

Occupational asthma caused by triglycidyl isocyanurate (TGIC)

P. PIIRILÄ, T. ESTLANDER, H. KESKINEN, R. JOLANKI, A. LAAKKONEN, P. PFÄFFLI*, O. TUPASELA, M. TUPPURAINEN and H. NORDMAN

Departments of Occupational Medicine and *Industrial Hygiene and Toxicology, Finnish Institute of Occupational Health, Helsinki, Finland

Summary

Background Polyester powder paints are extensively used in metal painting. Triglycidyl isocyanurate (TGIC), an epoxy compound, is often used as a hardener. Several cases of allergic eczema from occupational exposure to TGIC have been reported in the literature.

Objective We examined a 36-year-old non-smoking man who worked mainly as a spray painter, using a polyester powder paint containing 4% TGIC. During painting he used protective clothing and a motorized breathing protector. After 4 years he developed eczema on his hands, face and body, and an occupational allergic eczema caused by TGIC was diagnosed. He also suffered from powder-paint-related asthmatic symptoms.

Methods Occupational asthma was diagnosed in accordance with the accepted guidelines. Inhalation challenge tests were performed with the paint and TGIC.

Results Spirometry showed slight obstruction; the blood eosinophils and serum IgE value were elevated. Skin-prick tests with common environmental allergens were negative. The challenge test with lactose powder was also negative. A challenge test with a paint containing TGIC (4%) induced a dual reaction in PEF and a late 23% fall in FEV₁. A test with TGIC (4%) mixed with lactose induced a dual PEF reaction, and also dual changes in spirometry. The PD₁₅ in the histamine challenge test decreased significantly after the challenge tests.

Conclusions To our knowledge this is the first diagnosed case of occupational asthma caused by TGIC. This case report emphasizes the importance of protecting both the skin and respiratory tract of workers against chemicals such as TGIC, capable of causing skin and respiratory allergy.

Keywords: polyester powder paints, occupational asthma, contact dermatitis, triglycidyl isocyanurate (TGIC), epoxy

Clinical and Experimental Allergy, Vol. 27, pp. 510–514. Submitted 26 June 1996; revised 7 October 1996; accepted 12 November 1996.

Introduction

Nowadays powder paints are often used for painting metal objects. Polyester powder paints possess potential allergenic properties because they may contain sensitizers, i.e. epoxy resins and often also tiny amounts of cyclic acid anhydrides [1], which are known to be sensitizers [2]. In addition, pure polyester powder paints are usually hardened with triglycidyl isocyanurate (TGIC).

Correspondence: Dr P. Piirilä, Finnish Institute of Occupational Health, Topeliuksenkatu 41 aA, 00250 Helsinki, Finland.

TGIC is an epoxy compound with a molecular weight of 279.30 d; three glycidyl ether groups are coupled to a triazine ring. The molecular form of TGIC is presented in Fig. 1. TGIC is used mainly as a hardener in the thermosetting one-component polyester powder coatings. In addition, it is used in electrical insulation materials, resin-moulding systems, laminated sheetings, silk-screen printing coatings, tools, inks, adhesives, lining materials, and stabilizers for plastics. TGIC has also been studied as an antitumour agent [3], though in some experiments it has been shown to be mutagenic in mice [4].

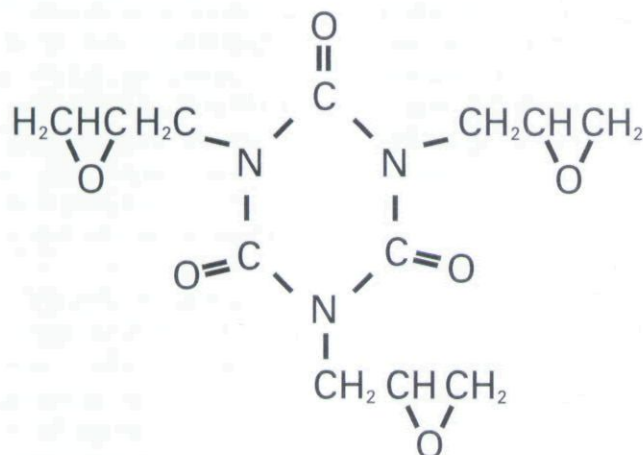


Fig. 1. The molecular structure of TGIC, triglycidyl isocyanurate.

TGIC has been reported to cause type IV sensitization and allergic contact dermatitis in powder paint production [5,6], in powder painting [7–9], in silk printing containing TGIC [10], and in TGIC production [11].

We report on a case of occupational asthma in a patient previously diagnosed to have allergic contact dermatitis due to TGIC. According to our examinations, also the occupational asthma was caused by TGIC.

Methods

Flow-volume spirometry was performed with a rolling seal spirometer (Mijnhardt, Vicatest 3) connected to a microcomputer (Medicro MR-3), and Viljanen's reference values were used [12]. The diffusion capacity measurement was made with a carbon monoxide single breath method (Jaeger Masterlab) using Viljanen's reference values [12]. Histamine challenge tests were performed according to Sovijärvi's method [13] with a Vitalograph bellow spirometer. The provocative dose causing 15% depression in FEV₁ (PD₁₅) was measured, and a change of 30% in PD₁₅ was regarded as significant [13]. The spirometric values during the challenge test procedure were followed up with a Vitalograph bellow spirometer connected to a microcomputer (Apple/Vitalograph Spirotrac II) and the peak flow values with a Wright peak flow meter. The long-term peak flow follow-up was performed with a mini-Wright peak flow meter twice a day. Work place peak flow follow-up was not performed, because the patient was on sick leave during these studies.

The challenge test was performed according to the principles of the European Academy of Allergology and Immunology [14] in a 6 m³ challenge chamber in the forenoons. Lactose was used for the control test. The challenge to the polyester powder paint from the work place (containing 4% TGIC) was done first with 1:1 dilution

with lactose, and on another day without dilution; finally the patient was challenged to TGIC, in 4% dilution: 4 g TGIC mixed with 96 g lactose. The challenges lasted 30 min. The symptoms and lung auscultation were also followed up. Peak flow values were followed up every 15 min during the first hour, then every hour until 8 hours, and every third hour until the next morning. The FEV₁ values were followed up every 30 min during the first hour, every other hour until 8 hours after the challenge test, and thereafter according to the patient's dyspnoea symptoms. For the diagnosis of asthma, a reduction of 20% in peak flow rate or FEV₁ was regarded as significant [15]. The response of the nasal membranes was followed up by anterior rhinoscopy and nasal status scoring by an otorhinolaryngologist [16].

The routine skin-prick tests were done with 20 common environmental inhalant allergens (Allergologisk Laboratorium A/S, ALK, Copenhagen, Denmark) [17]. The skin-prick tests and the specific IgE determination against phthalic anhydride (PA), maleic anhydride (MA), trimellitic anhydride (TMA) and TGIC were also performed. TGIC was conjugated with human serum albumin (HSA) according to the method of Howe [18] and conjugate was used for skin-prick tests; HSA conjugates were diluted to 1% (w/v) HSA with Coca's solution (0.5% sodium chloride, 0.3% sodium hydrogen carbonate, 0.4% phenol) containing 50% glycerol. Specific IgE against TMA, PA and MA were measured with the commercial Pharmacia CAP System (RAST RIA). For specific IgE determination for TGIC, the HSA-TGIC conjugate solution (at 2% HSA) was coupled to filter paper discs activated with cyanogen bromide [19]. The discs and Phadebas RAST (radioallergosorbent) technique (Pharmacia Diagnostics AB, Sweden) were used for specific IgE determination. Values <0.3 IU/L were considered negative.

Skin-patch tests were conducted with the Finn Chamber technique [20] on the back of the patient using a 46 h application time with three readings made by a dermatologist and scoring according to the guidelines of the International Contact Dermatitis Research Group (ICDRG). They included the European patch test standard series (Chemo-technique Diagnostics AB, Sweden) and other relevant series. Three types of the patient's powder paints including a polyester powder paint containing TGIC, an epoxy polyester and an epoxy powder paint were tested as a serial dilution mixed in petrolatum (pet).

Case report

The patient was a healthy 36-year-old non-smoking man with atopy in his family. He had suffered from a stuffy nose and sneezing not related to work for several years especially in the springs, but no atopic tendency had been verified earlier. He had worked as a spray painter since 1974. Powder paints had been used since 1977 in his workplace.

Before the examinations he had been painting 5–8 h daily with powder paints for about 7 years. During the painting he used protective overalls, leather gloves and a motorized breathing protector (Kemira Autoflow; classified as a THP2 protector [21]; nominal protection factor 50). The powder paint contained epoxy and polyester resins, tiny amounts of phthalic [1] and maleic anhydrides [22], and also triglycidyl isocyanurate (TGIC) 4% as a hardener. After electrostatic painting, the metal objects were heated in an oven at 200 °C for 15–30 min.

Since 1991 the patient had had eczema on his hands, arms, face and neck for 2 years, until in January 1993, contact dermatitis caused by TGIC was diagnosed at the Finnish Institute of Occupational Health (FIOH) by patch testing. The polyester powder paint 10% and 3.2% gave strong 3+ allergic reactions, as well as TGIC also tested as a dilution series in pet gave similar 3+ allergic reactions in 1%, 0.32% and 0.1% in pet. All the other patch tests gave negative results.

In addition to eczema, he had had symptoms of dyspnoea since September 1992, especially during and after work days. He also suffered from wheezing dyspnoea at night and during exercise. The symptoms were relieved during weekends. Inhaled terbutaline sulphate on demand had been started in February 1993. Since March 1993 he was on sick leave and his dermatitis was treated with corticosteroid ointments. During sick leave the respiratory symptoms worsened because he often visited his workplace without any protection.

In May 1993, the patient's chest X-ray and spirometry were normal. Slight bronchial hyperreactivity was found in the histamine challenge test (PD_{15} 0.56 mg). In the skin-prick tests, only birch pollen induced a slight reaction of

4 mm (histamine 8 mm). The skin-prick tests to TGIC, phthalic, trimellitic and maleic anhydrides, as well as the specific IgE measurement against them were negative. Serum total IgE was elevated, 6030 IU/L. In peak flow follow-up a regular 20% diurnal variation and significant bronchodilation responses of 17–20% were found (Fig. 2). After this peak flow follow-up the patient was treated with inhaled budesonide (0.8 mg a day) for three months before the specific challenge tests.

The diurnal peak flow variation had improved during the budesonide treatment and was lower than 10% in August 1993. Spirometry showed slight obstruction without any response to the bronchodilator. The single breath diffusing capacity was normal. Moderate bronchial hyperreactivity (PD_{15} 0.33 mg) was found in the histamine challenge test. The lactose control challenge test was negative. In the challenge test with paint containing TGIC mixed with lactose (1:1) a late 15% fall in PEF (11 h after the challenge test) was measured. On another day the test was repeated without lactose dilution, and a 15% fall in peak flow followed after 30 min and he felt tightness in chest. In the consequent values of FEV_1 or FVC no immediate drop was found, but this can depend on technical problems in FEV_1 measurement. A late 23% fall in FEV_1 11 h, and 17% fall in PEF 16 h after the challenge test were noted. In the challenge test with TGIC mixed with lactose, an immediate 17% fall in peak flow in 15 min was measured. In spirometry, 30 min after the challenge test a 9% drop in FEV_1 and 17% in FVC were measured. In addition, a late 16% fall in PEF and 19% in FEV_1 in 6 h and a 16% drop in PEF and 15% in FEV_1 13 h after the challenge were measured. On the day after the specific challenge test, the peak flow level reached the prechallenge level. The peak flow monitoring during the challenge tests is presented in Fig. 3. After the last specific challenge test the histamine challenge test was repeated on the following day showing moderate bronchial hyperreactivity. The PD_{15} was significantly lower than before the challenges, 0.18 mg. There were no changes in the clinical status of nasal or laryngeal membranes after the challenge tests, nor any dermatitis; the skin was well protected during the paint tests because of the verified TGIC eczema.

The patient's respiratory disease was diagnosed as occupational asthma caused by TGIC used as hardener in the polyester powder paint. The patient was considered to be incapable doing his work because of his occupational contact dermatitis and asthma caused by TGIC, and because the paints could not be replaced by other types of paints. The asthma medication with an inhaled steroid and beta-sympathomimetic inhalations, when necessary, was continued. The skin was treated with local steroids until the dermatitis disappeared. Re-training was recommended by the insurance company.

In the follow-up examinations the skin was symptomless

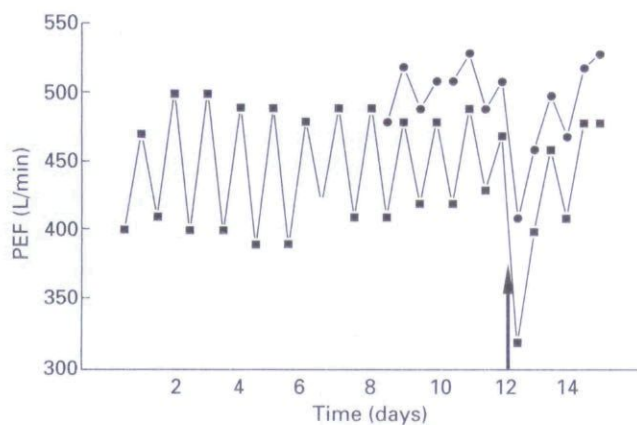


Fig. 2. Diurnal peak flow follow-up of the patient in May 1993 when the patient was on sick leave because of his eczema; the arrow indicates his visit to the work place. —■—, Basic value. —●—, After bronchodilation.

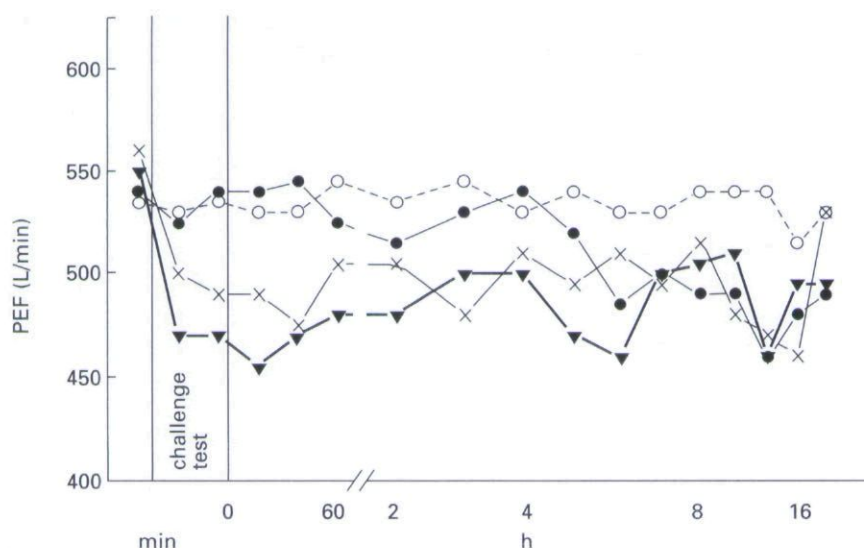


Fig. 3. The specific challenge tests in August 1993. -○-○-. Lactose, —●—, Polyester powder paint with TGIC, diluted. —x—, Polyester powder paint with TGIC. —▼—, TGIC with lactose.

and the histamine challenge test showed slight bronchial hyperreactivity in October 1993, 2 months after the diagnosis (PD_{15} was 0.42 mg). In March 1994, the bronchial hyperreactivity was moderate (PD_{15} was 0.31 mg).

Discussion

Though several reports on TGIC caused type IV reactions have published earlier [5–11], as far as we know, reports on respiratory symptoms caused by it have not earlier been reported. There is an increasing number of reports showing that type IV sensitizers can also induce type I allergic reactions or asthmatic reactions, e.g. nickel [23–25], epoxy resin [26], ninhydrin [27] and acrylates [28,29]; the same patient may even have had dermatitis due to type IV sensitization and type I respiratory symptoms [16,23,26] from the same agent. Only in some of these cases positive skin-prick tests and specific IgE to the causative agent have been demonstrated [25–27]. Our patient had an allergic eczema due to TGIC diagnosed with patch tests.

In addition to TGIC, the powder paint of our patient also contained other potential sensitizing agents, i.e. epoxy resin, phthalic anhydride and maleic anhydride [1,22]. The patient's asthmatic symptoms were work-related. In the PEF surveillance, a fall in PEF followed his visit to the workplace during his sick leave (Fig. 2). In the challenge tests both immediate and late reactions due to polyester powder paint were induced. The result was repeatable and there was a dose–response effect. Pure TGIC, diluted with lactose at a concentration similar to that in the powder paint, induced a reaction equal to the one which followed the test

with the original paint powder. Therefore, the challenges were not made with the other constituents of the paint, e.g. acid anhydrides. According to the skin-prick tests and tests for specific IgE our patient was not sensitized to the acid anhydrides.

Later we have carried out similar provocation tests to a worker with similar exposure and mild work-related respiratory symptoms, mainly cough. The tests were all negative. His bronchial hyperresponsiveness was normal.

In the present patient case, the repeatability and dose–response effect in the challenge tests, as well as increasing bronchial hyperreactivity after the challenge test speak in favour of a specific sensitization to TGIC. The mechanism of sensitization in cases of chemical asthma is not always quite clear. An IgE-mediated reaction cannot be totally excluded, although skin-prick tests to TGIC were negative and specific IgE could not be shown. The absence of the specific IgE can also depend on the method to test specific IgE with HSA-conjugation, which possibly is not good enough to detect specific IgE antibodies [26].

The present patient was using protective clothing and a motorized breathing protector provided with a dust filter, vizier and hood, and the protection is efficient enough against powder paint. The problem may not have been the poor fit of the protector, nor the properties of its filter, but rather the working room conditions. After powder painting, the patient worked without any breathing protector in the painting room where the powder paint particles floated in the air. Therefore, the sensitization of the skin and the respiratory tract are probably due to improper protection after painting. In powder painting,

the proper use of breathing protection and protective clothing, as well as painting in an isolated painting room are essential in avoiding the sensitization of the skin and respiratory tract.

In conclusion, the history, exposure and the findings based on the specific challenge test and measurements of bronchial hyperreactivity are diagnostic to occupational asthma caused by TGIC. In accordance with our present experience, both the skin and the respiratory tract should be properly protected against low molecular weight chemicals known as type IV allergens, which may also be potential type I allergens, such as TGIC.

References

- Pfäffli P. Sampling of airborne combustion fume for chemical analysis: Application to determination of phthalic anhydride in condensed powder paint fume. *Staub – Reinhaltung der Luft* 1994; 54:403–7.
- Venables KM. Low molecular weight chemicals, hypersensitivity, and direct toxicity: the acid anhydrides. *Br J Industr Med* 1989; 46:222–32.
- Piccart M, Rozenzweig M, Dodion P et al. Phase I clinical trial with alpha 1,3,5-triglycidyl-s-triazinetriene (NSC-296934). *Eur J Cancer Clin Oncol* 1981; 17:1263–6.
- Harris S (Ed.). TGIC toxicity update. *Powder coating Bulletin* 1988; (13)3:1–2.
- Foulds IS, Koh D. Allergic contact dermatitis from resin hardeners during the manufacture of thermosetting coating paints. *Contact Dermatitis* 1992; 26:87–90.
- Munro CS, Lawrence CM. Occupational contact dermatitis from triglycidyl isocyanurate in a powder paint factory. *Contact Dermatitis* 1992; 26:59.
- Mathias CGT. Allergic contact dermatitis from triglycidyl isocyanurate in polyester paint pigments. *Contact Dermatitis* 1988; 19:67–8.
- Dooms-Goossens A, Bedert R, Vandaele M, Degreef H. Airborne contact dermatitis due to triglycidyl isocyanurate. *Contact Dermatitis* 1989; 21:202–3.
- McFadden JP, Rycroft RJG. Occupational contact dermatitis from triglycidyl isocyanurate in a powder paint sprayer. *Contact Dermatitis* 1993; 28:251.
- Jolanki R, Kanerva L, Estlander T, Tarvainen K. Concomitant sensitization to triglycidyl isocyanurate, diaminodiphenylmethane and 2-hydroxyethyl methacrylate from silk-screen printing coatings in the manufacture of circuit boards. *Contact Dermatitis* 1994; 30:12–15.
- Nishioka K, Osagasawara M, Asagami C. Occupational contact allergy to triglycidyl isocyanurate (TGIC, Tepic). *Contact Dermatitis* 1988; 19:379–80.
- Viljanen AA, ed. Reference values for spirometric, pulmonary diffusing capacity and body plethysmographic studies. *Scand J Clin Invest* 1982; 42(suppl 159):1–50.
- Sovijärvi ARA, Malmberg LP, Reinikainen K, Ryttilä P, Poppius H. A rapid dosimetric method with controlled tidal breathing for histamine challenge. Repeatability and distribution of bronchial reactivity in a clinical material. *Chest* 1993; 104:164–70.
- Allergy practice forum. Guidelines for the diagnosis of occupational asthma. *Clin Exp Allergy* 1992; 22:103–8.
- Cartier A, Bernstein IL, Burge PS, Cohn JR, Fabbri LM, Hargreave FE, Malo J-L, McKay RT, Salvaggio JE. Guidelines for bronchoprovocation on the investigation of occupational asthma. *J Allergy Clin Immunol* 1989; 84:823–8.
- Kanerva L, Tupasela O, Jolanki R, Vaheri E, Estlander T, Keskinen H. Occupational allergic rhinitis from guar gum. *Clin Allergy* 1988; 18:245–52.
- Aas K, Belin L. Standardization of diagnostic work in allergy. *Int Arch Allergy Appl Immunol* 1973; 45:57–60.
- Howe W, Venables KM, Topping MD, Dally MB, Hawking R, Laws JS, Newman Taylor AJ. Tetrachlorophthalic anhydride asthma: evidence for specific IgE antibody. *J Allergy Clin Immunol* 1983; 71:5–11.
- Cesca M, Eriksson R, Varga JM. Radioimmunosorbent assay of allergens. *J Allergy Clin Immunol* 1972; 49:1–9.
- Pirilä V. Chamber test vs. patch test for epicutaneous testing. *Contact Dermatitis* 1975; 1:48–52.
- CEN (Commitee European de Normalisation). SFS-EN 146. European norm 146. Respiratory protective devices: Powered filtering devices incorporating helmets or hoods. Requirements, testing, marking. CEN 1995, Central secretariat; Rue de Stassart 36, B-1050, Brussels, Belgium, p. 5–66.
- Jilek JH. Powder coatings. Federation of Societies for Coatings Technology 1991. Blue Bell, PA, USA, pp. 7–27.
- Estlander T, Kanerva L, Tupasela O, Keskinen H, Jolanki R. Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis. *Clin Exp Allergy* 1993; 23:306–10.
- Mc Connel LH, Fink JN, Schlueter DP, Schmidth MG. Asthma caused by nickel sensitivity. *Ann Intern Med* 1973; 78:888–90.
- Malo JL, Cartier A, Doepner M, Nieboer E, Evans S, Dolovich J. Occupational asthma caused by nickel sulfate. *J Allergy Clin Immunol* 1982; 69:55–9.
- Kanerva L, Jolanki R, Tupasela O, Halmepuro L, Keskinen H, Estlander T, Sysilampi M-L. Immediate and delayed allergy from epoxy resins based on diglycidyl ether of bisphenol A. *Scand J Work Environ Health* 1991; 17:208–15.
- Hytönen M, Martimo KP, Estlander T, Tupasela O. Occupational IgE-mediated rhinitis caused by ninhydrin. *Allergy* 1996; 51:114–60.
- Savonius B, Keskinen H, Tuppurainen M, Kanerva L. Occupational respiratory disease caused by acrylates. *Clin Exp Allergy* 1993; 23:416–24.
- Lozewicz S, Davidson AG, Hopkirk A, Burge PS, Boldy D, Riordan JF, McGivern DV, Platts BW, Davies D, Newman Taylor AJ. Occupational asthma due to methacryl methacrylate and cyanacrylates. *Thorax* 1985; 40:836–9.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.