposures.

Physicians should be aware that some of the situations in which the exposure occurred may have been extremely frightening (e.g. explosion at work) and psychological factors which arise as a result may impact on recovery. [8] An inhalation injury can result in anxiety and fear about returning to the workplace. Hyperventilation and other breathing pattern disorders, inducible laryngeal obstruction, chronic rhinitis, perceived issues with chemical sensitivity and post-traumatic stress disorder may mimic asthma symptoms and should be explored and managed. IIA is not a prescribed disease and thus affected individuals are not eligible for IIDB, but not infrequently a personal injury claim will ensue.

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In addition to acute IIA, other possible phenotypes of IIA have been described, including asthma occurring as a result of repeated symptomatic high-level exposure to irritants (Brookes used the term "not-so-sudden-onset" IIA[4]) or chronic exposure to moderate dose irritants;[1,] the underlying mechanisms responsible for these conditions are less clearly defined and remain an active area of research interest.

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Appendix 2: Legislation and guidance relevant to workplace respiratory diseases.

The Health and Safety at Work Act, 1974.	The primary piece of legislation covering occupational health and safety in Great Britain. It sets out the general duties which: • employers have towards employees and the public; • employees have to themselves and to each other; • certain self-employed have towards themselves and others.
The Control of Substances Hazardous to Health Regulations, 2002.	COSHH is the law that requires employers to control exposure to substances that are hazardous to health. Employers are bound to: • find out what the health hazards are; • decide how to prevent harm to health ('risk assessment'); • provide control measures to reduce harm; • make sure these are used and are in good working order; • provide information, instruction and training for employees; • provide monitoring and health surveillance in appropriate cases; • plan for emergencies.
The Equality Act, 2010.	The Equality Act legally protects people from discrimination in the workplace and elsewhere; it replaced a raft of earlier anti-discrimination legislation. It applies to patients whose occupational asthma has had a 'substantial' and 'long-term' negative effect on their ability to do normal daily activities.
(M)SDS.	Every chemical agent used in industry is accompanied by a '(Material) Safety Data Sheet', akin to the warnings' leaflet in a package of medicine. Safety data sheets are readily available on-line (or through a patient's employer) and can be scrutinised for the mention of their respiratory sensitising potential, through the 'risk phrase' R42 or the 'hazard phrase' H334.
The 'hierarchy of control'.	An approach to the management of workplace risk through which risk should be reduced to the lowest reasonably practicable level by taking preventative measures, *in order of priority*. At the 'top' of the hierarchy is 'elimination' of the hazard at work (in this case a respiratory sensitiser); the provision of respiratory protective equipment (such as a face mask) lies at the bottom of the hierarchy.
The Reporting of Injuries, Diseases and Dangerous Occurrences Regulations, 2013.	RIDDOR puts duties on employers, the self-employed and people in control of work premises to report certain serious workplace accidents, occupational diseases (including occupational asthma) and specified dangerous 'near-misses'.
Industrial Injuries Disablement Benefit.	IIDB is a UK statutory compensation scheme available to employed earners who have developed one of a list of 'prescribed' occupational diseases; these include OA due to sensitisation.

Surveillance of Work-related and Occupational Respiratory Disease.	SWORD is the national reporting scheme for occupational lung disease that is funded by the HSE and run through the University of Manchester.

Appendix 3: Differential diagnosis of OA.

In addition to WAA and IIA, there are several other conditions with similar clinical presentations to allergic OA, which may also be work-related; these need to be considered carefully during the diagnostic process, and in many cases actively excluded.[1]

- Inducible laryngeal obstruction (ILO)[2] and breathing pattern disorder are distinct and well-described clinical entities that can be caused or exacerbated by work but may also co-exist with OA. The presence of certain clinical features such as throat tightness, hoarseness, and "air hunger" are clues that may be identified in the history. Fibre-optic nasal endoscopy whilst symptomatic (in some centres following specific provocation tests), cardio-pulmonary exercise tests and specialist physiotherapy assessment may be helpful in confirming these conditions.
- Hypersensitivity pneumonitis may present with work-related symptoms of cough, wheeze and breathlessness mimicking asthma, which may, or may not, be accompanied by constitutional symptoms of weight loss, fever, and general malaise. The most frequent cause in the UK is now metal working fluid, though exposures to avian proteins, moulds (including famers' lung) and some chemical causes (eg. di-isocyanates, epoxy resins) are all reported.[3]
- Obliterative bronchiolitis is a rare condition, characterized by sub-mucosal bronchiolar inflammation and peri-bronchiolar fibrosis. Occupationally, it is recently described in popcorn workers exposed to di-acetyl in butter flavourings,[4] but cases have also occurred in coffee processors,[5] and boat builders.[6] Onset of cough and breathlessness is usually insidious. Serial spirometry often shows rapidly progressive and fixed airflow obstruction, and full lung function testing confirms air trapping. HRCT may be ~~very~~ suggestive of the diagnosis, with air trapping and oligaemia (sharply defined mosaic attenuation), but lung histology may be required for diagnosis.
- Chronic obstructive pulmonary disease (COPD); although smoking is the principal cause, occupational exposures contribute significantly to the burden of disease (population attributable fraction reported to be 14%)[7] and there is good evidence that COPD can be caused by exposures to silica, coal mine dust, agricultural dust, textile dust, welding fume and cadmium fume. In some cases, differential diagnosis may be challenging, as some cigarette smokers with OA have co-existing COPD, and in other cases, patients with chronic OA have fixed airflow obstruction.

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Appendix 4: . Diagnostic tests for OA; a summary.

Test	**Sensitivity / specificity for a diagnosis of OA**	**Diagnostic utility**
History (expert).	Sensitivity ~90%, but specificity 27-50%.	Many patients with work-related symptoms do not have OA.
Questionnaires.	Generally sensitive but less specific.	Used for health surveillance. May be falsified.
Serial PEF.	Sensitivity of 75-82% and specificity of 79-88%. Low quality data significantly alter sensitivity and specificity.	Generally regarded as the best first-line approach to assessing the physiological response to inhaled agents in the workplace. Does not confirm the cause, except in cases when exposure varies by day or time of day. Also positive in WAA.
Immunological testing (skin prick testing and specific IgE).	HMW: sensitivity of 0.74 and specificity of 0.71. LMW: sensitivity of 0.28 and specificity of 0.89.	Confirm sensitisation if +ve. More useful for HMW allergens.
Spirometry.	Single and cross-shift measures have low sensitivity.	Used for asthma diagnosis and health surveillance. Baseline value useful for prognosis, and to judge changes over time in exposed workers.
Exhaled nitric oxide and sputum eosinophils.	Single measures have low sensitivity for OA. Increases the sensitivity of SIC.	Used for asthma diagnosis and as an additional test with SIC.
Non-specific bronchial hyper-responsiveness (NSBHR).	Single measures: sensitivity of 34-64% and specificity of 84-87%. Serial measures: sensitivity of 43-62% and specificity of 52-83%. Increases the sensitivity of SIC.	Single measures used for asthma diagnosis. May resolve within a few days of ceasing exposure in early OA. Serial measures more useful for confirming OA. Additional test with SIC.
Specific inhalation challenge (SIC).	Difficult to assess sensitivity and specificity as regarded as the gold standard diagnostic test (although false positive and negative responses occur). Increasing time since last occupational exposure reduces sensitivity. NSBHR, FeNO and induced sputum improve sensitivity.	Most UK patients do not require SIC for a diagnosis of OA. Only available in specialist centres. Useful for confirming novel causes and for diagnosis if other tests are not feasible or inconclusive. May cause asthma exacerbations.

Workplace challenge.	Difficult to assess sensitivity and specificity.	Alternative to SIC if exposures cannot be safely replicated. May confirm OA after -ve SIC.

Specific inhalation challenge (SIC)

In the UK, a positive SIC result is not required for government benefits or civil compensation, and the usual indications include:

- confirming new causes of OA
- identifying the exact cause to allow suitable workplace modifications
- confirming the diagnosis where other tests are not feasible or have been inconclusive

SIC is generally a safe procedure but should only be carried out in centres with relevant expertise and experience.[1,2] A positive SIC is generally defined as a fall in FEV_1 of ≥15% from baseline following exposure to an allergen, which may be seen as an early (within a few minutes), late (after 2 hours) or dual response.[2] Equivocal reactions can sometimes be clarified by finding changes in non-specific bronchial responsiveness, sputum eosinophils or FeNO.[2-4] The sensitivity and specificity of SIC are high but not easily quantified as the method is usually used as the reference standard for the diagnosis of OA. False negative tests may occur if the patient has not been exposed to the cause for a prolonged period or is challenged with either the wrong allergen or too low a concentration of the causative agent; irritant responses may result in false positive early responses.[2]

Workplace challenge

Challenges can also be carried out in the workplace (supervised by a suitably qualified healthcare practitioner), by collecting regular measurements of airway function (e.g. PEF or FEV_1) across a working shift.[5] Workplace challenges may be helpful in confirming OA where a high index of suspicion remains, despite a negative SIC, particularly for workers with potential exposure to more than one asthmagen in the workplace.[6] Analysis of the data produced can be carried out using the method described by Stenton *et al*.[7] This uses data collected on the non-exposed days to calculate a mean and 95% CI for PEF (or FEV_1) values at each time point through the day. Any values recorded during the exposed workdays falling below the 95% CI from the same time point of the non-exposed days, are used to identify a work-relationship.

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Appendix 5: Summary of potential employment options following a diagnosis of OA.

Options after diagnosis	Advantages	Disadvantages
No change: continue in current role with same level of on-going exposure.	Minimal socioeconomic impact.	Poorer prognosis for asthma. Risk of increasing sickness absence.
Continue in current role but with reduced exposure.	Minimal socioeconomic impact.	Reduction in exposure may not be sufficient to improve OA. Risk of increasing sickness absence. Needs supportive employer.
Redeployment within same company to non-exposed role.	May have minimal socioeconomic impact. Better prognosis for asthma.	May be lower paid or less skilled position. Relocation may impact on commute to work (distance, time, cost). Needs supportive employer.
Move to alternative employment without exposure.	Variable socioeconomic impact. Retraining opportunities. Better prognosis for asthma.	May be lower paid or less skilled position. Relocation may impact on commute to work (distance, time, cost). Retraining may be costly.
Ill health retirement / stop work.	Better prognosis for asthma.	Socioeconomic impact of early retirement.

Appendix 6: Audit

Audit tool for primary and non-specialist secondary care

The following audit criteria have been developed by the Clinical Statement Group, for use in a primary care, but may also be used in a non-specialist secondary care setting. The possibility of OA should be considered in all individuals of working age with new symptoms suggestive of asthma, reappearance of childhood asthma, deteriorating asthma control, or unexplained airway obstruction. The following should be documented in the healthcare records for all such patients (i.e., audit target = 100% of patients):

- what sort of work they do;
- if employed, whether symptoms are better on days away from work (e.g., rest days or holidays);
- for patients with either high risk jobs, or symptoms that improve away from work, what actions have been taken to ensure early referral for specialist assessment.

Audit tool for occupational asthma specialist services

Previous OA audit criteria were developed and published for the original Standard of Care in 2008[1] and, based on user feedback, adapted for the 2012 update[2]. A survey of UK specialist centres, carried out in 2018, found consensus agreement that it was important to have nationally agreed audit criteria to assess the quality of care received by patients with OA. Specialists were given the opportunity to agree or disagree with the existing audit criteria (published in 2012), and to suggest improvements. The following audit tool has been produced based on the existing audit criteria, and the results of the survey recommendations (audit target = 100% for each criterion).

All patients with suspected OA should, as a minimum, have the following clearly documented in their health records.

By first visit:

- a full list of relevant occupations held, their durations, and likely exposures;
- whether their current job is likely to involve exposure to a known asthmagen;
- presence or absence of asthma prior to entering their current job (or trade);
- presence or absence of work-related respiratory symptoms;
- presence or absence of work-related eye or nasal symptoms;
- duration and latency of any work-related symptoms reported;
- whether their workplace has occupational health provision;
- whether they are under OA health surveillance;
- whether they are aware of other affected workers in the same workplace;
- FEV_1, FVC, and the degree of airflow limitation, compared to predicted values.

By second visit:

- if performed, the results of serial PEF measurements for at least 3 continuous weeks including rest days, with at least 4 good quality readings per day, analysed to assess work relatedness;
- if performed, the results of other respiratory function tests (e.g. bronchodilator reversibility, FeNO, non-specific bronchial responsiveness);
- if performed, the results of appropriate specific IgE or skin prick tests.

Once a diagnosis of OA has been made:

- letter to patient confirming the diagnosis and (where appropriate) advice regarding likely health outcomes of continued exposure;
- compensation advice (IIDB and civil action) where appropriate to the case.

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