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Review

Chemical Respiratory Allergy and Occupational Asthma: What Are the Key Areas of Uncertainty?

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ABSTRACT: There is increasing concern about the association of respiratory disease with indoor air quality and environmental atmospheric pollution. Associated with this is the fact that in many countries there has been a significant increase in the prevalence of asthma. Against this background there is a need to address the toxicological, occupational and public health problems associated with the ability of some chemicals to cause allergic sensitization of the respiratory tract and occupational asthma.

By definition allergic sensitization of the respiratory tract to chemicals is dependent upon the stimulation of an adaptive immune response that leads to development of respiratory allergy and/or asthma. Although IgE antibody is associated typically with respiratory sensitization to protein allergens, there is less certainty about the role played by antibodies of this type in chemical respiratory allergy and occupational asthma. There are currently no validated or widely accepted methods/models for the identification and characterization of chemicals that have the potential to induce allergic sensitization of the respiratory tract.

These and other areas of uncertainty were debated during the course of and following a two day Workshop. The primary purpose of the Workshop was to consider the important clinical and toxicological issues associated with chemical respiratory allergy, and to identify key questions that need to be answered if real progress is to be made. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: respiratory allergy; respiratory hypersensitivity; occupational asthma; hazard identification; models; risk assessment

Introduction

Some chemicals are able to induce various types of allergic disease. Those of greatest relevance for occupational medicine are skin sensitization resulting in allergic contact dermatitis, and allergic sensitization of the respiratory tract associated with occupational asthma and rhinitis.

Allergic contact dermatitis is common and many hundreds of chemicals have been implicated as skin sensitizers (Gerberick *et al*., 2005). In contrast, chemical respiratory allergy is encountered less frequently and currently only 26 chemicals (16 of which are proteins) are classified as respiratory sensitizers under the European Union Directive 67/548/EEC on Classification and Labeling of Dangerous Substances (N.B. the EU criteria for classification as a respiratory sensitizer do not differentiate between substances that act through non-immunological or immunological mechanisms). A further 51 (non-protein) substances are classified as having the potential to cause sensitization by inhalation and skin contact (EC, 2004).

Chemicals known to cause allergic sensitization of the respiratory tract resulting in occupational asthma include the following: diisocyanates (such as diphenylmethane diisocyanate [MDI] and toluene diisocyanate [TDI]), acid anhydrides (such as trimellitic anhydride [TMA] and phthalic anhydride [PA]), some platinum salts, certain reactive dyes, glutaraldehyde, plicatic acid (from Western Red Cedar) and chloramine T (Bernstein *et al*., 2006; Graham *et al*., 1997). In humans allergic contact dermatitis is only rarely associated with chemicals that are known to cause allergic sensitization of the respiratory tract.

For a variety of reasons chemical respiratory allergy remains an important toxicological and occupational health issue (Kimber and Wilks, 1995). Of particular relevance is the fact that respiratory allergy is commonly associated with high levels of morbidity and has significant socio-economic consequences (Bernstein *et al*., 2006; Kimber and Dearman, 1997). Moreover, there are currently no formally validated or universally accepted approaches to hazard identification and characterization of chemical respiratory sensitizers. These issues pose important challenges for effective safety assessment.

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These challenges have been the motivation behind various workshops that have sought to bring together experts from a range of disciplines to define the problems associated with chemical respiratory allergy, and to develop a path toward solving the most pressing issues. A report on, and recommendations deriving from, a Workshop convened recently by the European Centre for the Validation of Alternative Methods (ECVAM) provides an in depth review and defines the current state of the science relevant to chemical respiratory allergy – the interested reader is directed there for a comprehensive overview (Kimber *et al*., 2007).

The primary purpose of this article, which was developed from a 2 day workshop on chemical respiratory allergy and asthma convened in London on 13–14 July 2006 (Appendix I), is to identify the key areas of uncertainty regarding the identification and characterization of chemicals that have the potential to induce chemical respiratory allergy, occupational asthma and other related health effects. An important consideration in this context is whether and to what extent the toxicological community is able to identify chemical respiratory allergens and to develop accurate risk assessments and risk management strategies.

Workshop Summary — The Key Points

The nature of the immunological processes and cellular/molecular events that result in the acquisition of allergic sensitization of the respiratory tract to chemicals is not well understood and remains controversial. There also exists some uncertainty about the clinical characteristics that may be associated with chemical respiratory allergy. The classic and archetypal symptoms include those of asthma and rhinitis, but other responses may sometimes complicate diagnoses, such as reactive airways distress syndrome (RADS) and extrinsic allergic alveolitis (EAA). RADS has the features of asthma and chemical sensitivity but is diagnosed only in about 10% of all cases of occupational asthma (Brooks and Lockey, 1981). EAA is a disease of the bronchioles/alveoli characterized by a decrease in functional lung capacity, while clearly linked to protein antigen exposure it has rarely been linked to chemicals (Bauer, 1995). A careful review of the clinical experience should help to put the likelihood of these other diagnosis in perspective.

As indicated above, it has proven difficult to develop methods for the identification of chemical respiratory allergens because of continuing uncertainty about the relevant immunological mechanisms. Unlike proteins, chemicals must associate with a larger carrier molecule in order to induce an immune response. The nature of this interaction, and of the carrier molecules, under relevant *in vivo* conditions is not well understood. While it is known that respiratory sensitization to protein allergens is associated with, and dependent upon, IgE antibody, there is no such consensus with respect to chemical respiratory allergy (Kimber and Dearman, 2002). Although there is evidence for specific IgE antibody production to the majority of chemicals confirmed as respiratory allergens, there are symptomatic individuals with diagnosed occupational asthma who seemingly lack detectable IgE. The latter is true especially with respect to the diisocyanates where a significant number of symptomatic patients are reported to lack measurable serum IgE antibody (Bernstein *et al*., 2002; Cartier *et al*., 1989). This may signal that other cell-mediated, IgE independent, immunological mechanisms promote sensitization of the respiratory tract to some chemicals. However, it remains possible that the lack of association with IgE antibody is due to technical difficulties in measuring the antibody and/or a reflection of the fact that serological studies have frequently been conducted some time after the last exposure to the inducing chemical allergen (Park *et al*., 2001; Tee *et al*., 1998). It may also be the case that the reagents used to detect antibody are inadequate under some circumstances (Karol, 2002). Nevertheless, the possible contributions of IgE-independent immunological processes cannot be discounted.

A major deficit in our understanding is the incomplete characterization of immune responses to chemical allergens that result in the acquisition of respiratory sensitization. There is wider agreement that irrespective of an absolute requirement for IgE antibody, the development of T helper (Th)2-type lymphocyte immune responses (characterized by IL-4, IL-5, IL-10 and IL-13 cytokine expression) favor allergic sensitization of the respiratory tract (Kimber and Dearman, 1999; 2005). However, Th1-type responses (characterized most prominently by IL-2 and IFN-γ expression) traditionally associated with contact sensitization may be of some consequence in some instances, and it may be that there is not always a clear demarcation between Th1- and Th2-type immune responses.

Historically, it has been assumed that sensitization of the respiratory tract to chemical allergens is acquired exclusively by inhalation exposure. However, animal studies, including one published more than 25 years ago (Karol *et al*., 1981), demonstrate that respiratory sensitization can be induced following dermal contact with the sensitizing chemical. More recent investigations have also shown that topical exposure of experimental animals to chemical allergens such as isocyanates and acid anhydrides can cause sensitization of the respiratory tract. Although evidence in humans for the importance of skin exposure in this respect is sparse, it is prudent to assume that sensitization of the respiratory tract can be acquired following skin contact with certain chemicals if the levels of exposure are sufficient. This is of more than academic interest since in the manufacturing environment, if there is inhalation exposure there is also likely skin exposure and vice versa. Whether thresholds of exposure required for sensitization vary according to the route of exposure

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is uncertain. Prospective exposure monitoring linked with medical surveillance is one way in which this issue might be addressed. It is important also to recognize that, although routes of exposure other than inhalation may cause sensitization of the respiratory tract, elicitation of pulmonary reactions requires encounter with the chemical via inhalation. Clearly this has important implications for risk management procedures to ensure the safety of those working with or using chemical respiratory allergens.

The urgent need for appropriate models to identify and characterize potential respiratory allergens was considered at length during the Workshop. One possible approach presented is based on the observation that chemical respiratory allergens will normally elicit a positive response in the local lymph node assay (LLNA), or other tests for skin sensitization. The proposed implication is that a chemical testing negative in the LLNA might be considered to lack both skin and respiratory sensitizing capacity. A positive response in the LLNA would clearly result in the chemical being considered a contact allergen, but would not necessarily indicate potential respiratory sensitizing potential – as only a small subset of chemicals that are positive in the LLNA are known to be respiratory allergens. Other considerations such as structural alerts (chemical stuctures that are similar to known respiratory allergens), or concerns based upon likely conditions of exposure might prompt further testing. For this purpose, techniques such as cytokine profiling, may prove useful in defining the immune response (Dearman *et al*., 2003; Van Och *et al*., 2002). Cytokine profiling seeks to identify potential chemical respiratory allergens by distinguishing them from contact allergens using cytokine secretion patterns elicited after repeated exposure of mice (or rats) to the test chemical. The hypothesis is that chemical respiratory allergens, in contrast to contact allergens, will preferentially induce a selective Th2-type immune response with production of cytokines associated with Th2 responses.

Other animal models for hazard identification and characterization were also considered. It was proposed that it might be relevant to consider whether a variant of the LLNA, based upon measurement of induced activation of lymph nodes draining the respiratory tract (rather than the auricular lymph nodes), might be of value in assessing hazards associated with inhalation exposure to chemicals (Arts and Kuper, 2007). A mouse model of asthma, that utilizes the soluble protein ovalbumin, was discussed. This model employs both dermal and inhalation exposures. The model produces characteristic findings of allergic asthma: Th2 responses with increased eosinophil levels and Type 2 cytokine production (IL-4, IL-5, IL-13) (Herrick *et al*., 2000).

Finally, discussion also focused on identifying chemical respiratory allergens based on their physical-chemical properties by using *in silico* and *in vitro* approaches. It has been suggested that chemical respiratory allergens may have different physico-chemical properties that distinguish them from skin sensitizing chemicals. This has been exploited in the design of (quantitative) structure-activity [(Q)SAR] models of chemical respiratory sensitizers (Cunningham *et al*., 2005; Karol *et al*., 2001, 1996). These models have not yet been validated. One difficulty with validation is the small number of chemicals that are known to be respiratory allergens.

The position currently, therefore, is that although progress has been made there is still no fully validated or widely accepted method available for the safety assessment of chemical respiratory allergens. Clearly this represents an important and unmet need. A test system to identify specific and selective endpoints for respiratory sensitization needs to be developed, validated and accepted. This will ultimately lead to accurate and reliable safety/risk assessments.

Progress will be facilitated by reaching consensus on chemicals that may serve as positive and negative controls for the evaluation of novel or modified approaches, and from closer and more effective interactions between respiratory physicians, industrial hygienists, toxicologists and immunologists.

Questions

Arising from the discussion during and following the Workshop it became apparent that the following important questions must be addressed:

1. Can criteria be established to define respiratory chemical allergens using information from clinical and/or experimental studies?
2. Is it possible to identify the routes of exposure through which chemicals may induce allergic sensitization of the respiratory tract?
3. Can dermal exposure result in acquisition of allergic sensitization of the respiratory tract to chemicals?
4. Can inhalation exposure to contact allergens induce or elicit respiratory allergy?
5. What is the role of IgE antibody in allergic sensitization of the respiratory tract to chemicals?
6. Are there mechanisms through which allergic sensitization of the respiratory tract can be achieved that are independent of IgE antibody?
7. Are there immunological mechanisms that are common to all instances of chemical respiratory allergy/occupational asthma, and common to all chemical respiratory sensitizers?
8. Does occupational asthma induced by chemicals differ from other forms of asthma (intrinsic or allergic) — and if so in what way(s)?
9. Is it possible to identify chemical respiratory allergens solely as a function of their physico-chemical

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properties, and if not what other criteria are needed to increase the feasibility of SAR for hazard identification?
10. Are there animal models that can be used (and harmonized) for hazard identification and characterization, and if not what are the limitations of the current approaches and how might they be refined?
11. What are the essential differences between contact allergens and respiratory chemical allergens and how might an appreciation of such differences be exploited for the purposes of safety assessment?
12. Is it possible to exclude the potential for chemicals to cause respiratory sensitizing activity based on a negative local lymph node assay?
13. Is it possible to achieve broad agreement on chemicals that can be used as positive and negative controls in the evaluation of new or modified methods for the identification of respiratory sensitizing chemicals?
14. How might closer interactions between respiratory/occupational physicians, industrial hygienists, toxicologists and immunologists be facilitated in the interests of developing more informed and more integrated approaches to tackling public and occupational health issues associated with chemical respiratory allergy?

It is anticipated that answers to these questions, some of which are likely to prove particularly challenging, will provide better insight into the chemical nature of respiratory sensitizers as well as improved understanding of the biological mechanisms through which chemicals induce respiratory sensitization. This new knowledge will in turn, translate into new opportunities to address more effectively the important toxicological, occupational and consumer concerns about respiratory sensitization and occupational asthma. It will also provide industry and regulatory agencies with the scientific foundation with which to reduce or eliminate the use of potential respiratory sensitizers in the workplace, home and public places.

Appendix I

The workshop was entitled Chemical Respiratory Allergy: Definition, Clinical Observations, and Safety Assessments. Its goals were to strive for agreement on defining chemical respiratory allergens and chemical respiratory allergy, determine if contact allergens have the potential to elicit respiratory sensitization, identify appropriate models to assess the potential for chemicals to induce respiratory sensitization, and determine if and how mechanistic understanding of chemical respiratory allergy can be incorporated in to models for hazard and risk assessment.

Program Outline

Clinical Aspects

- The physiology and pathology of respiratorym sensitization and airway inflammation: immunological versus irritant responses. Dr Mark Utell, University of Rochester Medical Center, Rochester (NY).
- Clinical aspects of chemical respiratory allergy. Dr Paul Cullinan, Royal Brompton Hospital, London.
- Immunological evaluation of chemical respiratory allergy. Dr David Bernstein, University of Cincinnati Department of Medicine, Cincinnati.

Research

- Animal models of asthma: comparison of skin vs airway routes of sensitization that can lead to asthma-like inflammation. Dr Christina Herrick, Yale University School of Medicine, New Haven.
- T helper 1 mediated allergic reactions in the respiratory tract: relevance for hazard identification of low molecular (lmw) allergens. Dr Frieke Kuper, TNO Quality of Life, Zeist.
- Relationships between skin and respiratory chemical allergens. Dr Ian Kimber, Syngenta Central Toxicology Laboratory, Alderly Park.
- Structure-activity relationships and models of chemicals causing respiratory sensitization. Dr Meryl Karol, University of Pittsburgh, Pittsburgh.

Methodology

- The identification of chemical respiratory allergens: the CTL approach. Dr Rebecca Dearman, Syngenta Central Toxicology Laboratory, Alderley Park.
- The identification of chemical respiratory allergens: the TNO approach. Dr Josje Arts, TNO Quality of Life, Zeist.
- The identification of chemical respiratory allergens: the RIVM approach. Dr Rob Vandebriel, RIVM, Bilthoven.
- Evaluation of chemical respiratory allergens: an industry view. Dr Kathy Sarlo, The Procter and Gamble Company, Cincinnati.

Risk Assessment

- Hazard identification, characterisation and the assessment of respiratory sensitisation risk for consumer products. Dr David Basketter, Unilever and St Thomas Hospital School of Medicine, London.
- Risk assessment aspects of respiratory sensitization. Dr Marcel van Raaij, RIVM, Bilthoven.

Regulatory Perspective

- Chemical respiratory hypersensitivity: UK regulatory perspectives. Dr Helen McGarry, Health and Safety Executive, Bootle.

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