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Corrections

See [1986;12\(2\):160](#) for a correction.

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Systemic reactions associated with polyisocyanate exposure

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NIELSEN J, SANGÖ C, WINROTH G, HALLBERG T, SKERFVING S. Systemic reactions associated with polyisocyanate exposure. *Scand J Work Environ Health* 11 (1985) 51–54. A spray-painter suffered attacks of chills, fever, general malaise, dyspnea and wheezing, headache, arthralgia, and leucocytosis a few hours after exposure to aerosols of varnishes containing two different polyisocyanates based upon monomers of hexamethylene or toluene diisocyanate. Immunologic studies revealed an increase in the serum immunoglobulin G level, but no specific antibodies against isocyanates conjugated to human serum albumin. The polyisocyanate level in the workroom air was high [a time-weighted average of 4.2 mg/m³, corresponding to 17 µmol NCO (isocyanate groups)/m³], the toluene diisocyanate monomer level being much lower (a time-weighted average of 0.03 mg/m³, corresponding to 0.3 µmol NCO/m³).

Key terms: air levels, chills, fever, HDI, hexamethylene diisocyanate, hypersensitivity pneumonitis, leucocytosis, spray painting, TDI, toluene diisocyanate.

Isocyanates are used in, eg, foams, synthetic rubbers, adhesives, and paints. They are known to produce irritation of mucous membranes at high levels in the air. A second type of reaction is airway obstruction in sensitive subjects at lower intensities of exposure. Type I allergy caused by specific immunoglobulin (Ig) E antibodies has been suggested as the pathomechanism of the latter reaction (1), even if the evidence is not fully consistent. However, there is a third, much less frequently noticed reaction pattern, reported in a handful of cases only (2, 4, 5, 7, 8, 12, 15), "flu-like" late reactions with general malaise, myalgia, fever, neutrophilic leucocytosis, diffuse infiltrate in the chest radiograph, reduced pulmonary volumes, low compliance, and impaired gas diffusion capacity in the lungs being the main clinical features, suggesting a type III response with hypersensitivity pneumonitis, which is also indicated by histopathology (4). Specific IgG antibodies of a precipitating type have been demonstrated in one case (15). The three different reaction patterns thus are similar to those reported in association with trimellitic anhydride (16).

The adverse reactions to isocyanates were first observed in connection with exposure to toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI), both of which have high vapor pressures. Diphenylmethane diisocyanate (MDI) was initially considered less toxic because of its low vapor pres-

sure. However, even MDI (or probably rather volatile isocyanate impurities) turned out to cause disease. Thus for medical and, probably more important, technical reasons, a new type of compound, polyisocyanates, based upon HDI or TDI, was introduced (3). These compounds are now widely used, mainly in paints and varnishes. While much is still unknown regarding the toxicity of the classical isocyanates, even less is known about the polyisocyanates (3). Only limited data on animal toxicity (13, 14) and a single case of adverse reaction in man, an immediate asthmatic reaction (1), have been reported.

In the present communication we report a case of hypersensitivity pneumonitis-like reaction to two different types of polyisocyanates. The exposure levels were measured.

Case history

The patient (a male 56 years of age) was first seen in June 1978. He had no history of atopy. From the age of 20 he had smoked, maximum consumption being 20 cigarettes per day, but in the last year only four cigarettes per day. He had a budgerigar at home. After school he worked as a carpenter. In 1977 he, in addition, started to spray-paint furniture in a spraying chamber. Two different two-component varnishes were used (A and B).

In 1977, when he was still only a carpenter, he had suffered several attacks of laryngitis and one episode of obstructive bronchitis. A few months after he had begun spray-painting, symptoms occurred in association with varnish A. Each time, after about an hour, he suffered dyspnea with cough and wheezing. After about a year each attack also included chills, general malaise, headache, and arthralgia. His body temperature rose to a maximum of 39.5°C in about 12 h,

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returning to the base line after an additional 24 h. Varnish B caused no such symptoms.

Varnish A contained initially a polyisocyanate of the biuret type, based upon HDI (Desmodur N[®], Bayer AG). Later on, a polyisocyanate of polyurethane type, based upon TDI (Desmodur L[®], Bayer AG), was used. The content of the monomer was 1 % or less for both polyisocyanates. The patient suffered identical attacks at exposure to both varnishes. Varnish B, which caused no symptoms, was a urea resin cured by p-toluenesulfonic acid.

Repeated physical examinations in 1978 at varying times after exposure (hours to days) revealed pulmonary rales on the left base. The chest radiograph was normal. In a spirometry test vital capacity (VC) was 4.3 l (expected value 4.8 l), forced expiratory volume in 1 s (FEV_{1,0}) was 2.8 l (expected 3.3 l), and FEV_{1,0}/VC × 100 was 72 (expected 71). There was

no eosinophilia. The total serum IgE was normal, but IgG was raised to 30 g/l (upper reference limit 15 g/l). A skin prick-test with a standard panel of 14 different common antigens was negative. He had no precipitating serum antibodies to farmer's lung antigens or paraqueto antigens (including budgerigar). Epicutaneous tests with the two polyisocyanates revealed a slight reaction after 2 h but thereafter soon faded.

When, in 1979, he was repeatedly studied at the worksite while spraying TDI-based polyisocyanate (varnish A), he suffered the typical attacks already described. There was a marked increase both in the white blood cell count (86 % neutrophils) and in temperature (figure 1). The lung function parameters deteriorated simultaneously (figure 2). Physical examination revealed rhonchi and rales. Chest radiographs showed no changes. Provocation with varnish B caused no symptoms, fever, leucocytosis, or lung function impairment.

At two of the provocations with the TDI-based polyisocyanate already mentioned, the exposure was measured by a liquid chromatographic method (10). The method involves absorption of the isocyanates in the breathing zone in a midjet impinger filled with 10 ml of the reagent [9-(N-methylaminomethyl)-anthracene $1 \cdot 10^{-4}$ mol · l⁻¹ in toluene]. Sixteen samples were obtained during periods of 15–30 min. Polyisocyanate standards with known composition were obtained from Bayer AG.

The time-weighted concentration of polyisocyanate in the breathing zone was 4.2 (sample range 1.5–7.4) mg/m³. The TDI monomer level was 0.029 (range 0.009–0.050) mg/m³.

Serum obtained in 1979 was studied further immunologically. A radioallergosorbent test (RAST) (1) revealed no specific serum IgE antibodies against HDI, TDI, MDI, and the two types of polyisocyanates conjugated with human serum albumin (HSA).

Prausnitz-Küstner tests with some of these conjugates (HDI-HSA, TDI-HSA, and MDI-HSA), as well as with HSA conjugates with p-tolyl monoisocyanate and phenyl monoisocyanate, were negative. Serum samples from the patient did not agglutinate sheep red blood cells coated with the conjugates by a modified chromium chloride procedure (11), and the result remained negative in an indirect Coombs' test using three different antihuman Ig sera. The conjugates did not cause precipitation when tested in gel diffusion assay according to Ouchterlony.

Further examinations were performed in 1981 and 1982, when the patient had been out of exposure for two to three years. Serum IgG was still high, 22 g/l. There was no reactivity in the skin prick-test or specific serum IgE or IgG antibodies [determined by enzyme-linked immunosorbent assay (ELISA)] to the aforementioned conjugates. HDI-HSA, TDI-HSA, and MDI-HSA did not release histamine from the patient's basophilic granulocytes in vitro.

Figure 1. Blood white-cell count and body temperature of a sensitive subject in connection with spray-painting with a varnish containing a polyisocyanate based upon toluene diisocyanate.

Figure 2. Lung function, ie, vital capacity (VC) and forced expiratory volume in 1 s (FEV_{1,0}), of a sensitive subject in connection with spray-painting with a varnish containing a polyisocyanate based upon toluene diisocyanate.

In a metacholine test in 1981 the patient displayed bronchial hyperreactivity (18 % decrease in FEV_{1.0} after a metacholine dose of 0.02 mg). The lung mechanics were normal at that time.

Discussion

Exposure to polyisocyanate varnishes is not harmless, at least not in spray-painting operations, as was clearly shown by our case, as well as by a single earlier-described one (1).

The polyisocyanate levels measured were considerable. The concentration ranged between 1.5 and 7.4 mg/m³, which corresponds to 5.4–30 μ mol NCO (isocyanate groups)/m³. Corresponding levels of a biuret-type of polyisocyanate induced toxic pulmonary effects in mice after 2 h of exposure (14). The concentrations are far above the tentative Swedish standard for polyisocyanate vapor (0.005 ppm, corresponding to 0.2 mg/m³ = 0.6 μ mol NCO/m³; ceiling concentration 0.01 ppm, corresponding to 0.3 mg/m³ = 1.2 μ mol NCO/m³). For aerosols (as in the present case) there is no hygienic standard.

The simultaneous concentrations of TDI monomer were much lower, 0.009–0.05 mg/m³, corresponding to 0.1–0.6 μ mol NCO/m³, a level generally well below the hygienic standard (0.005 ppm = 0.04 mg/m³, corresponding to 0.4 μ mol NCO/m³; ceiling level 0.01 ppm = 0.07 mg/m³, corresponding to 0.8 μ mol NCO/m³).

The hygienic conditions in our case were not exceptionally bad. Similar or even higher levels should be present in many other workshops, as has been shown in one other study (9). As the vapor pressure of polyisocyanates is low, occupational risks should mainly be encountered in operations where aerosols are produced.

As it is well known that NCO groups present in compounds with different chemical structure may cause adverse reactions, we consider it possible that those present in the polyisocyanates may have caused the toxic reactions, although we cannot exclude the monomers as the cause. We find it reasonable to establish a definite hygienic standard for polyisocyanates, both as an aerosol and as a vapor. One suitable way would be to employ a standard value expressed as the sum NCO in micromoles per cubic meter, including both monomer and polymers. The present standards for TDI and HDI may be used until more toxicologic information is available.

The general reaction pattern of our patient is interesting. As was already mentioned, only a few similar cases associated with isocyanate exposure have been reported. However, the phenomenon may not be very rare. The reaction is late and its association with isocyanate exposure is not well known. The cause may thus easily be overlooked.

Of particular interest is the fact that the reaction in our case was caused both by a biuret-type polyisocya-

nate based upon HDI and a polyurethane type based upon TDI. A cross-reactivity thus must exist.

We do not know the pathomechanism behind the reaction. In other reported cases, radiographic changes, the presence of precipitating antibodies, and/or histopathological findings suggested a hypersensitivity pneumonitis. We do not have such evidence, even though the serum IgG level was high in our case. The fact that our examinations did not reveal specific antibodies does not of course exclude the possibility of an allergy. The antibody concentration may be below the detection limit, or the antibodies may be directed against antigenic determinants in the complex of isocyanates and body proteins other than those present in our HSA conjugates. On the other hand, the most impressive clinical finding was the neutrophilic leucocytosis, similar to the reaction caused by thermal degradation products of polyfluoroethylene (6). Such a reaction might be mediated through a direct toxic nonallergic action upon pulmonary macrophages.

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