A New Methyl Bromide Gas Generator for Inhalation Toxicity Studies

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Abstract: A simple generator for methyl bromide gas has been newly developed by us. For inhalation toxicity studies, until now, there have been few generators capable of producing a constant and stable concentration of methyl bromide gas easily because of its high volatility. The principle of this new generator is based on gas-liquid equilibrium. The gas is generated from the surface of liquid methyl bromide in an evaporator made of a Teflon tube. The generator can produce up to 10,000 ppm of methyl bromide gas in a 0.1 m³ exposure chamber, and the concentration of this generated gas is able to be kept within ±0.8% over a long period of time. The generator has proved to be useful for investigating the effects of methyl bromide on health in inhalation toxicity studies.

Key words: methyl bromide, inhalation toxicity, generator.

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Introduction

Methyl bromide (CH₃Br) is a colorless gas that boils at 3.56°C and has a saturate gas pressure of 1,420 mmHg at 20°C. It is widely used as a fumigant to treat soil, grains and other commodities, mills, warehouses, and houses [1]. A typical response to exposure to methyl bromide gas at high concentrations is lung irritation with congestion and edema, which often develops into confluent bronchial pneumonia [1]. A chronic or repeated exposure to lower concentrations of the gas induces not only some pulmonary damage but also various neurological symptoms involving paralysis [2], dysmetria and optic atrophy [3]. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value (TLV) of 5 ppm [4].

In spite of the apparent toxicity, the mechanism of methyl bromide action is unclear. Since inhalation is by far the most significant route of exposure, an inhalation toxicity study is very important in investigating the mechanism of action or the health effects of methyl bromide. To perform this, a generator, which produces a known concentration of methyl bromide gas, is necessary. In particular, for chronic study, the generator should produce at a constant concentration over a long period of time. If the boiling point of a material, such as nitrogen gas, is very low, the gas could be obtained easily at a constant flow rate from the cylinder using a pressure regulator and a flow control valve. In this case, the
known concentration of the gas is prepared continuously by diluting the gas with air. On the other hand, in the case when the boiling point of a material, such as organic solvents, is higher than room temperature, there are many generators available, such as, diffusion tubes [5, 6], bubblers [7], counter current volatilization [8], syringe pumps [9] and a sintered sphere of glass beads [10].

We cannot however use the above methods for the generation of methyl bromide gas, because the boiling point of it is in between room temperature and freezing point and the phase is not stable. In addition, since methyl bromide is usually supplied as a liquid which is packed in a cylinder with a siphon, it flows from the bottom of the cylinder through the siphon with flushing when a valve of the cylinder is opened. In this case, it is difficult to maintain a constant gas concentration over a long period because accurate control of the flow rate is not easy during the liquid-vapor two-phase flow. Kent et al [11] prepared the methyl bromide gas in an exposure chamber for inhalation study using a gas cylinder. In their experiment, the relative standard deviation of the gas concentration was 8–18%. When we use a permeation tube [12], we can obtain the gas with much better stability over a long period of time, but the amount of gas obtained from the permeation tube is so small that it is not applicable for inhalation toxicity studies.

Therefore, we have developed a simple but useful methyl bromide gas generator for application to an inhalation exposure system, and studied its generating characteristics experimentally.

Experimental

Experimental apparatus

Figure 1 shows a schematic diagram of the experimental apparatus. The generator consists of a cylinder containing liquid methyl bromide (1), an evaporator made of a Teflon...
A New Generator for Methyl Bromide Gas

Table 1. Analytical conditions

<table>
<thead>
<tr>
<th>Gas chromatograph</th>
<th>Gasukuro Kogyo Model 370</th>
</tr>
</thead>
<tbody>
<tr>
<td>column</td>
<td>2 m×3 mm i. d. glass column</td>
</tr>
<tr>
<td>packing</td>
<td>15% PEG-20M on uniport B</td>
</tr>
<tr>
<td>carrier gas</td>
<td>N₂, 45 ml/min</td>
</tr>
<tr>
<td>column temperature</td>
<td>70°C</td>
</tr>
<tr>
<td>injection port temperature</td>
<td>150°C</td>
</tr>
<tr>
<td>Auto gas sampler</td>
<td>Gasukuro Kogyo GS-5000A</td>
</tr>
</tbody>
</table>

tube (8 mm inner diameter and 50 cm long)(4), three stop valves (2), (3), (6), a needle valve for flow control (7), and a rotameter (8). Glass wool (5) is packed at the top of the evaporator as a demister. Liquid methyl bromide is always drawn from the bottom of the cylinder to the evaporator through a siphon which is inserted in the cylinder. In the evaporator, both saturated gas and liquid methyl bromide exist in an equilibrium state. When the stop valve (6) and the flow control valve (7) are opened, only the gas flows from the top of the evaporator. In this case, the pressure in the evaporator decreases instantaneously, but a part of the liquid evaporates in order to maintain the equilibrium state. As the pressure in the evaporator is kept constant with the saturated gas, the flow rate also becomes constant until all of the liquid in the evaporator disappears. Because the liquid level in the evaporator is able to be observed from the outside of the tube, we can detect the last of the liquid in the cylinder when the liquid is introduced into the evaporator. We can thus avoid any trouble caused by a lack of liquid methyl bromide during the experiment.

An exposure chamber (volume 0.1 m³) (10) is made of stainless steel. Air in the chamber is made to flow from top to bottom by using an exhaust pump (13). The air flow rate is monitored with a rotameter (12) and is controlled with a needle valve (11). A small fan (9) is installed near the air and gas inlet to homogenize the methyl bromide gas in the chamber.

An auto gas sampler (Gasukuro Kogyo, GS-5000A) (14) and a gas chromatograph (Gasukuro Kogyo, Model 370) (15) equipped with a flame ionization detector (FID) are used for the gas sampling and for the determination of the gas concentration in the chamber, respectively.

Experimental procedure

The stop valve (6) is closed, and the valve of the cylinder (2) and stop valve (3) are opened to introduce the liquid methyl bromide into the evaporator (4). After the liquid in the evaporator reaches the desired level, the valves (2) and (3) are closed, and the stop valve (6) and the needle valve (7) are opened. The flow rate is monitored using the rotameter (8) which is calibrated with a soap film flowmeter and regulated by the needle valve (7). The generated gas is diluted with air, and introduced into the exposure
chamber. The air in the chamber containing methyl bromide gas is sampled automatically by the auto gas sampler at intervals of 5 minutes and the concentration is determined by the gas chromatograph. The analytical conditions used are shown in Table 1.

**Results and Discussion**

Generation characteristics of gas

Figure 2 shows a typical gas chromatogram of methyl bromide gas sampled in the exposure chamber. The gas flow rate was 15 ml/min and the dilution air flow rate was 25 ℓ/min. When the fan (9) is not operating, the gas concentration fluctuated when an animal cage was in the chamber. By using the fan, the concentration of the gas in the chamber could be kept within 0.8% during the experimental time of 6 hours, except at the initial transient period.

When the liquid methyl bromide was introduced into the evaporator without any traps, the liquid occasionally flowed over the evaporator to the needle valve (7). When this happened, the liquid evaporated at the valve, and the flow rate could not be kept constant but pulsed irregularly. In order to avoid this, glass wool was packed at the top of the evaporator. The glass wool could absorb the liquid and prevent an overflow to a certain extent. However, when the average liquid level exceeded the height of the evaporator, the glass wool became useless. The U-shaped tube was then connected between the stop valve (6) and needle valve (7) to trap the liquid.

The inside of the evaporator is kept at almost the saturated pressure of methyl bromide and the saturated pressure increases with the increasing temperature. As the gas flow rate depends on the pressure difference between the evaporator and the chamber, the flow rate may change with time because the room temperature is not always constant. In our experiment, however, the gas concentration was kept almost constant at the steady state condition as shown in Fig. 2. If a more accurate regulation is required, the evaporator

![Fig. 2. Temporal change of generated gas. gas flow rate=15 ml/min, air flow rate=25 ℓ/min.](image-url)
should be installed in a thermostatic bath or a water jacket that surrounds the evaporator keeping the temperature of the evaporator constant.

The gas concentration at steady state condition is determined by the ratio of methyl bromide gas flow rate and the total flow rate. The gas concentration can be easily adjusted to a desired value by only regulating the gas and the air flow rate.

The amount of liquid methyl bromide required, \( m \) (g), is estimated by the following equation.

\[
m = \frac{\pi D^2 \rho}{4} L = \frac{(Q_1 + Q_2) C t}{22.4 \frac{273 + T}{273}} \times 10^{-6} \tag{1}
\]

Where, \( D \) is the diameter of the evaporator (cm), \( L \) is the height of liquid in the evaporator (cm), \( Q_1 \) is the flow rate of methyl bromide gas (\( \ell/min \)), \( Q_2 \) is the air flow rate (\( \ell/min \)), \( C \) is the concentration (ppm), \( t \) is the generating period (min), \( \rho \) is the liquid density (\( g/cm^3 \)), \( MW \) is the molecular weight and \( T \) is the temperature (\( ^\circ C \)). From Equation (1), we can calculate the height of liquid level required for the experimental conditions. The density and molecular weight of methyl bromide are 1.732 and 94.95, respectively, and in this study, \( D = 0.8 \) cm, \( T = 25^\circ C \). Then, the required liquid height is:

\[
L = 4.46 \times 10^{-6} CQ t = 4.46 Q_1 t \tag{2}
\]

Where, \( Q \) is the total flow rate \( ( = Q_1 + Q_2 \) \( \ell/min \)). By introducing the liquid methyl bromide into the evaporator up to the desired height calculated by Eq. (2), an excess exposure could be avoided even in the case of trouble.

Under our experimental conditions, the practical range of methyl bromide gas flow rate and dilution air flow rate were \( 10 - 100 \) ml/min and \( 10 - 100 \) \( \ell/min \), respectively. We could therefore obtain from 100 to 10,000 ppm of methyl bromide gas in the 0.1 m\(^3\) exposure chamber. The generator can produce a wider range of methyl bromide gas if one exchanges the needle valves and the rotameters. However, when we use a larger exposure chamber in which a much larger air flow rate is used, a tube with a larger diameter and/or a longer length (height) as an evaporator must be selected. The appropriate diameter and length can then be calculated by Eq. (1).

Estimation of initial transient period

In Fig. 2, about twenty minutes was needed before a steady state concentration was obtained. This transient period depends on the size of the chamber and the air flow rate. For a inhalation study, it is very important to estimate this period, because inhalation should be carried out at a constant concentration. This transient period can be estimated by the mass balance of methyl bromide.

As the fan is installed near the top of the chamber, the air and the methyl bromide gas in the chamber is assumed to be mixed perfectly. In this case, the mass balance equation is shown as follows:
\[ V \frac{dC}{dt} = Q(C_0 - C) \]  \hspace{1cm} (3)

Where, \( C_0 \) is the gas concentration at steady state, \( V \) is the chamber volume and \( t \) is the time. Equation (3) can be solved easily under the initial condition of \( C=0 \) at \( t=0 \):

\[ C = C_0 \left(1 - e^{-Q/Vt}\right) \]  \hspace{1cm} (4)

Figure 3 shows the comparison of the experimental gas concentrations with the calculated ones from Eq. (4). The former are in good agreement with the latter. Therefore, we can predict the transient period up until the vapor concentration becomes a steady state for all experimental conditions.

**Conclusion**

The generator developed in this study is quite simple but when used it is able to maintain a constant concentration of methyl bromide gas in the exposure chamber over a long period of time. This generator is applicable not only to methyl bromide gas but also to other gases whose boiling points are similar to methyl bromide. We believe that our generator will prove to be useful in investigating health effects or the mechanism of action of toxic gases caused by inhalation.

**References**


臭化メチル吸入曝露実験のためのガス発生装置の試作

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要 旨：臭化メチルは、蒸留剤として、消毒に広く使用されているが、神経毒性があることが知られ、取扱いに注意を要する。臭化メチルの沸点が3.56℃と低く、常温ではガスであるため、主に吸入によって体内に取り込まれる。したがって、臭化メチルの生体影響を調べるためには吸入曝露実験を行う必要があるが、そのためには、一定濃度のガスを長時間安定して発生させることのできる装置が必要になる。そこで気液平衡関係を利用したガス発生装置を試作し、その発生特性を調べるとともに、曝露チャンバーに接続し、装置の有用性を検討し、その実用性が高いことが、実験的に明らかとなった。

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