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CASE REPORT

Occupational asthma due to formaldehyde resin dust with and without reaction to formaldehyde gas

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Occupational asthma due to formaldehyde resin dust with and without reaction to formaldehyde gas. C. Lemière, A. Desjardins, Y. Cloutier, D. Drolet, G. Perrault, A. Cartier, J.L. Malo. ©ERS Journals Ltd 1995.

ABSTRACT: We report the cases of three subjects who developed asthma after being exposed to formaldehyde dust or gas. For two subjects, specific bronchial provocation tests with formaldehyde gas did not cause significant bronchoconstriction, whereas exposure to formaldehyde resin dust did. One subject experienced asthmatic reaction after being exposed to formaldehyde resin dust and gas.

These findings suggest that the physical and chemical properties of formaldehyde are relevant to its likelihood of causing asthma.

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Formaldehyde is a low molecular weight organic chemical. It can act as a sensitizer at low concentrations and cause occupational asthma [1]. It can also have irritant effects at high concentrations (above 2.0 parts per million (ppm) or 3.0 $mg \cdot m^{-3}$) and cause immediate reactions that are related to histamine reactivity [2]. Formaldehyde is widely used in occupational settings (hospitals, furniture manufacturing, textiles, insulation). People can be exposed to formaldehyde as a gas [3, 4], or as resin dust [5, 6]. Previous reports have documented cases of occupational asthma due to gaseous formaldehyde [2, 7], or to urea formaldehyde dust [6]. We report two cases of occupational asthma due to formaldehyde resin dust in subjects who did not react to formaldehyde gas, and one case in a subject who reacted both to formaldehyde dust and gas. These observations suggest that the physical and chemical properties of a molecule are relevant to its likelihood of causing asthma.

Case reports

Subject No. 1

A 24 year old female was hired as a chemist in the Research and Development Department of a chemical factory in March 1993. She had no previous history of asthma or atopy and had never smoked. Her work in the laboratory involved two sequential steps. Firstly, she synthesized a resin from formaldehyde, phenol, caustic soda and water, heated at 80°C. Secondly, in a separate room, she prepared a polymer of phenol formaldehyde resin powder by adding oleic acid and glycol ethylene to the former resin, putting the resulting solution into a machine that sprayed it onto heated partitions and transformed it into a fine powder ("spray-dry" process). There were no available data on concentrations of formaldehyde resin powder in the workplace.

Two months after beginning this work, she developed headaches, nasal congestion, rhinorrhea and sneezing, as well as episodic wheezing, shortness of breath and chest tightness. Her symptoms usually started 3–4 h after exposure to phenol formaldehyde resin powder and lasted for 24 h. She was usually exposed 3–4 days a week for 2 h at a time. She had been awakened at night a few times because of rhinitis and headache after having been exposed to phenol formaldehyde resin powder. She usually improved within 2–3 days after stopping exposure to "spray-dry" as well as during weekends. She reported no symptoms when handling formaldehyde in liquid form or with the resin before it was processed in the "spray-dry" department. She was treated with budesonide, 200 µg *b.i.d.*, and salbutamol as needed, in October 1993. She stopped working at the end of October 1993 and rapidly became asymptomatic. She was able to stop

budesonide in December 1993. Skin tests performed by the prick method with 22 common inhalants showed immediate weal reactions to house dust mites (*D. pteronyssinus, D. farinae*), house dust, cat fur, dog fur and cockroach. Serial monitoring of peak expiratory flow rates for a period at work and away from work suggested work-related asthma.

Specific inhalation challenges were performed in November 1993. The forced expiratory volume in one second (FEV_1) was 3.5 L (100% pred) [8] with a forced vital capacity (FVC) of 4.5 L (110% pred). Nonspecific bronchial responsiveness to methacholine was assessed with a Wright nebulizer (output = 0.14 $L \cdot min^{-1}$) at tidal volume breathing for 2 min using the procedure of COCKROFT and co-workers [9]. The provocative concentration causing a fall of 20% in FEV_1 (PC_{20}) was 3.8 $mg \cdot ml^{-1}$, reflecting mild bronchial hyperresponsiveness [10]. Graphs of bronchial provocation tests are illustrated in fig. 1a. A control day without exposure did not show any significant changes in FEV_1. On the next day, the subject was exposed to phenol formaldehyde resin powder by tipping the dust from one tray to the other in a provocation chamber [11] in a progressive fashion for a total of one hour. One hour after the end of exposure to resin dust, the FEV_1 decreased from 3.6 to 2.9 L (21% fall). The day afterwards, the PC_{20} was 2.5 $mg \cdot ml^{-1}$, showing no significant changes [12]. On the third day, the subject was exposed to gaseous formaldehyde for 2 h in a provocation chamber. She breathed normally 20 cm away from a small jar filled with liquid formaldehyde [11]. No significant changes in FEV_1 occurred in the minutes and hours following exposure, the PC_{20} being unchanged (4.3 $mg \cdot ml^{-1}$) at the end of the day (not illustrated).

This unexpected result led us to carry out the following investigation, which took place 6 months after the subject had stopped using inhaled steroids. We exposed her to controlled concentrations of formaldehyde gas with a recently developed closed circuit inhalation challenge apparatus equipped with regulating and monitoring systems. She was progressively exposed for a cumulative time of 2 h, at concentrations of 1 $mg \cdot m^{-3}$ for the first 15 min, 2 $mg \cdot m^{-3}$ for the subsequent 30 min, and 3–3.5 $mg \cdot m^{-3}$ for the last 75 min (ceiling value: 3 $mg \cdot m^{-3}$ or 2.0 ppm). Again, there were no changes in FEV_1 nor in PC_{20} following exposure. To further demonstrate that the reaction experienced by our subject was not due to a non-specific irritant effect of formaldehyde, an asthmatic subject with a PC_{20} of 0.28 $mg \cdot ml^{-1}$ was asked to tip formaldehyde dust in the same way. No asthmatic reaction occurred. There was no increase in methacholine-induced responsiveness after the challenge (PC_{20} = 0.39 $mg \cdot ml^{-1}$).

Subject No. 2

A 28 year old male subject had been working since 1992 in a factory that processed wood chips into boards. He had never smoked and had a negative personal atopic history. Aspen wood chips are stirred with wax and a resin, including an amine (see below), phenol and formaldehyde. The subject first worked across several areas within the factory, but after he had been promoted to quality control he stayed mainly at the end of the wood

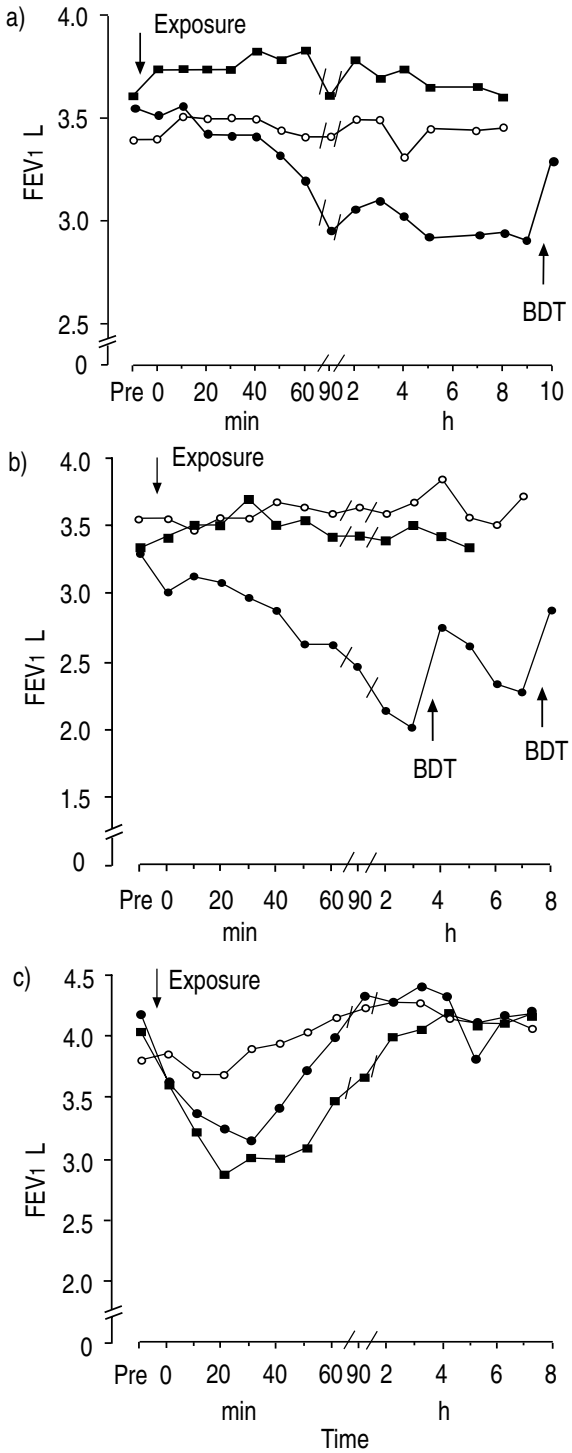

Fig. 1. – Results of specific inhalation challenges to phenol formaldehyde resin and formaldehyde gas in the three subjects. a) Subject No. 1. —○— : control day; —●— : phenol formaldehyde resin (60 min); —■— :formaldehyde gas (120 min). b) Subject No. 2. —○— : MEK thinner (30 min); —●— : phenol formaldehyde resin (30 min); —■— : formaldehyde gas (75 min). c) Subject No. 3. —○— : control wood-dust (30 min); —●— : phenol formaldehyde resin (2 min); —■— : formaldehyde gas (2.5 min). The duration of exposure is shown in parenthesis. Exposure to formaldehyde gas represents results obtained with the special apparatus (second exposure to formaldehyde gas for Subjects Nos. 1 and 2, the first test having been performed in a "realistic" way - more like the exposure at work). MEK: methyl ethyl ketone; BDT: bronchodilation therapy with inhaled salbutamol (200 µg); FEV_1: forced expiratory volume in one second. Note that the vertical axes are cut off from zero.

chip production line. In the summer of 1993, he started having episodes of shortness of breath, coughing and wheezing, usually in the afternoon during workdays. These symptoms improved in the evening and during weekends, and completely disappeared on holidays. Since his respiratory symptoms progressively worsened, he was transferred to the office within the factory, where he was no longer exposed to wood chips. He stopped working in December 1993 on the advice of a local chest physician, who performed serial monitoring of peak expiratory flow rates at work and away from work. He became completely asymptomatic. Skin tests with common inhalants (see above) were entirely negative. In February 1994, his FEV_1 was 3.8 L (86% pred) and his FVC was 5.5 L (108% pred), whereas his PC_{20} methacholine was 4.9 $mg \cdot ml^{-1}$, reflecting mild bronchial hyperresponsiveness. Serial monitoring of peak expiratory flow rates for a period at work and away from work was highly suggestive of work-related asthma.

Specific inhalation challenges were performed in February 1994 (fig. 1b). On the first day, used as control, the patient was exposed to a paint thinner (methyl ethyl ketone), which was nebulized for a 30 min cumulative period. No significant change in FEV_1 occurred within the next 8 h. Next, the patient was exposed to fumes from the heated resin containing phenol, formaldehyde and hexamethylenetetramine, in a progressive fashion for 5, 30 and 120 min, respectively, on three consecutive days, without developing any symptoms or changes in FEV_1 (not illustrated). Further inquiry about the work process disclosed obvious dispersion of phenol formaldehyde resin powder in the area, when it was poured through a large open funnel into the particle board oven, adjacent to the subject's work location. We therefore decided to pursue the challenge by having the subject inhale the phenol formaldehyde resin dust with our closed-circuit particle generator at concentrations lower than 10 $mg \cdot m^{-3}$ [13]. This resin contained 0.1–1% formaldehyde, 1–2% phenol, 3–7% sodium hydroxide and 5–10% hexamethylenetetramine. Two hours after starting the test, the FEV_1 decreased from 3.3 to 2 L (41% fall) and the subject began to complain of dyspnoea, chest tightness, wheezing and cough. These symptoms were partly relieved by salbutamol. Two months later, he was challenged with gaseous formaldehyde with the novel apparatus (see above) for a total of 75 min: he was exposed for 7.5 min to 1 $mg \cdot m^{-3}$ of formaldehyde, and then for 67.5 min to 2.5–3 $mg \cdot m^{-3}$ of formaldehyde. No change in FEV_1 occurred. At the end of the day, the PC_{20} methacholine was 7 $mg \cdot ml^{-1}$. Subsequently, asthma due to hexamethylenetetramine dust was ruled out (since this amine accompanied phenol formaldehyde within the resin used above), as the subject was exposed to the amine dust only for a 30 min cumulative period without significant change in FEV_1 following exposure (not illustrated). At the end of the day, PC_{20} methacholine was 13 $mg \cdot ml^{-1}$.

Subject No. 3

A 31 year old male subject had been working as a carpenter since 1983. He had had asthma in childhood. He had never smoked. He made furniture, cutting different types of wood (oak, pine, maple). He also cut boards made of pine and phenol formaldehyde (0.001%). In 1986, he started noticing nasal congestion, rhinorrhea and sneezing, as well as episodic wheezing, chest tightness and shortness of breath. He reported nasal congestion a few minutes after beginning work, but respiratory symptoms usually occurred in the evening or at night, often waking him up at night. These symptoms improved at weekends and on holidays. He was treated by salbutamol as needed. Skin tests with common inhalants were negative. In July 1994, after a day spent at work, his FEV_1 was 4.33 L (93% pred) with a FVC of 5.29 L (119% pred), whereas his PC_{20} methacholine was 2.0 $mg \cdot ml^{-1}$, reflecting mild bronchial hyperresponsiveness. Serial monitoring of peak expiratory flow rates for a period including time at work and time away from work was highly suggestive of work-related asthma.

Specific inhalation challenges were performed in October 1994. Graphs of specific inhalation challenges are shown in fig. 1c. On the control day, the subject was exposed to control wood-dust with a closed-circuit particle generator for a 30 min interval. No asthmatic reaction occurred. The PC_{20} was 1.0 $mg \cdot ml^{-1}$ at the end of the day. Because this subject was exposed to oak wood-dust at work, he was exposed to it first, with the closed-circuit particle generator for increasing intervals up to 2 h. No significant changes in either FEV_1 or in PC_{20} were documented after exposure. A few days later, we exposed him to phenol formaldehyde resin dust with the closed-circuit particle generator in a progressive fashion for a total of 2 min. He developed an isolated immediate reaction (fig. 1c). At the end of the day, the PC_{20} was significantly reduced (0.17 $mg \cdot ml^{-1}$). A week later, we exposed him to formaldehyde gas with the closed-circuit inhalation challenge apparatus for a cumulative interval of 2.5 min at a concentration of 1 $mg \cdot m^{-3}$. The subject developed an isolated immediate asthmatic reaction (fig. 1c). The PC_{20} was 0.1 $mg \cdot ml^{-1}$ at the end of the day.

Discussion

Two subjects presented asthmatic reactions with formaldehyde resin dust but not with gaseous formaldehyde, whereas one subject experienced an asthmatic reaction with both formaldehyde resin dust and gas. We can reasonably exclude that the asthmatic reaction can be explained in an irritant, nonspecific way. A control asthmatic subject exposed to formaldehyde resin dust in a similar way to Subject No. 1 did not experience an asthmatic reaction. The two other subjects were exposed to formaldehyde dust using a particle generator, which allows for the exposure of subjects to concentrations below the threshold limit value (TLV)- short-term exposure limit (STEL) levels. WITEK *et al.* [14] failed to demonstrate irritant effects among 15 asthmatic volunteers after exposure to 2.0 ppm formaldehyde for 40 min in an environmental chamber. It is unlikely that the lack of reaction after exposure to formaldehyde gas in the case of our

first subject could be attributed to an inhibitory effect of inhaled steroids. Indeed, oral and inhaled steroids can block the late or even the immediate reaction to allergen challenge. However, this has been shown by administering this treatment immediately before the challenge [15]. In Subject No. 1, the last dose of inhaled steroids took place 10 h before the challenge. Moreover, the challenge to formaldehyde gas was performed the day after the challenge to formaldehyde resin. It is highly unlikely that inhaled steroids could suppress an asthmatic reaction, when the same subject on the same treatment experienced an asthmatic reaction the day before.

Although asthma-like symptoms are often reported after exposure to formaldehyde [16, 17], few cases of workers with occupational asthma due to either gaseous or particulate formaldehyde have been documented through objective means [2, 6, 7]. However, in these reports, the relevance of the physical and chemical state of formaldehyde in causing asthma was not explored. Interestingly, FRIGAS *et al.* [5] reported a case of severe asthma that developed following insulation of a house with urea formaldehyde foam. Bronchial challenge with the buoyant dust of the foam caused an asthmatic attack but inhalation of formaldehyde gas did not. The authors speculated that as urea formaldehyde foam was a complex mixture of compounds, some of which are unknown, formaldehyde was not the cause of their patient's asthma. An alternative hypothesis would be that the patient described by FRIGAS *et al.* [5] may still have suffered from asthma due to formaldehyde foam dust, even though she did not react to formaldehyde gas.

The physiopathology of occupational asthma caused by low molecular compounds remains unclear. Some chemicals can induce respiratory symptoms similar to an allergic type I reaction by binding to a protein *in vivo* and acting as an hapten, but they can cause disturbances in the respiratory tract through nonimmunological mechanisms. They are able to interfere with receptor proteins or enzymes. WASS and BELIN [18] postulated a correlation between the ability of a substance to react with proteins and its potential to induce respiratory tract dysfunction. They developed an *in vitro* method for predicting sensitizing properties of inhaled chemicals. Based on these assumptions, the physical and chemical state of formaldehyde (gas or dust) could significantly affect the likelihood of asthma occurring after exposure.

The reaction of formaldehyde with urea or phenol results in the formation of a complex mixture of a high molecular weight polymer with small percentages of unreacted formaldehyde and other additives (catalysts, plasticizers, *etc*.). Thus, occupational asthma caused by high molecular weight polymers of formaldehyde existing as dust, but not by formaldehyde oligomers or monomers existing as gas, is analogous to our cases of occupational asthma due to toluene diisocyanate (TDI) or hexamethylene diisocyanate (HDI) prepolymers, without bronchial reaction to HDI or TDI monomers [19, 20]. The physical state of HDI and TDI monomers greatly differs from that of HDI and TDI prepolymers. HDI prepolymers are encountered as a gas, with a molecular weight in the few hundred daltons; TDI prepolymers take the form of an aerosol, with a molecular weight in the few thousand daltons.

AGIUS *et al.* [21] underlined the potential importance of bifunctional reactivity of low molecular weight substances in their propensity to cause asthma. Many compounds which cause occupational asthma have at least two reactive functions (*e.g* ethylene diamine, piperazine, phenylene diamine) as opposed to their monofunctional counterparts (ethylamine, piperidine, aniline), which do not cause occupational asthma. It can be hypothesized that the likelihood of causing asthma is related to the bifunctional reactivity. Formaldehyde (HCHO) does not have bifunctional reactivity. However, in aqueous solution it exists almost exclusively as a diol (methane diol), with supposedly altered functional reactivity. Consequent to this hypothesis, the fact that urea or phenol formaldehyde resins are high molecular weight polymers is probably relevant to the likelihood of causing asthma. IMBUS [22] suggested that formaldehyde dust that is absorbed onto particles could cause pulmonary reactions and greater airway response than the formaldehyde gas alone. The mechanism is that particulate formaldehyde could reach the lower respiratory tract more easily than formaldehyde gas. Moreover, formaldehyde gas can be largely absorbed on the upper respiratory tract and little of it would reach the lower respiratory tract.

The novel closed-circuit apparatus used to expose our three subjects to formaldehyde gas is a modification of a previously described methodology adapted for use with either alhedydes or amines existing in gaseous form [13, 23]. With this apparatus, we can obtain safe and non-irritant concentrations of the occupational agent. Controlling the exposure with precision also allows us to examine dose-response relationship in subjects with occupational asthma. This procedure allows for exposure to stable concentrations of the occupational agent in a dose-response fashion.

From the practical point of view, these three cases emphasize the need to expose subjects to the occupational agent in the same physical and chemical state usually encountered at work. Specific inhalation challenges in the laboratory should indeed mimic the work exposure as closely as possible, as originally proposed by PEPYS and HUTCHCROFT [12].

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