Mechanisms of Occupational Asthma Induced by Isocyanates

FRÉDÉRIC DESCHAMPS,*† ALAIN PREVOST,‡ FRANÇOIS LAVAUD§ and SERGE KOCHMAN‡

*Department of Occupational Diseases, Hopital Maison Blanche, 45 Rue Cognacq—Jay 51092, Reims Cedex, France; †Institut Jean-Godinot, 1 Avenue du Général Koénig, 51056, Reims Cedex, France; ‡Department of Respiratory and Allergic Diseases, Hopital Maison Blanche, 45 Rue Cognacq—Jay 51092, Reims Cedex, France

Isocyanates are some of the most important low molecular weight chemicals associated with occupational asthma. These compounds are often volatile and they are highly reactive on mucous membranes, especially the conjunctivae and respiratory tract. Despite numerous data derived from experimental and clinical investigations, there is no agreement concerning the real mechanisms involved in isocyanate-induced occupational asthma. In fact, the cause of occupational asthma is multifactorial. The aim of this paper is to review the involved physiological causes of isocyanate-induced asthma; the main mechanisms are immunological, pharmacological and/or irritative. © 1998 British Occupational Hygiene Society. Published by Elsevier Science Ltd.

INTRODUCTION

Isocyanate-induced asthma is probably the most frequent type of occupational asthma in industrial countries (Diller, 1980), but the mechanisms of acute and chronic toxicity of isocyanates are still largely unknown.

The term 'isocyanate' should be understood as the collective term characterizing substances with free NCO-groups, therefore including mono-isocyanates, di-isocyanates, poly-isocyanates and prepolymeres (Fig. 1).

The aim of this paper is to update the different mechanisms of isocyanate-induced asthma.

Although isocyanate-induced asthma has been recognized for over 40 years (Fucks and Valade, 1951), the mechanisms of the reaction are still highly controversial (Karol, 1988). Numerous recent data derived from experimental and clinical investigations suggest that the cause of isocyanate-induced occupational asthma is multifactorial. Consequently, we are far from having an unitary model (Pauli and Kopferschmitt-Kubler, 1991).

A feature of isocyanate-induced asthma is that symptoms develop in only a small percentage of exposed workers (5–10%) (Pham et al., 1988; McKay and Brooks, 1984). A latent period after first exposure of 3 or 4 years is more frequent than acute symptoms after only a few days or weeks. Late asthmatic reactions are more frequent than early ones for sick workers exposed to isocyanate (Mapp el al., 1988), and are usually more severe and last longer. Patients with these features of asthma are often symptomatic several months or years after the end of exposure (Fabbri and Mapp, 1992; O'Byrne et al., 1987). Finally, little is known regarding the levels of exposure necessary to produce asthma. In general, the pathological features observed in isocyanate-induced asthma are not different from those of status asthmaticus seen in non-occupational asthma (Hogg, 1985). Lungs are over-inflated, airways are plugged with mucus containing abundant exudate, and the bronchial epithelium is extensively desquamated. The mucosa is oedematous and markedly infiltrated with eosinophils.

In effect, three main physiological origins can be identified. There are the pharmacological (Dewair et al., 1983), the irritant (Bernstein, 1982; Davies and Pepys, 1979), and the immunological mechanisms (Karol, 1981, 1986). These may act separately or simultaneously, and their presence varies with individual patients and occurrences of exposure.

PHARMACOLOGICAL THEORY

Isocyanates act as partial adrenergic receptor agonists (Butcher et al., 1980). The pharmacological theory of increased beta-adrenergic blockade is a possibility (Cartier et al., 1989). Davies et al. (1977) have suggested that isocyanates reduce the ability of beta-adre-
Fig. 1. Synthesis of isocyanates and polyurethane.

nergic receptors to produce cyclic adenosine monophosphate in sufficient amounts to maintain bronchial tone (Mapp et al., 1988).

Isocyanates may cause a pharmacological disturbance of the control of the bronchial smooth muscle; toluene di-isocyanate (TDI) is found to affect prostaglandin receptors in vitro (Wass and Belin, 1989). However, it is unclear if these results reflect the in vivo conditions. Furthermore, isocyanates have been shown to be potent inhibitors of acetylcholinesterase from human erythrocytes (Wass and Belin, 1989). Isocyanate-induced asthma could in fact result in a chronic irreversible dysfunction of autonomic control of bronchial tone, or a hyper-reactivity of bronchial smooth muscle, or a chronic inflammatory reaction in airways (Paggiaro et al., 1988).

Tachykinins may play a critical role in the increase of in vivo responsiveness of bronchial smooth muscle which follows exposure to isocyanate in guinea pigs. This effect may be due both to release of tachykinins and to inhibition of neutral endopeptidase or cell membrane-bound enzyme which cleaves tachykinins (Fabbri and Mapp, 1992).

IRRITATIVE THEORY

The disaster which occurred at Bhopal India, in December 1984, tragically confirmed the acute toxicity of isocyanates (Bignon et al., 1988).

High concentrations (above 500 ppb) produce acute inflammation of the conjunctivae and of the mucous membranes of the upper and lower respiratory tract. The mechanism is one of direct toxicity and the severity of the response depends on the level and duration of exposure (Diem et al., 1982). There is a variable inflammatory infiltrate of the bronchi. It is assessed by broncho-alveolar lavage and mucosal biopsy. These investigations show increased percentages of eosinophils (Saetta et al., 1992) or sometimes of neutrophils. Chemotaxis and random migration of eosinophils and neutrophils are increased compared with the normal range. Electron microscopy shows that the basement membrane thickness is similar in control subjects. In vivo studies show after a single exposure to high isocyanate atmospheres (55 mg m⁻³) rapid coagulation and necrosis of the bronchial epithelium. Animals die due to occlusion of bronchioles by necrotic tissue, inflammation and edema (Duncan et al., 1962). No significant correlation is found between histological parameters and physiological data (Saetta et al., 1992). In fact, this inflammatory cell reaction is non-specific for isocyanate-induced asthma.

Reactive airway disease syndrome (RADS) is an example of irritant-induced asthma. RADS can be generated by other chemicals. It is defined as onset of symptoms after a single overexposure to isocyanates within 24 h after the first contact. There is a persistence of symptoms for at least 3 months, of simulated asthma with cough, wheeze and dyspnea (Brooks et al., 1985).

IMMUNOLOGICAL THEORY

Several immunological mechanisms may be involved. Atopy does not seem to be a factor of individual predisposition to isocyanate-induced asthma.
Isocyanate induced asthma

(Diller, 1988). Likewise, no geographical or ethnical effect on prevalence is found. Isocyanate asthma is a complex syndrome. Isocyanates combine covalently with body proteins to form hapten-protein conjugates (Kochman et al., 1990) (Fig. 2). Isocyanate-specific IgE is present in a small number of individuals (Butcher et al., 1980; Prevost et al., 1994). An association between the presence of isocyanate-specific IgE, immediate symptoms and heavy exposure to isocyanate is found (Keskinen et al., 1988). In contrast, most delayed reactions give negative results with Radio-allergo-sorbent test (RAST). High total IgE levels are frequently associated with RAST positivity. However, all these features are not fully understood. In the studies related to isocyanate-exposed workers, an average of 15% of symptomatic subjects have these specific antibodies. In fact positive RAST varies from 0% (Keskinen et al., 1988) to 75% (Danks et al., 1981).

Intracutaneous skin testing with human serum albumin (HSA) bound to isocyanate generally produces significant immediate-type wheal and flare reactions in a quarter of symptomatic and none in asymptomatic patients (Karol et al., 1978; Baur et al., 1984). This test has a good specificity but a poor sensitivity. In fact, there is a good correlation between RAST and the results of skin testing. These give evidence of the existence of an immunologically-mediated sensitization of type I to isocyanate components.

IgG antibodies may be produced in patients sensitized to isocyanates. Isocyanate specific IgG have been found in some instances, but not in others. Qualitative and quantitative aspects of isocyanate specific IgG antibodies are similar, even higher than IgE levels (Karol and Kamat, 1988; Baur et al., 1994; Baur, 1986). Recent assessments of specific IgG antibodies against isocyanate-induced asthma showed a close association with positive bronchial inhalation (Cartier et al., 1989). Higher levels of isocyanate human-serum-albumin specific IgG can be observed in asymptomatic persons exposed to isocyanate with lower frequency, than in symptomatic patients (Baur et al., 1994).

Levels of IgM specific antibodies to isocyanates have also been found to be increased in humans in a particular circumstance (Karol and Kamat, 1988). This was the case of the population exposed to the industrial gas leak in Bhopal on 2 December 1984. The exposure to methyl-isocyanate was high and acute. But most of these antibodies were not detected one year after the acute exposure.

Regarding the T-cell mediated mechanism, it has been suggested that allergen-induced delayed asthmatic reactions are analogous to allergen-induced delayed cutaneous reactions (Erjefalt and Persson, 1992). This is characterized by an acute inflammatory reaction with infiltration of the bronchial mucosa by neutrophils, eosinophils and mononuclear cells. Broncho-constriction and airway inflammation are involved and the presence of polymorphonuclear leukocytes is required for hyper-responsiveness to occur. The structure and the source of the chemostatic factors which attract neutrophils and eosinophils into airspaces, as well as the mediators released by these cells, are unknown (Paggiaro et al., 1988).

The small number of proven examples of sensitization to isocyanates is not necessarily only because of inadequate methods for reliably identifying specific immunoglobulins of each class of isocyanates. For example TDI bound to HSA containing more than forty moles of isocyanates per mole of HSA is a less potent antigen than TDI-HSA containing around twenty moles of isocyanates per mole of HSA (Baur et al., 1984). But this technical finding cannot explain the presence of a majority of isocyanate-induced asthma patients without immunoreactivity.

CONCLUSION

The low prevalence of specific IgE and other antibodies suggests that an immunological mechanism is not the major cause of isocyanate-induced asthma. On the other hand, the pharmacological and irritative hypotheses cannot explain the majority of other situations of isocyanate-induced asthma. Further studies are needed to evaluate and to confirm these and possibly new hypotheses.
**REFERENCES**


**Citations continued...**