

Isocyanates

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Isocyanates were first described by Wurtz in 1848 (1) and are characterized by the highly reactive $-N=C=O$ group. Nowadays, a total of at least 2.5 million tons per year of different forms and derivatives are used in the manufacture of polyurethane foams, various plastics, paints, adhesives, binding agents, coating materials etc. A new application is consolidation of loose rock zones in coal mining or tunnelling. Polyisocyanates with low vapor pressures and compounds whose isocyanate groups are blocked by different chemicals are thought to reduce the health risk of exposed workers.

Air concentrations of isocyanates are often high and above the current threshold limit value (TLV; 0.01 or 0.005 ppm in most countries) in small companies such as furniture makers, car repair shops and building firms where modern processing is not available and ventilation systems are inadequate (2).

It should be mentioned that MDI, which was thought to give lower gaseous concentrations and therefore replaced TDI in many factories, forms a considerable amount of dimers and polymers that are not adequately evaluated by routine measurements (3, 4).

Clinical features of isocyanate hypersensitivity

Several reports indicate that prevalence and incidence of isocyanate-induced symptoms depend on the exposure degree ranging between 0 to more than 10%. The most frequent clinical diagnosis of symptomatic workers is bronchial asthma, followed by rhinitis, conjunctivitis, chronic obstructive lung disease and cutaneous disease. Allergic alveolitis and isolated systemic symptoms such as fever rarely occur (2).

1. Isocyanate asthma and COLD.

As reported by several authors, isocyanates are able to induce immediate, late and dual asthmatic responses. In addition, chronic obstructive lung diseases which persists despite avoidance of the causative agent are described. According to the results of immunological testing, we can subdivide isocyanate-induced obstructive airway diseases into two subgroups:

- the IgE-mediated subgroup
- the non-allergic subgroup.

By means of isocyanate-HSA conjugates in the RAST, intracutaneous test and bronchial challenge test, a differentiation between the two subgroups is possible. I should mention that the HSA conjugates were found to be the most sensitive compounds for this testing. However, it cannot be excluded that additional new antigen determinants formed upon the reaction of isocyanates with soluble human proteins are not detected by these compounds. By definition, negative results in the immunological testing indicate a non-allergic (toxic) pathomechanism of the disease. Approximately 86% of asthmatic isocyanate workers belong to the latter group, and approximately 14% show evidence of an IgE-mediated origin (2). Possible pathogenic mechanisms involved in non-allergic isocyanate asthma are

- inhibition of choline esterase (probably leading to a local increase of the bronchoconstrictor acetylcholine)
- neurally transmitted inflammatory reactions.

2. Isocyanate alveolitis

Several case reports (5-10) provide strong evidence that isocyanates can cause allergic alveolitis. Recently, we saw 12 such cases. Isocyanate-specific IgG antibodies could be detected in each of these workers, and the vital capacity and CO transfer factor were impaired in most of them. In addition, 7 patients showed abnormal X-ray findings, and all of them had repeatedly noticed shortness of breath and fever for several hours after exposure.

BAL and transbronchial biopsies performed 5 times revealed lymphocytic alveolitis. 2 workers were subjected to bronchial challenge tests with isocyanate atmospheres; and the typical restrictive ventilation pattern associated with fever and leucocytosis was obtained.

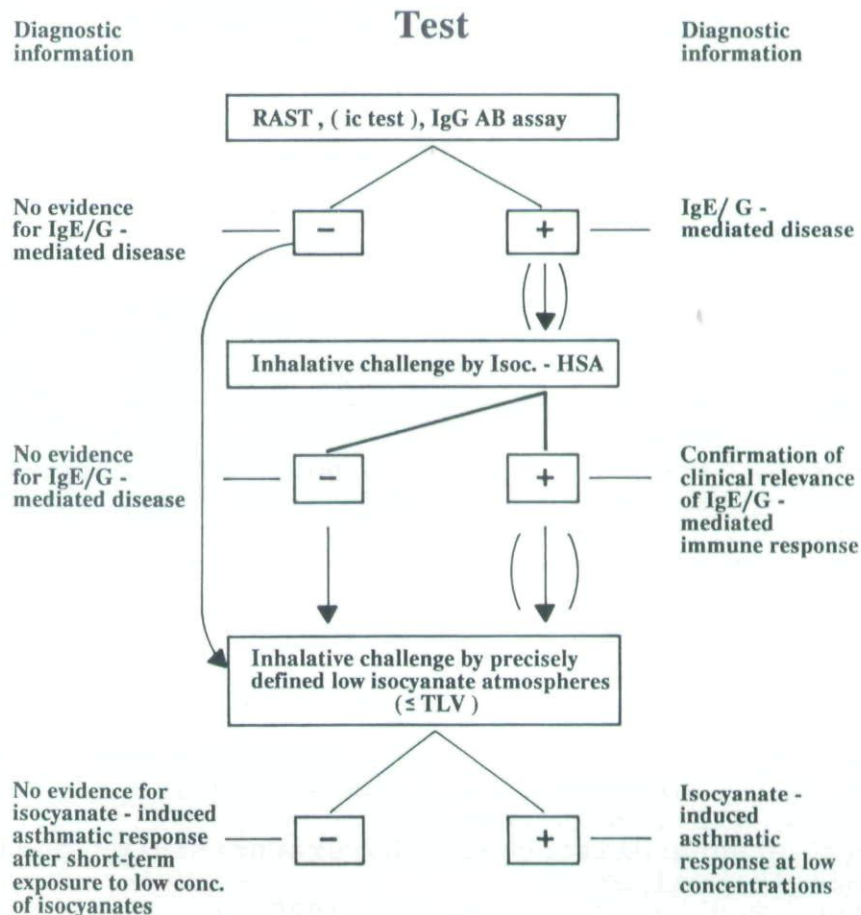
Diagnostic testing

Symptomatic isocyanate workers should be screened by RAST and an IgG Ab assay for isocyanate-specific antibodies. In case of immunologic sensitization, isocyanate-HSA conjugates can be used in challenge tests to confirm the clinical relevance. Challenge tests with precisely defined isocyanate atmospheres are recommended in doubtful situations (Fig. 1)

Long-term effects of isocyanates in asymptomatic workers

Several reports indicate declines in FEV_1 , vital capacity and/or CO transfer factor related to the concentration and duration of isocyanate exposure (11-13). According to Musk et al. (14), isocyanate concentrations in the range of 1/10 of the TLV does not cause a significant change in FEV_1 during a 5-year period.

Recommended diagnostic procedure in case of suspected isocyanate - induced disease



Anderson et al (15) report mutagenic action of TDI and MDI in *Salmonella typhimurium*; these authors concluded that isocyanates have a potentially mutagenic and carcinogenic effect on man. However, the clinical relevance of these results has not been proven at this time.

Conclusion

Isocyanate air concentrations represent a health hazard. They have dose-dependent effects on the respiratory tract, the lungs, the skin and the eyes. Approximately 1/7 of the pulmonary symptoms are immunologically mediated. The risk of lung function deterioration also exists for asymptomatic workers. A new TLV of 0.005 ppm is recommended, and concentrations above this value should be avoided. By means of modern processing and adequate ventilation systems, isocyanate air concentrations in workplace atmospheres can be reduced to extremely low levels. Continued exposure after the development of symptoms often results in chronic obstructive lung diseases which may be lifelong (16-20).

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