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Contemporary Review

# Classification of chemicals as respiratory allergens based on human data: Requirements and practical considerations

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ABSTRACT

Occupational asthma is an important health problem that can include exacerbation of existing asthma, or induce new asthma either through allergic sensitisation, or non-immunological mechanisms. While allergic sensitisation of the respiratory tract can be acquired to proteins, or to low molecular weight chemicals (chemical respiratory allergens) this article is on the latter exclusively.

Chemical respiratory allergy resulting in occupational asthma is associated with high levels of morbidity and there is a need, therefore, that chemicals which can cause sensitisation of the respiratory tract are identified accurately. However, there are available no validated, or even widely accepted, predictive test methods (*in vivo*, *in vitro* or in silico) that have achieved regulatory acceptance for identifying respiratory sensitising hazards. For this reason there is an important reliance on human data for the identification of chemical respiratory allergens, and for distinguishing these from chemicals that cause occupational asthma through non-immunological mechanisms.

In this article the reasons why it is important that care is taken in designating chemicals as respiratory allergens are reviewed. The value and limitations of human data that can aid the accurate identification of chemical respiratory allergens are explored, including exposure conditions, response characteristics in specific inhalation challenge tests, and immunological investigations.

## 1. General introduction

Asthma is an inflammatory disease of the respiratory tract associated with narrowing of the airways and wheeze. It has been estimated that globally more than 339 million people had asthma in 2016 (WHO, 2016) and that in 2017 the incidence rate of new asthma cases was 43.12 million per year (Mattiuzzi and Lippi, 2020).

One manifestation of asthma is occupational asthma, and it has been estimated that this represents between 10% and 20% of all cases of asthma in adulthood (Malo et al., 2015; Maestrelli et al., 2020). A working definition of occupational asthma is: '*variable airways narrowing causally related to exposure in the working environment to airborne dust, gases, vapours or fumes*' (Newman Taylor, 1980). Occupational asthma is now a common, and probably the most common, work-related respiratory disorder in industrialised countries (Blanc et al., 1999; Kogevinas et al., 1999).

There is a long history of respiratory diseases associated with the workplace, and some examples were recognised as early as 460BC by Hippocrates as being associated with certain occupations, such as metal working and fishing (Peterson, 1946). Some of the first reports describing occupational asthma being linked with specific exposures included those implicating castor bean dust (Bernton, 1923), gum arabic (Spielman and Baldwin, 1933), wood dust (Ordman, 1949), phthalic anhydride (Kern, 1939) and platinum salts (Hunter et al., 1945). There is now evidence that a number of chemicals and chemical classes are commonly associated with occupational asthma, and these include the diisocyanates, acid anhydrides, aliphatic amines, wood dusts, fluxes, chloroplatinate salts and certain reactive dyes (Chan-Yeung and Malo, 1993; Baur, 2013; Baur and Bakehe, 2014).

Although both chemical and proteins can induce occupational asthma, the focus of this article is on occupational asthma associated with exposure to low molecular weight chemicals. No data currently exists allowing an estimation of the relative contribution of irritant and immunological mechanisms to the development of new cases of occupational asthma. Nevertheless, for important reasons, that will be discussed below, there exists a critical need to identify accurately those

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chemicals that are true respiratory allergens and that can cause asthma via allergic sensitisation of the respiratory tract, and to distinguish these from chemicals that are able to provoke occupational asthma through other non-immunological mechanisms. Here the challenges which need to be addressed in achieving this objective will be explored, together with the pivotal role that accurate interpretation of human data plays in the correct assignment of chemical asthmagens.

## 2. Mechanisms and phenotypes of occupational asthma: an overview

Occupational asthma is associated with substantial morbidity and is an important health concern giving rise to important social and economic burdens (Mapp et al., 2015; Bakerly et al., 2008; Kenyon et al., 2012; Feary et al., 2016; Tiotiu et al., 2020). It is commonly defined in terms of symptoms and association with the workplace environment, rather than as a function of causative pathogenic mechanisms. This is unfortunate because asthma, including occupational asthma, can be associated with two broad classes of mechanism.

One is allergic asthma which is characterised by allergic sensitisation of the respiratory tract; a process that – by definition – is dependent upon immunological mechanisms. The other is asthma resulting from non-immunological mechanisms. The latter can take a variety of forms that will be considered later (Maestrelli et al., 2020).

It is important to acknowledge again here that occupational allergy resulting from allergic sensitisation can be induced by low molecular weight chemical allergens, and by high molecular weight protein allergens. This article will focus exclusively on the former when considering allergic asthma.

There is a failure to distinguish between allergic asthma and asthma associated with non-immunological mechanisms, and this is reflected in regulatory definitions (Kimber et al., 2001). For example, in the European Chemicals Agency (ECHA) Guidance for the Implementation of REACH (ECHA, 2017) the following definition of a respiratory sensitiser is used:

> *'A respiratory sensitiser is an agent that will lead to hypersensitivity of the airways following inhalation exposure of that agent. Respiratory sensitisation (or hypersensitivity) is a term that is used to describe asthma and other related respiratory conditions ….irrespective of the mechanism (immunological or non-immunological) by which they are caused'* (ECHA, 2016).

Similarly, the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) indicates that evidence of an immunological mechanism does not have to be proven for classification of a chemical as a respiratory sensitiser (UN, 2019).

This is very different from the situation that pertains to dermatitis resulting from chemical exposure, where in a regulatory context a clear distinction is drawn between allergic contact dermatitis resulting from skin sensitisation, and non-allergic or irritant contact dermatitis which is independent of an immunological mechanism (ECHA, 2016).

Before examining why the failure to distinguish between allergic and non-allergic asthma is necessary but problematic, and the how best such discrimination can be achieved, it is helpful to consider briefly relevant pathogenic mechanisms.

### 2.1. Chemical respiratory allergy

In common with all forms of allergic disease, the development and expression of chemical respiratory allergy occurs in two phases. In the first phase (the sensitisation phase) exposure of an inherently susceptible subject to the inducing chemical allergen will provoke an immune response that if of the appropriate quality and sufficient vigour will cause the acquisition of respiratory sensitisation. If the now sensitised subject is exposed subsequently, by inhalation, to the same chemical allergen then a stronger and more aggressive secondary immune response will be elicited provoking inflammation and changes to the airways that result in respiratory allergy, asthma and rhinitis. This is the second or elicitation phase (Kimber et al., 2011, 2018).

A detailed survey of the relevant immunological mechanisms of chemical respiratory allergy is beyond the scope of this review. The important point is, however, that there remains uncertainty about the precise nature of the immune response(s) that drive the acquisition of sensitisation (Kimber et al., 2014b, 2018). There is reason to suppose that IgE antibody can play an important role as this class of antibody is implicated in the development of many forms of allergy, including for instance respiratory sensitisation to proteins and food allergy. The difficulty is, however, that it has not been possible in many confirmed cases of chemical respiratory allergy to identify allergen-specific IgE antibodies (Cartier et al., 1989; Cullinan, 1998; Tee et al., 1998; Kimber and Dearman, 2002; Pronk et al., 2007; Kimber et al., 2014a). It might be that this is a technical issue, not least because chemical-specific IgE antibody is notoriously difficult to detect, the implication being that IgE antibody may be associated much more commonly with chemical respiratory allergy than is often assumed (Kimber et al., 1998; Kimber and Dearman, 2002; Wisnewski et al., 2004; Ott et al., 2007; Wisnewski, 2007: Budnik et al., 2013). Irrespective of this, it is difficult to make a case that IgE antibody has a mandatory and universal causal relationship with the acquisition of respiratory sensitisation to chemicals. What is probably less contentious is that chemical respiratory allergy is associated with the induction of Th2-type immune responses; Th2 cells being a sub-population of T helper (Th) cells that are associated with allergic sensitisation (and IgE antibody production) (Kimber et al., 2014b, 2018).

One consequence of this uncertainty about the precise cellular and molecular mechanisms that result in chemical respiratory allergy is that there is a lack of consensus regarding legitimate endpoints for putative predictive test methods. This has significantly hampered the development of coherent strategies using *in vivo* and/or *in vitro* methods for the identification of chemical respiratory allergens.

Another cause of uncertainty has been the routes of exposure through which allergic sensitisation of the respiratory tract to chemicals can be acquired. Although there is no doubt that inhalation exposure is relevant, there is a persuasive body of clinical and experimental evidence, and growing acknowledgement, that sensitisation of the respiratory tract to chemical respiratory allergens can be induced through skin exposure (Karol et al., 1981; Rattray et al., 1994., Kimber and Dearman, 2002; Tarlo and Malo, 2002; Bello et al., 2007; Redlich and Herrick, 2008; Redlich, 2010; Tsui et al., 2020).

As a result of these uncertainties, and in particular the absence of agreement on the relevant endpoint(s) for predictive tests, the position presently is that there are no validated test methods, or even widely accepted test methods, for the identification and characterisation of chemical respiratory allergens. This situation does not reflect a lack of interest or endeavour. A variety of approaches has been proposed including animal methods (mouse, rat and guinea pig), *in vitro* approaches, and assessments based upon quantitative structure-activity relationships (QSAR), but none has been formally validated or gained regulatory acceptance. Experimental approaches that have been, or are being, explored for hazard identification have been reviewed recently (Arts, 2020). The toxicological challenges with respect to hazard identification and risk assessment have been reviewed elsewhere (Holsapple et al., 2006; Kimber et al., 2007, 2014a; Boverhof et al., 2008; Isola et al., 2008; Basketter and Kimber, 2011; Cochrane et al., 2015; North et al., 2016).

The important conclusion in the context of this article is that there are available presently no validated test methods that have gained regulatory acceptance for the identification of chemical respiratory allergens. Although some of the approaches that are being explored currently may bear fruit in the future, the position currently is that there is a heavy reliance on human data for determining whether a chemical

has the potential to induce respiratory allergy, and to distinguish true respiratory allergens from chemicals that elicit occupational asthma through non-allergic mechanisms that do not require induction of an immune response. The reasons why it is important to distinguish accurately between these classes of chemicals will be discussed later in this article.

### 2.2. Non-immunological mechanisms of occupational asthma

As indicated above, non-immunologic asthma can take a variety of forms (Vandenplas, 2011; Tarlo and Lemiere, 2014; Arts and Kimber, 2017; Maestrelli et al., 2020) and these are summarised in Fig. 1 (that, for completeness, also includes allergic asthma). The most important mechanistic driver is irritation. Three types and causes of non-immunologic occupational asthma are recognised:

- Exposures in the workplace can trigger the reactivation of quiescent asthma, also described as a worsening of existing asthma due to conditions at work (*asthma exacerbated by work* in Fig. 1) (Henneberger et al., 2011; Friedman-Jimenez et al., 2015; Tarlo, 2016; Bradshaw et al., 2018; Lau and Tarlo, 2019). A variety of exposures have been implicated (Maestrelli et al., 2020). Estimates of the prevalence of work aggravated or work exacerbated asthma among new cases of occupational asthma has been judged to be in the region of 20%–35% (Reinisch et al., 2001; Henneberger et al., 2011).
- Exposure to irritant substances, over time (commonly multiple exposures) and at sufficient levels, can provoke an inflammatory reaction in the airways resulting in non-specific bronchial hyperresponsiveness (*irritant-induced asthma* in Fig. 1). Any irritant exposure in the workplace has the potential to cause asthma in previously non-asthmatic subjects, with the substances implicated most frequently including disinfectants, chlorine or chlorine-releasing cleaning agents, acids and caustic agents (Zock et al., 2001; Evans et al., 2008; Li et al., 2018; Carder et al., 2019; Su et al., 2019)
- In contrast to the above, where irritant-induced asthma characteristically develops over time with chronic moderate irritant exposures, the Reactive Airways Dysfunction Syndrome (RADS) describes a new onset of asthma developing rapidly (within 24 h) of inhalation exposure to a high level of an irritant gas, vapour or fumes (*single exposure/[RADS]* in Fig. 1). RADS can be provoked by a wide variety of substances in subjects without pre-existing asthma, and is frequently associated with accidental spills (Brooks et al., 1985; Alberts and Brooks, 1996; Brooks and Bernstein, 2011; Tarlo, 2014).

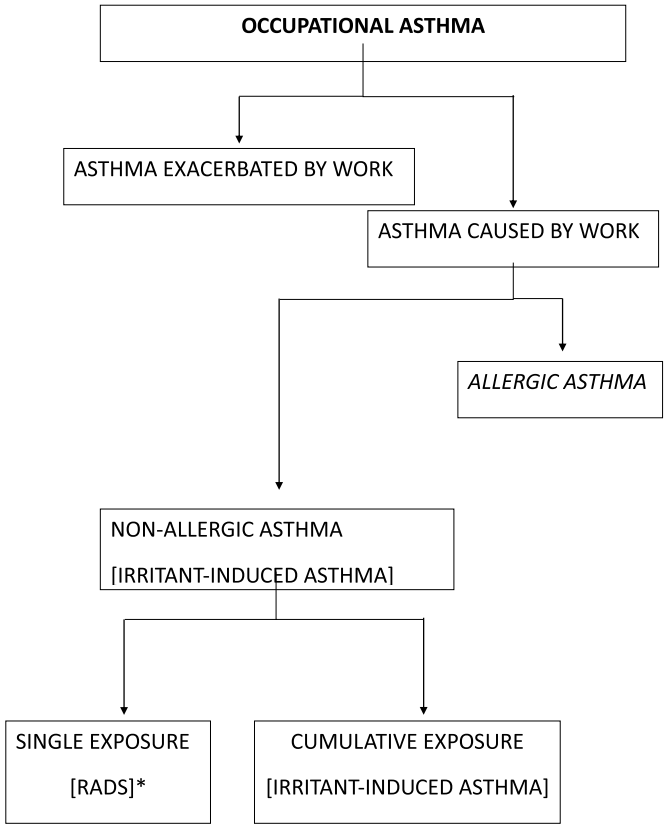


**Fig. 1.** A shema summarising the different types and causes of occupational asthma.
* Reactive Airways Dysfunction Syndrome.

Several mechanisms may contribute to the development of irritant-induced (non-immunologic) asthma including transient receptor potential (TRP) channels, a large family of ion channels (Zholos, 2015; Belvisi and Birrell, 2017) and neurogenic inflammation (Vandenplas et al., 2014b; Yang and Li, 2016).

## 3. Diagnosis of occupational asthma

The first need is to establish a firm diagnosis of occupational asthma, irrespective of whether this is driven by allergic sensitisation or non-immune mechanisms. A detailed survey of the available diagnostic procedures is not necessary here, and relevant expert reviews are available elsewhere (Klees et al., 1990; Malo, 1993; Tarlo et al., 2008; Cartier and Sastre, 2011; Tiotiu et al., 2020). It is, however, relevant to identify briefly here the most important criteria which are as follows: (a) the need for a firm diagnosis of asthma by a physician having considered differential diagnoses (such as, for instance, bronchiolitis, pneumoconiosis etc), (b) the diagnosis should include demonstration of a significant improvement in FEV1 following administration of a bronchodilator, and (c) there should be a clear association between asthma and patterns of work, together with work-related changes in spirometry, and/or non-specific bronchial hyperresponsiveness (ECETOC, 2017; Arts, 2020).

It should be possible, based upon the application of these criteria, to determine whether respiratory symptoms are truly associated with exposures in the workplace environment and can be designated as occupational asthma.

The more difficult task is to distinguish between non-immunologic occupational asthma in which cellular damage and associated inflammation are responsible for the acquisition of asthma and occupational asthma that is induced by an allergic mechanism involving sensitisation i.e. covalent binding of substances to proteins within the respiratory tract.

However, before considering how this might be achieved in practice, it is relevant to examine why discrimination between different phenotypes of occupational asthma, and between chemical respiratory allergens and chemicals causing non-immunologic asthma, is important.

## 4. The importance of distinguishing between chemical respiratory allergens and chemicals that drive non-immunological asthma

There are a number of reasons why such discrimination is important.

### 4.1. Precision of hazard descriptors, avoidance of over-regulation, and harmonisation with contact dermatitis

The current regulatory definition of a respiratory sensitiser embraces both chemicals that induce asthma or hypersensitivity of the airways by

non-immunologic mechanisms, and *true* chemical respiratory sensitisers that induce allergic asthma. Thus, under the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals, those that are classified as respiratory sensitisers (H334) have a hazard statement of '*may cause allergy or asthma symptoms or breathing difficulties if inhaled*' (UN, 2019). As discussed earlier, the guidance provided by ECHA (2017) indicates that in the case of low molecular weight chemicals the term respiratory sensitisation is applied '*irrespective of the mechanism (immunological or non-immunological) by which they are caused*'.

This contrasts with contact dermatitis where a clear distinction is drawn between allergic contact dermatitis requiring an immune response (skin sensitising chemicals, H317), and irritant contact dermatitis where no immune response is needed (skin irritants, H315) (ECHA, 2016). At very least there should be consistency and harmony between the classification of skin and respiratory sensitisers and while this is not currently achievable due to limitations in our understanding of the complex mechanism involved and their interaction, we should nevertheless strive in this direction.

More importantly the failure to distinguish between different mechanisms of occupational asthma complicates and compromises the development of predictive test methods and the identification of structural alerts for use in QSAR strategies (some databases include chemicals of both types without drawing any distinction). Furthermore, the absence of a more differentiated classification of chemicals associated with occupational asthma can result in the inappropriate and unnecessary designation of non-immunological asthmagens, that may well already be classified for respiratory irritation properties being assigned the status of a 'Substance of Very High Concern' (SVHC) as defined under Article 57 of the EU REACH Regulation (ECHA, 2016) with subsequent inclusion onto the Candidate List to Annex XV to REACH and the restrictions that this designation imposes.

### 4.2. Dose metrics

The current regulatory classification of respiratory sensitisers obscures the fact that, in general terms, compared with allergic asthma caused by true respiratory sensitisers, asthma associated with irritation generally requires higher levels of exposure. An appreciation of differences in potency, and of the fact that continued exposure to true respiratory allergens will be characterised by an increasing level of sensitisation that in turn results in heightened responsiveness and more severe reactions, are important elements of accurate risk assessment, and effective risk management (Kimber et al., 2011). Naturally, an appreciation of whether occupational asthma has developed due to allergic sensitisation, or via a non-immunologic mechanism, influences subsequent clinical management (Lau and Tarlo, 2019).

### 4.3. Routes of exposure

The development of occupational asthma driven by non-immunological mechanisms relies on irritation induced by inhalation exposure to the causative agent. In contrast, and as discussed earlier, there is an understanding now that some (and probably many or most) chemical respiratory allergens can induce sensitisation of the respiratory tract by skin contact (Karol et al., 1981; Rattray et al., 1994., Kimber and Dearman, 2002; Tarlo and Malo, 2002; Bello et al., 2007; Redlich and Herrick, 2008; Redlich, 2010; Tsui et al., 2020). This has important implications for risk assessment and risk management, and a clear discrimination between true respiratory sensitisers and non-immunologic asthmagens would aid in identifying appropriate measures to ensure worker safety.

## 5. Diagnosis of occupational allergic asthma and identification of chemical respiratory allergens

For the reasons outlined above it is important to characterise carefully occupational asthma, and to distinguish between allergic and non-allergic phenotypes. Not only is this important for clinical and regulatory purposes, it also represents a key element in the identification of true chemical respiratory allergens.

As discussed earlier in this article, for a number of reasons there are presently no widely accepted, or formally validated methods (*in vivo, in vitro* or in silico) for the identification of chemical respiratory allergens. As a consequence, there is necessarily considerable reliance for hazard identification on information derived from human studies.

Therefore, it is appropriate to consider here how clinical studies and human data can provide information that assists in the identification of chemical respiratory allergens and aids in distinguishing these from non-immunologic causes of occupational asthma.

As discussed previously, the first step requires confirmation that the observed respiratory effects are consistent with a diagnosis of asthma, and that the asthma is truly work-related. However, this diagnosis of occupational asthma *per se* does not indicate that the asthma results from allergic sensitisation, or that the suspected causative agent is a respiratory allergen. To confirm (or deny) respiratory sensitisation additional data are required as summarised below.

### 5.1. Exposure, prevalence and worker history

There is a critical need for robust exposure data. It is necessary to establish whether, in addition to the presumed causative agent, there are opportunities in the working environment for exposure to other chemicals (at the induction and/or elicitation stage), including chemical allergens, that might confound the diagnosis.

There is a reliance on the use of questionnaires/clinical histories to confirm or deny that there is a work-related pattern of disease that supports a diagnosis of occupational asthma, and whether there are confounding factors such as pre-existing respiratory health issues, and/or exposure to materials that could impact on the development of allergic or inflammatory responses. Although such questionnaires may be sufficient for clinical diagnostic purposes, they do not commonly provide definitive information regarding the causative agent, or whether there have been opportunities for co-exposure to other recognised asthmagens. Moreover, such questionnaires do not necessarily allow exacerbation of pre-existing asthma to be distinguished from newly acquired irritant or allergic asthma.

It is proposed also that information on the prevalence of respiratory effects as a function of the number of exposed workers should be considered (ECHA, 2017). Although such data may serve to confirm an important occupational health issue, and from a regulatory perspective contribute to assessment of potency, they would not assist in determining whether the observed work-related asthma was attributable to respiratory sensitisation or another cause.

### 5.2. Specific inhalation challenge tests

Specific inhalation challenge (SIC) tests are considered the gold standard for diagnosis of asthma, but they are difficult and costly to perform, and potentially dangerous for the patient, and can be subject to false negative and false positive outcomes (Vandenplas et al., 2014a).

Nevertheless, the results of such tests can be informative if challenge is performed with the suspected causative agent (free from impurities). There is a general acceptance that an Early Asthmatic Reaction (EAR) observed in a SIC provides a reliable indication of the involvement of irritant mechanisms. In contrast, the assumption that provocation of an isolated Late Asthmatic Reaction (LAR; hours following challenge) is characteristic of sensitisation to a chemical allergen is less certain. Thus, in a recent large study an association (but not a universal association) was found between occupational asthma caused by chemical allergens and late responses (an odds ratio of 1.52; confidence intervals: 1.09–2.08) (Vandenplas et al., 2019). However, this appears not to be a general rule since it has also been reported that inhalation challenge of

13 cleaning employees with occupational asthma with bleach (chlorine, which lacks sensitising potential) elicited two late asthmatic reactions and one dual (early and late) asthmatic reaction (Sastre et al., 2011). Taken together the data suggest that it would be inappropriate to regard elicitation of a LAR in a challenge test as providing firm evidence of an allergic mechanism.

There is available other evidence from animal models that irritant mechanisms can be involved in the expression of LAR. It is important therefore to be aware of irritant thresholds when conducting challenge tests.

In Brown Norway rats steroid treatment inhibits inflammatory cells (activated mucosal mast cells associated with eosinophils and Th2 lymphocytes) influx into the lung (Bousquet et al., 2000; Barnes, 2008).

Moreover, in the same model, the non-specific cation channel blocker (ruthenium red), a specific TRPA1 (Transient Receptor Potential Ankyrin) inhibitor (HC-030031), and an anti-cholinergic agent (tiotropium bromide) revealed that treatment which attenuated early asthmatic reactions (EAR) failed to impact on LAR. Also, while anaesthesia failed to impact on EAR, it abolished LAR, pointing to different mechanisms underlying EAR and LAR with the involvement of non-immune pathways in the latter (Raemdonck et al., 2012).

Further evidence in Dunkin Hartley guines pigs with the combined administration of the β2-agonist bronchodilator olodaterol and the long-acting anticholinergic tiotropium showed complete inhibition of allergen-induced EAR and SAR (Smit et al., 2014).

While later studies by the same group using C57BL/6 mice showed conflicting results (Baker et al., 2017), because the Brown Norway rat and C57BL/6 mouse models demonstrate phenotypic features of allergic asthma, including the LAR, and its susceptibility to clinically effective agents that are similar to human, the overall evidence from these animal models indicate an important role for non-immunologic mechanism in the development of LAR in humans.

### 5.3. Immunological investigations

Measurement of immune responses to the causative agent can strongly support a diagnosis of allergic occupational asthma. However, such assays are not always easy to perform, and can be subject to interpretive difficulties. There are 3 main approaches. The first is measurement of chemical allergen-specific IgE antibodies. Although as discussed earlier, it has not been possible to identify IgE antibodies in all patients with confirmed chemical respiratory allergy (particularly in subjects with diisocyanate-induced asthma), the finding of specific IgE antibodies is very suggestive of an allergic phenotype. The absence of detectable specific IgE antibodies does not, however, preclude chemical respiratory allergy. The second approach is based upon skin testing of subjects by intradermal injection of small quantities of the causative agent. An immediate inflammatory reaction at the site of injection is also indicative of allergic sensitisation. Finally, in some investigations it has been possible to demonstrate in patients T lymphocyte responses directed at the inducing chemical allergen; a result that is also indicative of allergic sensitisation (Frew et al., 1998).

### 5.4. Integration of human data

It will be clear from the above summary that there is no easy answer to achieving a clear distinction between chemical respiratory allergens and non-immunologic asthmagens using human data. The results of specific inhalation challenges can be informative, but not definitive. Although there is a view that provocation of late asthmatic reactions is associated selectively with allergic asthma, it is clear that this is not a universal rule.

The results of immunology testing can be very helpful. Certainly it is the case that the clear demonstration of IgE antibody specific for the presumed causative agent would point strongly to an allergic mechanism. However, the reverse is not necessarily true. Given the technical difficulties associated with the detection of IgE antibody reactive with chemical allergens, the absence of IgE does not necessarily exclude allergic sensitisation. Skin prick tests have the potential to be more informative, and a positive test would certainly signal allergic sensitisation, but this method – especially in the context of chemical allergens – is likely prone to false positives and false negatives. Other immunological investigations are really research tools, and although they might provide useful information – such as the presence of allergen-reactive T lymphocytes – they would have to be interpreted with care.

The conclusion drawn is that collectively human data can be informative, and sometimes provide a basis for distinguishing between allergic asthma and non-immunologic asthma. Thus, for instance, provocation of an immediate reaction in a challenge test, coupled with a negative skin prick test and the absence of detectable IgE antibody would suggest an irritant mechanism. Similarly, late asthmatic reactions together with a clear demonstration of specific IgE antibody and positive skin prick tests would be consistent with allergic sensitisation. However, in practice such clear differences will commonly not be observed, in which case a weight of evidence approach will have to be adopted.

Irrespective of how the data are interpreted it is very important, for the reasons described above, for there to be a high level of certainty before a chemical is designated as being a respiratory allergen. Examples exist in the literature where evaluations of chemicals that had been implicated as respiratory allergens have found this classification cannot be supported based on a detailed review of the available data (Borak et al., 2011; Arts and Kimber, 2017).

## 6. Concluding comments

It is clearly important that chemical respiratory allergens are identified accurately and distinguished from other chemicals that may cause occupational asthma through non-immunological mechanisms. Correct assignment prevents inaccurate and inappropriate classification, with the unnecessary restrictions that this imposes, facilitates the development and validation of novel methods for the identification and characterisation of chemical respiratory allergens, and underpins clinical diagnosis and management, and the adoption of relevant health and safety measures in the workplace.

In the absence of validated methods there is commonly a reliance on the use of human data to determine whether occupational asthma is caused by exposure to a chemical respiratory allergen, or is driven by some other mechanism. As discussed in this article, these data that can provide a basis for achieving this, but they need to be evaluated with care, and consideration given to factors that might confound accurate interpretation. The need is that occupational asthma is diagnosed accurately, and that relevant data are reviewed to establish whether the cause is allergic sensitisation or non-immunologic in nature. It is essential, therefore, that a complete clinical history is taken, and that the causative agent is identified and possible confounding exposures evaluated. Further, clinical characterisation in the form of specific inhalation challenges may be informative, although it must be appreciated that the latency of induced reactions (EAR and LAR) does not necessarily provide a reliable distinction between allergic and non-allergic asthma. Finally, immunological analyses measuring skin prick test reactivity and the identification of specific IgE antibody can provide important information if interpreted appropriately.

In an area where classification is currently generic, and where no predictive methods have gained regulatory acceptance, relevant human data, from a variety of sources, if interpreted carefully, can potentially provide a basis for accurate assignment of chemical respiratory allergens. There is a need for occupational health physicians and toxicologists to draw on their combined skills and experience to improve our ability to distinguish between different causes of occupational asthma.

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## CRediT authorship contribution statement

**Mark A. Pemberton:** Conceptualization, Funding acquisition, Writing – review & editing. **Ian Kimber:** Writing – original draft.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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