

This article reviews the physical chemistry of the safe production of hydrogen peroxide vapor and how to maintain a constant concentration of the vapor in a chamber. This article also reviews the calculations and procedures used to obtain the maximum concentration of vapor without allowing condensation of liquid to occur.

The Physical Chemistry of Decontamination with Gaseous Hydrogen Peroxide

by Carl Hultman, Aaron Hill, and Gerald McDonnell

Introduction

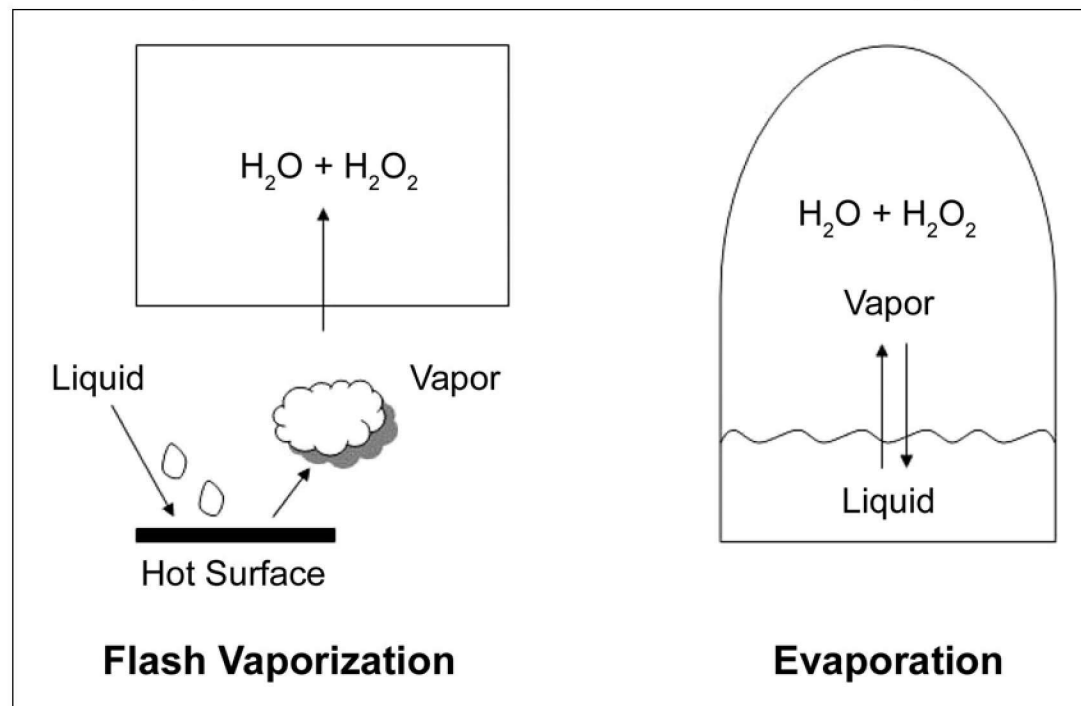
The decontamination of surfaces contaminated with microorganisms within critical, enclosed areas is an important consideration to pharmaceutical, research, and other facilities. A safe and reliable way to decontaminate hard surfaces (including those in isolators, laminar flow cabinets, and cleanrooms) involves exposing the surfaces to gas-phase hydrogen peroxide.^{1,2,3} Gas phase hydrogen peroxide is a known rapid, broad-spectrum antimicrobial which, as part of a controlled process, can allow for reproducible area decontamination. Hydrogen peroxide also has a rather safe profile, both from a user and environmental perspective, in comparison to traditional fumigation methods that have used

formaldehyde, ethylene oxide, or propylene oxide gas. An understanding of the physical chemistry behind the generation and control of gaseous hydrogen peroxide is important to optimize the safety, efficacy, and reproducibility of a given decontamination process. This article discusses the physical chemistry behind a typical process and the procedures needed to achieve optimal decontamination using gaseous hydrogen peroxide.

Liquid and Gaseous Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is widely used as an antiseptic, disinfectant, and sterilant.⁴ It is a desirable biocide because it demonstrates broad spectrum antimicrobial activity, has low toxic-

Figure 1. Hydrogen peroxide vaporization processes.



Hydrogen Peroxide Weight (%w/v) t = 25 C	
Vapor	Liquid
1.87	32.1
8.0	55.7
24.1	73.9
35	77.8
56.4	88.3

Table A. Equilibrium concentrations of hydrogen peroxide vapor that will form (evaporate) over liquid hydrogen peroxide (see Figure 1, *Evaporation*).

ity, and breaks down into water and oxygen in the environment. For example, liquid hydrogen peroxide solution is used directly on the skin at up to 6% w/v and at higher concentrations as a general surface disinfectant. Pure hydrogen peroxide exists as a liquid at room temperature (25°C) and atmospheric pressure (101.35kPa). For antimicrobial applications, greater efficacy is observed as the concentration is increased, which is particularly important to achieve sporicidal activity; however, at high concentrations, liquid hydrogen peroxide is unstable/reactive and may be explosive or undergo spontaneous combustion depending on how it is handled.^{5,6} Therefore, liquid preparations are used at lower concentrations diluted in water (generally 3 to 59% by weight) and often in synergistic formulations with other biocides (including peracetic acid). The antimicrobial activity of hydrogen peroxide is dramatically increased when in a gaseous phase. For example, the efficacy of hydrogen peroxide against bacterial spores has been shown to be similar at a gaseous concentration of 1mg/L in comparison to ~400mg/L in liquid.⁵ To generate the gas, it is necessary to heat liquid hydrogen peroxide, generally by flash vaporization on a hot surface that will be discussed in more detail. Under these gaseous conditions, even lower concentrations (~0.1mg/L) of peroxide are rapidly antimicrobial and may be used to achieve sporicidal activity.

A further consideration in the comparison of liquid and gaseous peroxide is material compatibility; attention should be focused on two factors when considering surface contact:

1. the effect of the material on the decomposition rate of the peroxide (therefore loss of activity)
2. the effect of hydrogen peroxide on the material itself.

With liquid hydrogen peroxide (of about 45% by weight or more), the possibility of forming detonatable mixtures on reaction with organic substances may exist. Commonly used materials have been categorized into four different classes according to the suitability of exposing these materials to liquid concentrations equal to or higher than 90% by weight of peroxide in water.⁷ Of note, Class 4 materials may cause decomposition of hydrogen peroxide, and particularly with concentrated liquid peroxide, cause damage to the surface or form explosive mixtures. Some of these Class 4 materials include wood products and polymers such as neoprene, buna rubber, silicone rubber, and tygon. These materials may undergo degradation and/or cause spontaneous combustion. Other Class 4 metals, including copper, lead, magnesium

alloys, and stellite #6, act as catalysts that accelerate the decomposition of peroxide and also may encourage combustion when in contact with other materials. Lubricants such as silicones, paraffin, and aroclors also are Class 4 materials. Highly concentrated solutions of peroxide also may degrade certain electrical components or other materials; an example is that liquid hydrogen peroxide can attack the plasticizers in PolyVinyl Chloride (PVC), thus making the surface brittle after extended exposure. Additionally, certain grades of stainless steel, such as 304 grade, can show slight corrosion or discoloration for liquid peroxide solutions ranging from 10 to 100% by weight.

Hydrogen Peroxide Evaporation and Condensation

Hydrogen peroxide vapor can be conveniently produced from hydrogen peroxide/water solutions by two distinct processes, evaporation and flash vaporization - *Figure 1*. It is important to note that both processes will produce different concentrations of hydrogen peroxide vapor in a given volume. When liquid hydrogen peroxide is allowed to evaporate into a dry, enclosed space, the concentration of hydrogen peroxide in the vapor state is much lower than the concentration in liquid state - *Figure 2*. This occurs because the water leaves the mixture at a higher rate than the peroxide due to the higher vapor pressure of water. For instance, if a 35% (by mass) hydrogen peroxide/65% water mixture evaporates into a dry enclosed space at 25°C, the resulting gas will consist of 2.15% (by mass) hydrogen peroxide and 97.85% water at saturation. Saturation refers to the point at which the air can not hold further peroxide/water and at which point condensation (or precipitation) or water/peroxide will occur. The concentration at which this occurs (referred to as the 'dew' point) can be predicted based on the peroxide/water concentrations, and the temperature of the gas - *Figure 2*. A detailed discussion of this phenomenon is discussed in the literature.⁵

The evaporation rate can be increased by applying an energy source, for example heat can be applied to boil the peroxide/water solution. Since water has a lower boiling point than hydrogen peroxide, the water will vaporize at a higher rate, giving a higher concentration of water in the gaseous state and an increased concentration of hydrogen peroxide in liquid state. With time, the higher peroxide liquid concentration may become unsuitable for materials in contact with the liquid and can pose a safety risk.

The equilibrium concentration of peroxide in the vapor over a liquid is always lower than the concentration in the liquid. Table 1 shows the concentration of peroxide in the vapor over liquid solutions at different peroxide concentrations at 25°C. The equilibrium concentration of peroxide in the vapor is always lower because the water escapes the liquid at a higher rate than the peroxide. The reverse is true when peroxide/water vapor condenses to the liquid state. As shown in Table A, the equilibrium concentration of the liquid formed when a vapor of 35% by weight peroxide condenses is about 77.8% by weight peroxide. This is because the peroxide in the vapor has a greater desire to enter the liquid state than

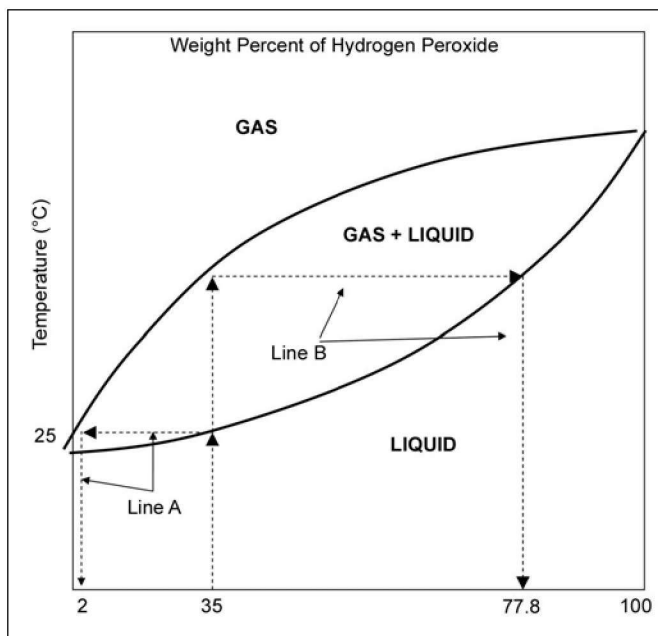


Figure 2. A representation of the Hydrogen Peroxide/Water Phase Diagram. The upper solid line indicates the point at which the gas mixture is formed (note higher concentrations at higher temperatures) and the lower solid line when liquid is present. Line A shows the conversion of 35% liquid peroxide/water mixture (at 25°C) to vapor at ~2% peroxide. Line B shows the condensation of 35% gaseous peroxide/water mixture to liquid at ~78%.

the water in the vapor. Therefore, the peroxide condenses at a higher rate than the water, causing the higher concentration of peroxide in the resulting liquid.

Flash vaporization is a distinct process which can be achieved by applying energy, e.g., by direct application of a peroxide/water mixture to a hot surface - *Figure 1*. Flash vaporization forces the water and hydrogen peroxide in the liquid solution to evaporate *simultaneously*, thereby producing gaseous concentrations of water and peroxide at approximately the same concentration as the starting liquid mixture. The gas concentration will stay constant as long as condensation does not occur. Table B shows the concentrations of hydrogen peroxide that will saturate the vapor and cause condensation. If the gas concentration is increased above saturation or if cooled to below the dew point, condensation will occur. For example, when condensation occurs with a gas at ~35% by weight peroxide it will condense as a liquid at ~77.8% by weight peroxide - *Figure 2*.

Physical Chemistry

The vapor pressures of gases over multi-component liquid solutions may be calculated using the following equations:^{5,8,9}

$$P_{p(\text{gas})} = X_{p(\text{liq})} Y_p P_p^o \quad (1)$$

$$P_{w(\text{gas})} = X_{w(\text{liq})} Y_w P_w^o \quad (2)$$

$$Y_{w(\text{liquid})} = \exp\left[\frac{(1-X_w)^2}{RT}\right] (B_0 + B_1(1 - 4X_w) + B_2(1 - 2X_w)(1 - 6X_w)) \quad (3)$$

$$Y_{p(\text{liquid})} = \exp\left[\frac{X_w^2}{RT}\right] (B_0 + B_1(3 - 4X_w) + B_2(1 - 2X_w)(5 - 6X_w)) \quad (4)$$

where:

- $P_{p(\text{gas})}$ is the vapor pressure of the peroxide in the vapor in atmospheres
- $P_{w(\text{gas})}$ is the vapor pressure of water in the vapor in atmospheres
- X_p and X_w are the mole fractions of peroxide and water respectively in the liquid
- Y_p and Y_w are the activity coefficients for peroxide and water respectively in liquid solution

P_p^o and P_w^o are the equilibrium vapor pressures in atmospheres of pure peroxide and water respectively at the temperature of interest. B_0 , B_1 , and B_2 are empirically determined constants for hydrogen peroxide with the values shown below.

$$B_0 = -752 + 0.97t \quad t \text{ in degrees centigrade}$$

$$B_1 = 85$$

$$B_2 = 13$$

Vapor pressure data may be converted into gas phase concentration units of mg gas per liter using the ideal gas equation as shown below.

$$\text{mg/liter} = P(\text{Mol Wt})(1000 \text{ mg/g})/RT \quad (5)$$

The concentration in mg/liter calculated from equation five is the concentration at a given temperature that will cause condensation, where, P is pressure in atmospheres, Mol Wt is the molecular weight of the gas of interest in grams/mole, R is the ideal gas constant 0.082 latm/deg mole, and T is temperature (°K).

Achieving Optimal Concentration of Peroxide in Vapor Form

As more vapor at a composition of 35% by weight peroxide is introduced into an enclosed chamber, the pressure and concentrations of the peroxide/water vapor in the chamber will increase. Eventually, a high enough concentration (expressed in mg/liter) will be reached at the operating temperature to cause the undesirable condensation of liquid in the chamber. The maximum allowable concentration of peroxide in the vapor that will not cause condensation may be calculated using Equations one through five. One of the complications associated with condensation is that undesirable high concentrations of peroxide liquid solutions will be formed on surfaces. Also, as liquid condenses, it may not uniformly cover all solid surfaces which may lead to non-uniform disinfection/sterilization of surfaces. Other complications associated with condensation will be elaborated on in a later section. The gaseous state for hydrogen peroxide when used for decontamination is advantageous because:

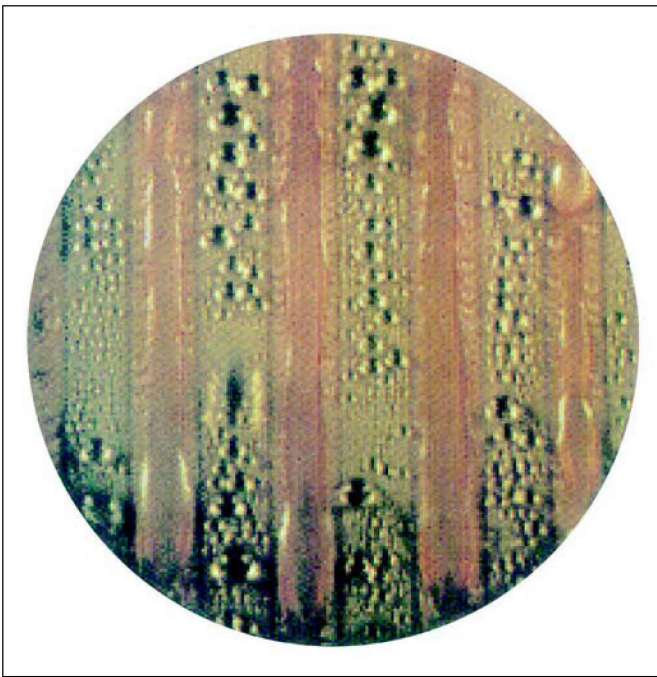


Figure 3. Dropwise condensation on contaminated metal surface.

1. Gas will have uniform contact with all exposed surfaces, thus assuring that all surfaces are uniformly decontaminated.
2. Gas will have uniform contact with surfaces with complex topographies. Examples include horizontal or vertical surfaces, cracks, and complex curvatures.
3. Gas may be safely maintained in the chamber.
4. Gas may be efficiently and quickly removed from the chamber at the end of a given decontamination time thus decreasing cycle time.

As the antimicrobial efficacy increases with increased peroxide concentration, it is desirable to get the peroxide concentration in the gas as high as possible in the chamber without having condensation occur. It is possible to calculate the maximum pressure (and/or concentration) of peroxide (or mg/L of peroxide in the chamber) that will initiate condensation using Equations one through five by knowing:

1. the concentration of the flash vaporized gas being used to fill the chamber
2. the total pressure in the chamber
3. the humidity in the carrier gas (e.g., air used to circulate gas into and out of the chamber showing the design of the decontamination system - Figure 4) and the decontamination chamber
4. the chamber temperature^{5,8,9}

As these equations can often be time consuming to do by hand, computer programs have been developed to calculate the optimum decontamination conditions for any given enclosed volume.¹⁰ Table B shows examples of the maximum peroxide concentration allowed in the chamber to prevent condensation of liquid at various temperatures at two different humidity levels for the carrier gas. Calculations assumed flash vaporization of 35% by weight peroxide. Note that increasing the relative humidity in the carrier gas decreases the maximum concentration of peroxide that may be achieved in the decontamination chamber.

Why Condensation Should be Avoided

As described above, high concentration of peroxide in the liquid state (as occurs with condensation) can be antimicrobial, but also poses some further disadvantages. The first is material compatibility. As shown in Figure 1 and Table A, the concentration of a liquid formed when 35% by weight gas condenses will be about 78% by weight peroxide. This is higher than the recommended maximum concentration of 45% by weight peroxide to assure suitable interactions with other materials. As discussed above, this peroxide concentration or higher may not only cause spontaneous combustion and also may accelerate decomposition of peroxide or cause degradation of materials. Incompatible materials can include painted surfaces and electronics. Peroxide condensation also can decrease the useful life of chamber materials in particular, those used in flexible-walled isolators. Once the condensate is formed it will eventually have to be evaporated from the chamber as peroxide is removed at the end of a decontamination phase. The slow evaporation will cause the peroxide concentration in the liquid to reach even higher unsuitable concentrations regarding safety and degradation of materials.

Decontamination reproducibility is a further concern. When condensation occurs, the surfaces in the chamber may not get uniformly exposed, depending on how condensation occurs. Condensation can occur either in a drop wise or film form, depending on the nature of the contact surface. The determining property is the surface tension of the solid surface. In general, film condensation occurs if the surface tension of the solid is at least 10 dynes/cm higher than the surface tension of the liquid condensing. The surface tension of liquid peroxide/water solutions range from 73 dynes/cm (pure water) to

Temperature(°C)	Maximum Hydrogen Peroxide Concentration (no condensation) (mg/L)	
	0% Relative Humidity Carrier Gas	10% Relative Humidity Carrier Gas
0	0.35	0.28
10	0.77	0.63
20	1.56	1.28
30	3.01	2.50
40	5.49	4.60
50	9.60	8.11
60	16.13	13.68

Table B. Maximum peroxide vapor concentration at various temperatures.

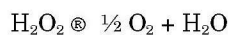
about 80 dynes/cm (pure peroxide). The surface tension for 78% by weight peroxide liquid is about 78 dynes/cm. Therefore, drop-wise condensation will occur on solid surfaces with surface tensions less than about 88 dynes/cm when gas at 35% by weight peroxide vapor is condensing. Recall that 35% by weight peroxide vapor condenses as 78% peroxide in the liquid. Polymer materials surface tensions typically range from 20 to 45 dynes/cm or lower. Therefore, drop wise condensation should occur on most polymer materials. Clean metal and glass surfaces typically have surface tensions that are higher than 200 dynes/cm. Contamination on a metal or glass surface may dramatically drop the surface tension allowing for drop wise condensation. Figure 3 shows how a contaminant on a metal surface causes drop wise condensation. This will not allow the entire surface to be exposed to liquid resulting in a non-uniform surface exposure to peroxide. Even if film wise condensation occurs, there is a possibility of non-uniform liquid exposure on the surface due to developing liquid flow patterns on vertically sloped surfaces.

A further complication associated with condensation of liquid is the additional time required to remove peroxide from the chamber at the end of an exposure phase. Gas can quickly be removed from the chamber by purging with an inert gas (such as air). Additional time is necessary to remove peroxide in the liquid form due to the time required to evaporate the liquid from all surfaces. If a material is permeable to liquid water or peroxide, additional time will be needed to remove any liquid that absorbed into the solid surface. Examples include porous materials and certain polymers, which are permeable to liquid water and/or peroxide.

Finally, condensed peroxide at high concentration may have un-suitable (even violent) reactions with certain materials in the decontamination chamber. Special safety precautions should be in place to handle any standing liquid hydrogen peroxide condensate that can be violently reactive and will cause severe burns.

Decomposition of Hydrogen Peroxide

Hydrogen peroxide, especially in gaseous form or impure liquid solutions, is not a very stable compound. In particular, it spontaneously decomposes to form oxygen and water as shown below:



Therefore, the concentration of peroxide gas in the sterilization chamber will steadily decrease over time, depending on the chamber area, material of construction, contents, etc. A simple procedure to maintain a constant peroxide concentration involves continually circulating the gas in the sterilization chamber through a system that regenerates fresh peroxide vapor as shown in Figure 4. This design is successfully used in gaseous hydrogen peroxide decontamination systems. Fresh peroxide gas produced from a flash vaporizer is introduced into the chamber as gas in the chamber is removed, thereby maintaining a consistent peroxide vapor concentration. Further, the removed peroxide gas can be

decomposed to water and oxygen in a destroyer and the water removed in a dryer. Drying the carrier gas stream is important as the water content in the carrier gas will affect the point at which condensation will occur as shown in Table B. For example, at 25°C, the maximum allowed concentration of peroxide vapor drops from 2.184 mg/liter to 1.805 mg/liter as the moisture content in the carrier gas goes from 0% RH up to 10% RH. This is a 17.4% drop in the maximum allowed peroxide concentration that may be introduced into the decontamination chamber.

Measuring and Controlling Peroxide Gas Concentration

As shown above, Equations one through five may be used to calculate the maximum level of hydrogen peroxide that may be achieved in a chamber without causing condensation. Once the maximum peroxide vapor concentration is known, it is possible to develop an operating cycle that gives the maximum concentration of peroxide while preventing condensation. The controlled variables for the cycle will include air flow rate, rate of injecting liquid peroxide into the flash vaporizer, concentration of the liquid to be flash vaporized, and the chamber temperature, volume, and humidity level. The peroxide and water concentrations during a cycle can be monitored using either infrared spectroscopy or electrochemical methods.^{10,11} It is desirable to run the peroxide concentration as high as possible, but at the same time reducing the risk of producing condensation (typically targeting less than 90% of the saturation level). It should be noted that these detector systems can only be used to monitor *gas* concentrations, where condensation of liquid will cause the sensor to fail. Overall, higher levels of peroxide vapor concentration will result in higher kill rates and therefore shorter cycle times, but it is recommended that this should be balanced by ensuring that condensation does not occur. Once the cycle is developed for a given volume and temperature, it may not be

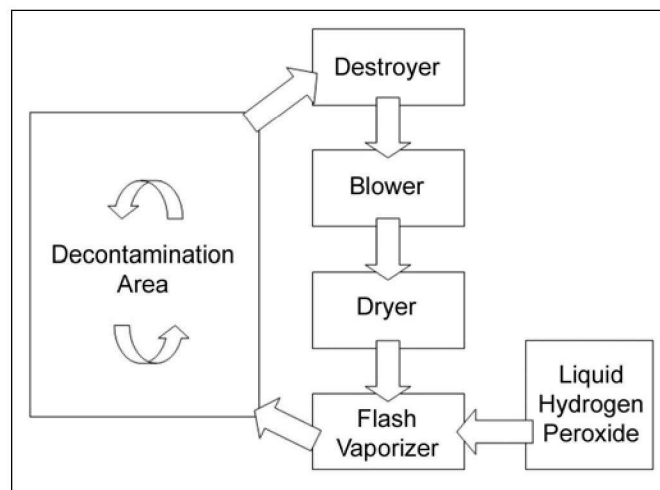


Figure 4. Typical Vaporized Hydrogen Peroxide (VHP) decontamination system. Vapor is produced by flash vaporization of liquid hydrogen peroxide and blown into a volume to be decontaminated. The vapor concentration is held constant by a constant flow of gas through a destroyer (e.g., x), air blower.

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