Closed-circuit Apparatus for Specific Inhalation Challenges With an Occupational Agent, Formaldehyde, in Vapor Form*

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Specific inhalation challenges are an important tool for confirming occupational asthma. In recent years, we have described two closed-circuit apparatuses that allow exposure to stable and controlled concentrations of particles and isocyanate gases. More recently, we developed a similar apparatus that generates chemicals in vapor form. The aim of this work is to describe its performance in the specific case of formaldehyde. This instrument is made of four parts: a generator as such, an exposure chamber, a monitor, and an automated regulatory system. This apparatus was assessed in four subjects suspected of having formaldehyde-induced asthma or alveolitis. The concentrations of formaldehyde were increased from 0.5 to 1 mg/m³ to 3 mg/m³ keeping the concentration at a value of 3 mg/m³ or less (threshold limit value). The dispersion of obtained values by comparison with the median data (6 values) was as follows: maximum value, 12 to 84%; minimum value, 20 to 58%; interquartile range, 0.13 to 0.9 mg/m³. We observed that target concentrations took a few minutes to be reached, but, once they were obtained, delivered concentrations were stable. The new vapor-delivery apparatus allows us to obtain concentrations of formaldehyde that are close to target concentrations with an acceptable dispersion of values around target concentration. Its use should be extended to other chemicals besides formaldehyde. (CHEST 1996; 109:1631-35)

Key words: bronchial provocation tests; occupational lung diseases

Asthma is now the most common occupational respiratory ailment. Its diagnosis is based on several tools, including specific inhalation challenges in which subjects are exposed to the suspected occupational agent in a controlled way under close supervision in a hospital laboratory. These tests were first proposed by Pepys and Hutchcroft¹ in the 1970s. In recent years, our group has made efforts to improve the method of these tests to make them safer and more accurately interpretable. We first described and validated an apparatus that can generate particles.²⁴ We then developed an apparatus that can generate isocyanates as a vapor.⁵

Occupational agents responsible for asthma are frequently present as vapors.⁶,⁷ We developed an apparatus to expose subjects to vapors. Vapor state is obtained when there is a balance between one physical state of a substance (solid or liquid) and its gaseous state. For every chemical compound, this balance between the solid and liquid phase is obtained at a given temperature. The goal of this article is to describe this method and its specific use in the case of formaldehyde, which is an agent commonly used in various laboratories, insulation materials, and boards and can cause occupational asthma.⁶,⁷ We also present preliminary data on the stability of obtained concentrations by comparison with target concentrations in four subjects who were suspected of presenting with occupational asthma or alveolitis and who underwent specific inhalation challenges.
**Materials and Methods**

**Vapor Apparatus**

The device for exposure to formaldehyde consists of four parts: (1) a generator; (2) an exposure chamber; (3) a monitoring device; and (4) an automated regulatory system (Fig 1). Formaldehyde vapor is generated by heating solid paraformaldehyde placed in a small tube in a silicon bath at 80°C. Air (0 to 2 L/min), taken from the hospital’s general compressed air system, is forced into the small tube that contains paraformaldehyde as a carrier gas for the formaldehyde vapor to the exposure chamber. A part of this airflow can be eliminated by an exhaust pump to obtain the desired concentration. This air is then diluted with a constant flow of air at 50 L/min, which is sent to the exposure chamber after having been properly humidified with a humidifier (approximately 50% humidity in the specific case of formaldehyde). The exposure chamber consists of a vertical acrylic (Plexiglass) tube (size=15 cm diameter×1.5 m long) covered inside with Teflon. There are three holes in the middle portion of the wall of the cylinder. The first hole allows the subject to breathe the vapor through a loose and comfortable orofacial mask, through the mouth, the nose being clipped. A unidirectional thin membrane prevents vapor from escaping through the face mask when the subject is not breathing through the apparatus. The second hole is a port that allows for on-line sampling of the air. This air is monitored by a vibroacoustic spectrophotometer (Brüel and Kjaer; Naerum, Denmark). The third hole allows for sampling of air for further chemical analysis. The extra air that is not inhaled by the subject is removed by an exhaust pump and adsorbed. The expired air is vented outdoors with a tubing system after being adsorbed. A computer controls the overall function of the system by adjusting pressure within the exposure room (this pressure should be null, so that as much flow enters and exits the system), the humidity of air coming into the exposure chamber (approximately 50%) (as assessed with an Omega thermohygrometer; Stanford, Conn) and the flow of air, which should be approximately 50 L/min.

Correspondence was assessed between the readings (Brüel and Kjaer) and the chemical analytical method proposed by the National Institute for Occupational Safety and Health (NIOSH). In 12 samplings ranging from 0.5 to 8 mg/m³, the regression coefficient was 0.99 with a mean tendency for having higher readings by 0.7 mg/m³ for the monitor (Brüel and Kjaer).

**Tests in Laboratory**

Before using the apparatus on human subjects, we tested it in the laboratory. The apparatus was connected to a ventilator to mimic human breathing and appreciate its behavior during changes of pressure induced by the ventilator in the exposure chamber. Concentrations of formaldehyde were set at 1, 2, and 4 mg/m³ to assess the stability of concentrations.

**Subjects**

Four subjects suspected of having occupational asthma or alveolitis due to formaldehyde were exposed to formaldehyde vapor with the new closed-circuit apparatus. The complete case histories of three of these four patients with confirmed occupational asthma are presented elsewhere. Briefly, two subjects were found to have occupational asthma to formaldehyde resin dust but not formaldehyde vapor, whereas the other subject reacted to formaldehyde in both particle and vapor forms. The fourth patient had a negative inhalation challenge.

**Study Design**

The four subjects were exposed to formaldehyde vapor with the new closed-circuit apparatus. Duration of exposure and target concentrations are reported in Table 1. The three subjects suspected of having occupational asthma due to formaldehyde (cases...
Many tests were performed in laboratory to obtain satisfactory results. We report herein one instance in which three targeted concentrations of formaldehyde were tested: 4, 2, and 1 mg/mL. When a stable concentration was reached, a ventilator was connected to the exposure chamber. This ventilator mimicked human breathing at tidal volume. We obtained a satisfactory stability of concentrations during the three plateau periods, and, at a time of modification from one concentration to the next, it took only a few minutes to get stable concentrations (Fig 2).

Tests in Subjects

Obtained concentrations were close to target concentrations (Table 1). The distribution of concentrations was not normal in cases 1, 2, and 4. The distribution of concentrations was not skewed to the right (ie, obtained concentrations did not exceed targeted concentrations) except for the targeted concentration of 3.0 mg/m³ in case 2 (see below), in whom there was such a tendency.

Subject 1

This patient was exposed in such a way as to attempt to get concentrations of 1, 2, and 3 mg/m³ in a progressive and sustained manner; the subject remained exposed during a total interval of 2 h. As shown in Figure 3, for the last concentration that was planned (3.0 mg/m³), it took a little longer to get a stable concentration, and in some instances, the maximum targeted concentration of 3.0 mg/m³ was exceeded. This is probably due to the fact that the staff were using this new apparatus for the first time.

Subject 2

This subject was exposed at two targeted concentrations (Table 1). As shown in Figure 3, we obtained

![Figure 2. On-line 1-min values for readings of formaldehyde values during tests in laboratory. Arrows show the start of ventilator.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21733/ on 06/25/2017)
Subject 4

The target concentration was 2 mg/m³. Figure 3 shows individual data during the exposure period of 2 h. We increased the concentration to 3 mg/m³ after 15 min of exposure but, because of overshooting, we decided to reduce the concentration, setting it back at 2 mg/m³ where it remained very stable for the remaining period of exposure (approximately 110 min).

Discussion

Specific inhalation challenges are a useful means of establishing the association between exposure to an occupational agent and the development of asthma. Although there are various means to investigate subjects with potential work-related asthma,10 for most, specific inhalation challenges are still considered as the gold standard to confirm the condition.11,12 The methodology of specific inhalation challenges was proposed by Pepys and Hutchcroft1 more than 20 years ago; using this procedure, exposure is realistic in that its aim is to reproduce conditions of exposure at work without, in most instances, direct monitoring and information on the dose of agent that is administered by inhalation. The tests should be performed in specialized centers.

Several authors have proposed methods for generating and monitoring concentrations of formaldehyde for specific inhalation challenges.13-17 Nordman and coworkers13 performed bronchial provocation with formaldehyde vapor by evaporating 35 or 70 µL of an aqueous solution of formaldehyde in a 10-m³ exposure chamber. There was no on-line assessment of concentrations during exposure. Burge and coworkers14 carried out bronchial provocation tests with formaldehyde gas by diluting solutions of formaldehyde with distilled water to yield solution of formaldehyde at various concentrations (0.1%, 1%, 10%, etc). Subjects were exposed by painting formaldehyde solutions on a paper surface. Atmospheric concentrations were measured 11 times during formaldehyde exposure. It was not possible to determine accurately the atmospheric end target concentration of formaldehyde that was obtained. Indeed, these authors reported no data on stability and variations of delivered concentrations. A similar approach was proposed by Hendrick and coworkers.15 Frigas and coworkers16 proposed to generate formaldehyde (using a Dynacalibrator; Metronics; Santa Clara, Calif). The accurate delivery was confirmed by measuring the concentration of formaldehyde vapor at the entry of the inhalation portion of the system. The authors do not give data on stability or variations of delivered concentrations. Finally, a generator of formaldehyde was proposed by Balmat.17 The generator allows for constant formaldehyde levels by heating paraformaldehyde. Delivered concentrations over a 3-day assessment varied by ±11% (95% confi-
chamber. However, this apparatus generates formaldehyde in a large (34 m³) exposure chamber and it seems difficult to rapidly modify concentrations of formaldehyde with this system. Although the general principles of the latter system are similar to our method, our closed-circuit apparatus offers many advantages. First, it makes it possible to modify concentrations in the exposure chamber rapidly and as needed. Second, because our exposure chamber is relatively small and of a closed-circuit type, exposure is by inhalation only, and there is no exposure of the personnel responsible for testing. Finally, there is an automatic feedback to regulate various parameters, including the concentration of formaldehyde as well as pressure and humidity of the air directed into the exposure chamber.

In order to improve the method and the reproducibility of these tests, we proposed to generate the occupational agent in a manner that can allow the delivery of accurate and stable preset concentrations. This makes it possible to deliver doses below the recommended threshold limit value-short-term exposure level values so as to be nonirritant. This is particularly valuable in the cases of asthmatic subjects in whom nonspecific irritant reactions should be avoided. Also, the dose should be delivered in a progressive way, generating dose-response curves in a safe and acceptable way in humans. Indeed, the ability to generate concentrations in a progressive fashion should enable us to avoid provoking severe immediate asthmatic reactions, the main threat encountered with specific inhalation challenges in humans. Based on the description of this new method, one can conclude that it is possible to get preset concentrations of formaldehyde and to maintain these concentrations in a stable manner. Adjusting of concentrations from one level to the next was a bit more difficult when we exposed subjects, probably because of the personnel’s inexperience; indeed, it took a few minutes for this to be accomplished in a satisfactory way, with reasonable stabilization of concentrations. For the tests done with the ventilator, adjustment from one concentration to the next was faster. Stabilization of concentrations in humans can be improved by disconnecting the subject from the exposure chamber, which we did not do in this study.

We did not make direct comparison of our new method with a more conventional approach that would be to expose the individual in a small cubicle in a realistic way as described by Pepys and Huchcroft. The experience we have with this approach is that it is not possible to obtain concentrations that are as stable as with a smaller closed-circuit method even if direct monitoring of concentrations is possible. We already showed the superiority of the latter approach in the case of particles and isocyanates. Depending on what type of formaldehyde is being used at work, the dust or the vapor, the exposure situation of the workplace can be reproduced using a particle or the vapor generator we now describe. The described method needs to be further validated in a larger number of subjects. This method also needs to be extended to other occupational agents that exist in vapor form. It is now our effort to try other vapors such as colophony, glutaraldehyde, and various amines that are commonly incriminated as causes of occupational asthma.

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REFERENCES

1 Pepys J, Huchcroft B]. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. Am Rev Respir Dis 1975;112:829-39
17 Balmat JJ. Generation of constant formaldehyde levels for inhalation studies. Am Ind Hyg Assoc J 1985;46:690-92