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Review

Thresholds in chemical respiratory sensitisation

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ABSTRACT

There is a continuing interest in determining whether it is possible to identify thresholds for chemical allergy. Here allergic sensitisation of the respiratory tract by chemicals is considered in this context. This is an important occupational health problem, being associated with rhinitis and asthma, and in addition provides toxicologists and risk assessors with a number of challenges.

In common with all forms of allergic disease chemical respiratory allergy develops in two phases. In the first (induction) phase exposure to a chemical allergen (by an appropriate route of exposure) causes immunological priming and sensitisation of the respiratory tract. The second (elicitation) phase is triggered if a sensitised subject is exposed subsequently to the same chemical allergen *via* inhalation. A secondary immune response will be provoked in the respiratory tract resulting in inflammation and the signs and symptoms of a respiratory hypersensitivity reaction. In this article attention has focused on the identification of threshold values during the acquisition of sensitisation.

Current mechanistic understanding of allergy is such that it can be assumed that the development of sensitisation (and also the elicitation of an allergic reaction) is a threshold phenomenon; there will be levels of exposure below which sensitisation will not be acquired. That is, all immune responses, including allergic sensitisation, have threshold requirement for the availability of antigen/allergen, below which a response will fail to develop. The issue addressed here is whether there are methods available or clinical/epidemiological data that permit the identification of such thresholds. This document reviews briefly relevant human studies of occupational asthma, and experimental models that have been developed (or are being developed) for the identification and characterisation of chemical respiratory allergens.

The main conclusion drawn is that although there is evidence that the acquisition of sensitisation to chemical respiratory allergens is a dose-related phenomenon, and that thresholds exist, it is frequently difficult to define accurate numerical values for threshold exposure levels. Nevertheless, based on occupational exposure data it may sometimes be possible to derive levels of exposure in the workplace, which are safe.

An additional observation is the lack currently of suitable experimental methods for both routine hazard characterisation and the measurement of thresholds, and that such methods are still some way off. Given the current trajectory of toxicology, and the move towards the use of non-animal *in vitro* and/or *in silico*) methods, there is a need to consider the development of alternative approaches for the identification and characterisation of respiratory sensitisation hazards, and for risk assessment.

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Contents

1. Definitions

Allergy: The adverse health effects that might result from the stimulation of an adaptive immune response.

Allergic sensitisation: A state of heightened sensitivity/responsiveness to a specific allergen resulting from previous exposure and immunological priming.

Allergic contact dermatitis/contact allergy: An allergic disease of the skin that is elicited following topical exposure to a chemical allergen to which skin sensitisation has previously been induced.

Allergic sensitisation of the respiratory tract: A state of heightened sensitivity/responsiveness of the respiratory tract to a specific allergen resulting from prior exposure and immunological priming.

Chemical respiratory allergy: An immune mediated hypersensitivity reaction to an exogenous low molecular weight chemical resulting in symptoms such as asthma and rhinitis.

Asthma: A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T lymphocytes, neutrophils and epithelial cells. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airway obstruction that is often reversible, either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli, either irritant or allergenic (NHLBI, 1991; Apter, 2008).

Allergic rhinitis: Inflammation of the mucus membrane of the nose caused by an allergic response.

2. Introduction

A wide variety of natural and man-made materials can cause allergic sensitisation of the skin or respiratory tract in susceptible individuals.

It has been proposed that respiratory sensitisers could be identified as substances of very high concern (SVHC) in the European regulatory context, since it is not routinely possible to identify a threshold for the adverse effects they cause (ECHA, 2012). The primary aim of this document is to review and discuss scientific evidence that chemical respiratory allergy can be regarded as a thresholded effect.

Commonly encountered examples of respiratory sensitisers are proteins (pollen, dust mite excreta and animal dander etc.). In this case the mechanisms resulting in allergic sensitisation are relatively well understood. In susceptible subjects exposure to the inducing allergen provokes an IgE antibody response. Such antibody distributes systemically and associates *via* specific membrane receptors with mast cells, including mast cells in the respiratory tract. At this point sensitisation has been acquired. Subsequent inhalation exposure of the sensitised subject to the inducing allergen will trigger an allergic reaction. The antigen