REVIEW ARTICLE

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New trends in application of the fumigation method in medical and non-medical fields

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Abstract

Introduction. In the twentieth century, fumigation became a very popular method of disinfection, although in the same century many agents used as fumigants were withdrawn for ecological reasons. Fogging (fumigation) is a relatively new disinfection technology using dry fog, which behaves more like a gas and easily fills the sanitized space, reaching all surfaces in the room. The undoubted advantage of fumigation is the possibility of disinfecting difficult to clean areas. Fumigation has become particularly important in the twenty-first century due to procedures related to combating and preventing the spread of the coronavirus that causes COVID-19.

Objective. The aim of this review article is to summarize the current state of knowledge in the field of fumigation on the basis of past results of original research, taking into account new trends and possibilities of its application.

Brief description of the state of knowledge. Due to the fact that fumigation is safe for apparatus, equipment, and electronics, while simultaneously enabling the highest possible bactericidal and virucidal levels, this method is widely used in various areas, both medical and non-medical. Fogging technology is used in the medical, pharmaceutical, and food industries, as well as in transportation, for air fumigation or surface disinfection in closed spaces, such as hospital and laboratory rooms, incubators, refrigerators, ships, trucks, railway containers, and aircraft, to name only a few. The most common fumigants are hydrogen peroxide and peracetic acid, and their mechanism of action is related to their oxidizing properties.

Summary. Hydrogen peroxide and peracetic acid are highly effective and non-toxic fumigants that can be safely used for fogging laboratory and medical equipment, pharmaceutical facilities, hospital rooms, and animal breeding rooms.

Key words

hydrogen peroxide, peracetic acid, fogging, fumigation, Formaldehyde

INTRODUCTION

In the twentieth century in this century, as well as in this century, fumigation has become a very popular method of disinfection, whereas many agents used as fumigants have been withdrawn for ecological reasons. Dry fogging (fumigation) is a relatively new decontamination technology using a mist that behaves more like a gas and easily fills the sanitized space. In contrast to wet fog, ultra-fine particles of the dry mist settle on the surfaces after some time; hence, dry mist does not wet surfaces with which they are in contact [1]. The undoubted advantage of fumigation is the ability to disinfect areas that are difficult or even impossible to clean manually by wiping.

Disinfection is a process conditioned by many factors. Its effectiveness depends mainly on the duration of action and concentration of the disinfectant, as well as on temperature, humidity and surface target. Widely used decontamination methods are based on liquids or gases, and the preparations used in them are divided into bactericidal, virucidal, and fungicidal, depending on their antimicrobial activity [2, 3].

Modern fumigant research is not concerned with establishing a lethal dose, as is already known for most compounds, but is more geared towards finding ways to minimize effective doses of available disinfectants by studying their mechanisms of action and physical conditions, and combating microbial resistance [4]. Due to the fact that fumigation is safe for equipment, and at the same time enables the highest possible bactericidal level, this method is widely used in various areas, both medical and non-medical [5]. Fogging technology is used in the medical, pharmaceutical, and food industries, as well as in transportation for air fumigation or surface disinfection in closed spaces, such as hospital and laboratory rooms, isolation rooms, incubators, warehouses, refrigerators, ships, trucks, railway containers, and aircraft [4, 6].

In the twenty-first century, in the era of a global pandemic, fumigation may play one of the key roles in fighting and preventing the spread of COVID-19. Fumigation can also be performed in public places and medical areas. Infection with the SARS-CoV-2 virus occurs primarily through secretion or droplets from the respiratory tract, which are released when infected people cough, sneeze, talk, or sing. The particles released from the respiratory system contain the virus and can reach the mouth, nose or eyes of a healthy person by the air-droplet path and cause infection. Another equally important mode of transmission of the virus is the contact route, and hands are its essential element. After touching contaminated surfaces and objects, the hands carry the virus to the areas of the mouth, nose, and eyes; the virus remains in an active, infectious form from several hours to several days on various surfaces. Fogging can disrupt such virus transmission pathways, and fumigation is therefore used to disinfect public places as well as medical areas [7].

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OBJECTIVE

The aim of this review article is to summarize the current state of knowledge in the field of disinfection by air, based on the results of original scientific research, and to identify new trends in its application.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Methods of disinfecting the environment. Disinfection of the environment is performed by direct or indirect methods using various products and processes. Direct methods are carried out using a liquid disinfectant that is spread over the surface to be disinfected. Indirect methods include fumigation, defined as an antimicrobial process performed indirectly in a closed space. An example of fumigation is fogging, the indirect application of a biocidal liquid in the form of a dry fog. A variety of oxidants is often used in the fumigation process, such as ozone, chlorine dioxide, and hydrogen peroxide. Hydrogen peroxide is a widely used disinfectant and exhibits particularly rapid antimicrobial activity in gaseous form. The dry mist fogging technique ensures that the disinfectant does not condense and keeps the gas phase below the dew point, while the wet mist fogging process wets the surfaces being disinfected. The two processes differ in antimicrobial activity, compatibility with surfaces, and safety [1].

AREAS OF APPLICATION OF FUMIGATION

Medical areas. Although thorough cleaning and disinfection of surfaces are essential for the implementation of infection prevention programmes, traditional manual cleaning and disinfection in medical laboratories and healthcare settings are often insufficient. A non-contact method that very effectively complements manual disinfection is fumigation [3]. Most medical devices are complex and constructed from a wide variety of chemically and physically sensitive materials. A good solution in this situation is use of the fumigation method due to the fine size of the dry drops of non-falling fog and excellent bactericidal activity. The bactericidal effect and the lack of a negative functional effect on the equipment was proven by exposing personal computers to the effect of dry peracetic acid mist for a period of 6 months [1].

Hospital environment. The hospital environment can be a reservoir and source of transmission of various pathogens, including those that are antibiotic-resistant, e. g., methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecalis, Klebsiella pneumoniae*, among others. Many microorganisms are able to survive for long periods on a variety of surfaces. The use of the correct concentration of the disinfectant is essential in the effectiveness of the disinfection process, which can be achieved without the involvement of cleaning personnel. Most importantly, airborne hydrogen peroxide can reach places inaccessible to typical manual cleaning [8].

Hydrogen peroxide in the form of mist can be an effective method of disinfecting a hospital environment. Viruses belonging to the family *Caliciviridae* may also be controlled by fumigation with hydrogen peroxide. To carry out an effective process, it is sufficient to spray 50 ml of 30% hydrogen peroxide within 24 minutes. Noroviruses are the leading cause of the non-bacterial gastroenteritis in humans and are common in hospitals, institutions, cruise ships, hotels, and other places where large groups of people are present in a relatively small confined area, allowing the virus to spread rapidly [9].

In addition, the possibility of using disinfectants based on hydrogen peroxide to reduce multi-drug resistant pathogens on surfaces, such as beds, curtains and furniture, has been identified. The advantage of the fumigation method was two-fold in a hospital setting: a patient care area could be disinfected quickly without moving patients to adjacent rooms [10, 11, 12].

Medical laboratories. In clinical laboratories, pathogens are routinely cultured which can contaminate air and surfaces and are highly resistant to disinfection. Laboratory tests have confirmed the effectiveness of fogging with hydrogen peroxide on surfaces experimentally contaminated with different pathogens. On the basis of the obtained results, it was found that fumigation with hydrogen peroxide can be an alternative to traditional cleaning [13].

Another area of risk in the medical sphere are air filters, where microorganisms and dust accumulate. One study assessed the effectiveness of hydrogen peroxide fogging without closing disinfected areas, such as ventilation systems and ambulance vehicles [10]. In this case, fumigation is also a good option because of the ease of spreading the mist and its ability to penetrate through small filter holes. Virucidal, bactericidal, and fungicidal activity on air filters was demonstrated in the tests conducted with hydrogen peroxide vapour at a concentration of 30–35%. At the same time, hydrogen peroxide proved safe in terms of its environmental friendliness due to its final decomposition into oxygen and water [6].

Adenovirus contamination is a big problem in life science laboratories and during pharmaceutical production processes due to the fact that adenoviruses are widely used in the biomedical and industrial environment, as they are an excellent tool for gene transfer. Research confirms the effectiveness of inactivation of recombinant adenovirus with 45-minute exposure to hydrogen peroxide mist [14]. Other studies also proved that peracetic acid is an effective agent for inactivating viruses in cell culture laboratories via fumigation [15].

In laboratories with a high level of biosafety, all used materials must be effectively disinfected. This can be a problem for items that cannot be autoclaved or subjected to disinfectant fluids. Tests have been carried out with various viral agents, including representatives of several families of *Orthomyxoviridae*, *Reoviridae*, *Flaviviridae*, *Paramyxoviridae*, *Herpesviridae*, *Picornaviridae*, *Caliciviridae*, and highly infectious bacterial agents such as *Yersinia pestis* and *Bacillus anthracis*. Hydrogen peroxide vapour is a potentially useful fumigant for the decontamination of materials exiting the laboratory. One study showed that this agent could be an excellent substitute for formaldehyde fumigant. Hydrogen peroxide in the form of a mist very effectively destroys any potential viral and bacterial contamination (in liquid or dried state) on objects, and at the same time does not damage laboratory equipment [16]. The activity of evaporated hydrogen peroxide against exotic animal viruses has been demonstrated. In other studies evaluating the inactivation of *Francisella tularensis* on surfaces made of various materials (acrylic, glass, polyamide, polyethylene, polypropylene, silicone rubber, and stainless steel) using hydrogen peroxide fumigation, the bactericidal effect was observed within two hours [17]. This is particularly advantageous due to the possibility of using this pathogen as a potential biological weapon [16, 18].

In laboratory animal housing, fumigation with hydrogen peroxide has also proven to be effective. It can be used in this environment due to the broad spectrum of antimicrobial activity, environmental friendliness, and minimal burden for employees. Apart from virucidal, bactericidal, fungicidal, and sporicidal activity, no signs of corrosion or functional damage were detected after repeated disinfection. Bio-decontamination with hydrogen peroxide in the fog phase has proven to be a very effective method of decontamination of animal rooms and laboratory equipment [19]. In another study, in addition to the effectiveness of hydrogen peroxide fumigation in disinfecting rooms, its usefulness demonstrated has been demonstrated in the decontamination of laboratory equipment, such as ultracentrifuges, freeze dryers, and dental instruments [20].

Food industry. The main challenge in the food industry is to avoid contamination of raw materials and finished products by spoilage microorganisms [21]. Fogging ensures even delivery of an appropriate dose of disinfectant to all areas. Research on the operation of the fogging method in the food industry was not very popular and its beginnings are quite distant. The antimicrobial effect of chlorine mist sprayed in the air was discovered in 1975. In 1995, it was established that fogging is less effective than other disinfection methods, such as the use of ozone or ultraviolet radiation. In 1999, fogging was shown to reduce the number of microorganisms on upward facing surfaces relative to incident rays, while it was proven to be ineffective on vertical or downward facing surfaces [22].

Fumigation is used quite extensively by producers of salads, sandwiches, ready meals, and dairy products. It is also used in food equipment such as freezers and refrigerators, in cheese maturation rooms, production areas, and process lines. Studies have shown that the fog should be most effective when the diameter of the peracetic acid droplets is between 10–20 µm. Droplets of this size range are well dispersed and fall off in about 45 minutes [23]. In addition, fumigation is often used for pest control in warehouses of agricultural products (cereals, cherries, strawberries, apples, tomato). The high permeability of dry fog increases the shelf life and promotes the rapid elimination of pests. For example, studies found that acetic acid not only prevented tomatos from rotting, but also had no apparent phytotoxic effects on the fruit [24]. No other method achieves immediate effect without having to transfer the products and the contents of a room [25].

Transportation. Despite the fairly widespread use of disinfectant mist in the food industry, most of the research related to transportation focuses on vehicles of the medical and pharmaceutical industries [23]. Based on the literature, it can be concluded that fumigant hydrogen peroxide is effective against a wide spectrum of microorganisms and is safe for general use and for sensitive equipment, including those found inside aircraft and vehicles [26].

Studies conducted to inactivate *B. anthracis* spores in the metro system by fogging with peracetic acid and hydrogen peroxide have shown that the effectiveness of the fog largely depends on the decontaminated material. Several published studies have compared the effectiveness of various disinfectants on smooth surfaces, such as glass and steel, and porous materials such as concrete. For example, fumigation has been found to be effective when decontaminating rooms or buildings that contain different surfaces in a sealed area. In addition, the use of fogging can provide an easier and cheaper decontamination solution in the event of *B. anthracis* being released over a large area [27, 28, 29].

ANTIMICROBIAL PROPERTIES OF FUMIGATION AGENTS

Hydrogen peroxide. The interest in environmentally friendly non-toxic biocides has never been so high as it is today. The non-toxicity of hydrogen peroxide has been valued for a long time, especially in disinfectant applications on antiseptic and general surfaces. It has been confirmed that different mechanisms of action of hydrogen peroxide in gaseous and liquid form have different effects on bacteria and viruses, which translates into their differential effectiveness [30].

Most of the described studies of the mechanism of hydrogen peroxide action on DNA have been carried out using low concentrations with long exposure times; thus, the biocidal mechanism under study calls into question the effective use of hydrogen peroxide as a surface disinfectant. The killing of microbes due to DNA damage depends on iron ions tightly binding to DNA at high concentrations of hydrogen peroxide; however, the importance of hydrogen peroxide's reactions with cellular components, including proteins, is also gaining importance [3].

According to a report of the World Health Organization, hydrogen peroxide is among the most widely used disinfectants that have been shown to be effective against SARS-CoV-2 [31]. In tackling the COVID-19 pandemic, some countries have approved non-contact methods of spraying chemical disinfectants (e.g., evaporated hydrogen peroxide) in healthcare facilities. However, fogging methods complement, but do not replace manual decontamination procedures in the fight against this disease [32].

Peracetic acid. Peracetic acid is a clear, colourless solution with an astringent acetic odour. Typically, it is formed by reacting hydrogen peroxide with acetic acid in the presence of a catalyst, such as sulfuric acid. To prevent the reverse reaction, the solution is fortified with an excess of acetic acid and hydrogen peroxide [33]. Although peracetic acid is the product of the chemical reaction between hydrogen peroxide and acetic acid, it is more effective than hydrogen peroxide because of its lipid solubility and strong antimicrobial activity at low temperatures [1].

Peracetic acid is widely used as a disinfectant, *inter alia*, because its bactericidal effect occurs after 30 minutes of exposure to dry fog, while spores and viruses require an hour's exposure. After contact with dry fog, no visible damage or changes were found to computers, cables, and hard drives. However, metal screws that were initially shiny and smooth turned dull [1].

Table 1. Effectiveness of three chemical agents for disinfection

Disinfectant	Advantages	Disadvantages	Mechanism of action
Hydrogen peroxide	Decomposition into non-toxic byproducts (water and oxygen).	Hydrogen peroxide in the form of a mist has shown an inability to oxidize amino acids. Resistance of micro-organisms to hydrogen peroxide depends largely on the production of superoxide dismutase, catalase, and other peroxidases.	Oxidizing agent reacts with cellular biomolecules. Produces reactive oxygen species (hydroxyl radicals, superoxide anions) that attack essential cellular components such as DNA, lipids, and proteins. Liquid hydrogen peroxide oxidizes cysteine, methionine, and other amino acids, and damages the microbial cell membrane.
Peracetic acid	Low temperature performance. Non-toxic by products: water, oxygen, and carbon dioxide. Lipid solubility and strong antimicrobial activity at low temperatures.	Ordinary steel, non-galvanized iron, copper, and bronze are susceptible to corrosion.	Antimicrobial effect to strong oxidizing properties and oxidative potential. Oxidation of amino acid residues as a result of binding free radicals with cellular proteins of microorganisms. Reactions between radicals and proteins cause a loss of protein activity, resulting in inhibition of the vital functions of microorganisms.
Formaldehyde	Very effective against a variety of microorganisms, including very stable viruses.	Toxic and carcinogenic effects, and potentially explosive. Formaldehyde for fumigation is made from granular paraformaldehyde. The gas formed under the influence of temperature is neutralized with ammonium carbonate, which leads to the formation and deposition of a white powder on all disinfected surfaces.	Chemically modifies vital cell components, including DNA and proteins, thereby leading to cellular dysfunction. Covalently modify proteins, inhibiting their functions.

Compiled using 20, 30, 33, 35, 36 and 37.

Formaldehyde. The earliest reports of the use of formaldehyde as a fumigant date back to 1880 and it has been used for decades in the fumigation of laboratories [34]. In fact, in the past, equipment and heat-sensitive materials that otherwise could not be disinfected were decontaminated with formaldehyde [2]. Hydrogen peroxide is a safe alternative to the use of these toxic gases that require neutralization before release to the atmosphere [19]. Comparison of three chemical agents for disinfection is shown in Table 1.

SUMMARY

Nowadays, disinfectants are widely used in households, hospitals, drug production, and food processing, which contributes to the formation of microorganisms resistant to these types of substances [38, 39]. The emergence of resistance to disinfectants also contributes to the rise of antibiotic resistance through a common selection of genes [9]. With the increasing resistance of microorganisms to antibiotics, it is essential to rationally use disinfectants with an appropriately selected active substance. Among the microorganisms that are particularly difficult to control are spore-forming bacteria, which have a structure and sensitivity to physical and chemical factors that differ from vegetative forms. Studies have shown that peracetic acid and hydrogen peroxide are effective disinfectants against spores, but the use of hydrogen peroxide requires high temperatures and high concentrations [12].

The effectiveness of fogging with hydrogen peroxide and peracetic acid has been proven in numerous scientific studies [29, 40]. Their additional advantage is their environmental friendliness due to the resulting non-toxic decomposition products and their broad spectrum of action [26]. Hydrogen peroxide and peracetic acid can safely be used as a mist to disinfect laboratory and medical equipment, pharmaceutical facilities, hospital rooms, and animal housing, but a greater antimicrobial effect can be obtained on hard and smooth surfaces than on porous surfaces. On smooth objects, microorganisms rest on the surface, therefore their direct contact with the disinfectant is possible, which is unfortunately difficult in the case of materials such as fabrics, carpets, or wood. In the case of porous materials, the fumigant must additionally penetrate the fabric, carpet, or wood fibre before it comes into contact with microorganisms or their spore forms, which undoubtedly influence its effectiveness [18, 41].

The COVID-19 pandemic hit even the most powerful economies in the world, and the sectors most affected appear to be sales, production, transportation, and tourism. As a result of the easy transmission of the SARS-CoV-2 virus, the disinfection of specialized vehicles (ambulances) and public transportation has become particularly important. In addition, spray disinfection allows for rapid decontamination of large areas, such as public transit stations, airports, shopping malls, theatres, and medical care facilities. Fumigation can play one role among the many ways to tackle the societal challenges of the COVID-19 pandemic [42].

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