Archives of Materials Science and Engineering

Volume 56
Issue 2
August 2012
Pages 53-60

International Scientific Journal published monthly by the World Academy of Materials and Manufacturing Engineering

Antibacterial properties of copper and its alloys

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Received 19.06.2012; published in revised form 01.08.2012

ABSTRACT

Purpose: The goal of the work is analysis of the knowledge extent on the bactericidal activity of copper and its alloys.

Design/methodology/approach: Analysis of publications on the antibacterial properties of copper in the engineering and medical journals, taking also into account publications on the earliest documented employment of copper as the bactericide or medicine.

Findings: Analysis of the investigation results presented in more than 350 scientific publications and reports worked out under commission from the Ministry of Health, including 312 scientific publications from the years 1892-1973, indicate to the antimicrobial action of copper and its alloys, which killing bacteria and viruses slows down growth of the microorganisms, and especially of: cobacillus, Legionella pneumophila, Salmonella, Staphylococcus aureus, poliovirus.

Research limitations/implications: Application of the acquired research results in hospitals, outpatients' clinics, and other public medical centres, will make it possible to reduce morbidity resulting from infections, especially of patients after serious medical treatment, operations, or after the complex antibiotic cure which has led them to decline of immunity.

Practical implications: Reduction of health care costs is possible in every country by implementation of the acquired investigation results, as a consequence of the decreased treatment costs, by shortening the patients' stay in a hospital. According to the assessment of the Department of Health of the United Kingdom these savings total to 1 billion pounds a year.

Originality/value: Implementation of the analysis of results of investigations on the bactericidal activity of copper and copper based alloys will add to the increase of the patients' safety level in the public medical centres.

Keywords: Metallic alloys; Electron microscopy; Heat treatment; CuTi4 alloy

Reference to this paper should be given in the following way:

J. Konieczny, Z. Rdzawski, Antibacterial properties of copper and its alloys, Archives of Materials Science and Engineering 56/2 (2012) 53-60.

MATERIALS

1. Introduction

Pure copper and its alloys are characteristic of the unique mechanical- and physical properties. As early as in 1913 copper was established a standard for the electrical conductivity. Currently, copper and its alloys are widely used in many branches of the modern engineering. The extensive scope of application of pure copper results from its very good electrical- and thermal conductivity (being inferior in this respect only to silver), good cold- and hot workability, and high corrosion resistance. Thanks to these unique properties it finds application in electronics, radio engineering, and electrical engineering.

Therefore, copper and its alloys enjoy continuous interest from both scholars and engineers [1-10].

Regrettably, engineers and designers forgot in the last years about the unique antibacterial properties which are characteristic of copper, and which were used in the last centuries, in particular, in places coming often in contact with human skin like, e.g., door handles.

Copper is one of the first metals which were known to people. The beginning of smelting, casting, and forging of copper is dated about 5000 BC, however, smelting of copper from the complex ores containing arsenic (As) and lead (Pb), is dated 1000 years later, and obtaining bronze by fusing copper with tin ore and copper with tin is dated at 2500-2200 BC.

The first recorded cases of using copper as the bactericidal agent come from the Smith's Papyrus, considered to be the first and oldest medical document in history of mankind [13], whose authorship is ascribed to Imhotep, the Egyptian doctor and architect serving Pharaoh Djoser. It comes from ca. 1700 BC, however, it is based on texts coming from 3200 BC [14]. Copper and its compounds were recommended as medicine for "trembling of the limbs" (this term was used probably for epilepsy), treatment of burn wounds, skin diseases (itching), and also skin tags on the neck. Copper in different forms was used for treatment of diseases: from the metal copper splinters and chips, to naturally occurring copper salts and oxides. Malachite ($Cu_2CO_3(OH)_2$) was used quite often, called by the contemporary the "green pigment" or chrysocolla (copper silicate), or cupric chloride.

Because of the easy access to copper, it was an important medicine also in the ancient Greece. It was recommended in the collection of the Hippocratean works (*Corpus Hippocraticum*) assembled probably by the Alexandrian scholars in III century BC for treatment of ulcerations connected with varices. To prevent infection of the raw wounds sprinking them was recommended with a mixture of a dry powder from cupric oxide and copper sulphate. The antiseptic treatment of wounds was done with a mixture of honey and the red copper oxide.

The Greek scholar Pedanius Dioscorides gave the recipe in his book *De Materia Medica* in the first century AD for obtaining the green pigment by exposing the metallic copper to the action of the boiling vinegar vapours. The drug prepared that way was recommended as remedy of eye ailments, like the bloodshot eyes, inflammation of eyes, leucoma (white corneal opacity, causing loss of its transparency), cataract, and „fat in the eyes" (most probably referring to trachoma – viral infectious disease of conjunctiva and cornea [15].

Also at the same time the Roman doctor Aulus Cornelius Celsus, who began practising medicine during the reign of Tiberius (14 to 37 AD) in his book *De Medicina* recommended in treatment of the venereal diseases using a medicine being a mixture of pepper, myrrh, saffron, and boiled antimony sulphide and cupric oxide. He recommended for treatment of the nonhealing ulcerations using the cupric oxide mixed with other components, including rose oil ensuring the suitable consistency [13].

The cause-and-effect relationship between germs and development of a disease was discovered in XVIII century. Only then the scientists became aware of the antibacterial potential of copper. Copper is used currently for production of bactericides and fungicides, oral hygiene products, in the pharmaceutical industry, and also for applications in the HVAC systems (heating, ventilation, and air conditioning systems), and also in water distribution and production of the medical instruments.

Scientific research has confirmed that copper may suppress the serious pathogens which are the imminent danger to health or even lives of people. These are, first of all, the methicillin-resistant Staphylococcus aureus (*MRSA*), infection with *Clostridium difficile* (usually this infection occurs at hospitals, as infections with *Clostridium difficile* bacteria are commonly the effect of antibiotics), *Escherichia coli* (E.coli, colibacilli), and also *legionella pneumophia* (characteristic of Legionellosis). Moreover, copper demonstrates properties destroying the type A flu viruses. Therefore, it may be an agent suppressing the danger of the avian flu epidemy.

The importance of counteracting infections in the health service buildings is testified by the fact that according to the European Centre for Disease Prevention and Control (ECDC) about three million of infections connected with health service leads to about 50,000 demises yearly in Europe. It should be marked that about 80% of infectious disease are transferred by touch contact. Among microorganisms which are the reasons for hospital-acquired infections, the following are named: *MRSA*, *Escherichia coli*, *Klebsiella pneumoniae* i *Clostridium difficile*. Although the hospital-acquired infections may not be avoided, it was found,basedon investigations, that the number of infections may be reduced by minimum 15%.

Investigations carried out in the USA, Japan, Great Britain, and Germany confirmed that copper plays an important role in deducing the risk of transferring bacteria which imperil people in the public buildings, hospitals, and food producing institutions.

Prevention of transferring the dangerous bacteria which are the reason for numerous incidences of diseases has also the economic aspect. The European Centre for Disease Prevention and Control has estimated that cure of one case of infection with *Clostridium difficile* costs about 5,000-15,000 EUR. If the European Union is populated by 457 million people, then infections with *Clostridium difficile* cost three billion EUR yearly. It is expected that this amount will double within the next 40 years.

It is estimated that about 80% of the infectious diseases are transmitted by contact. The equipment used commonly in hospitals (furniture, medical utensils) is made from aluminium and stainless steel, which makes an impression of being clean, yet may be the source of the pathogenic and lethal bacteria and viruses. The most common infections in hospitals are caused by: methicillin-resistant *Staphylococcus aureus* (*MRSA*), colibacilli, like *Escherichia coli*, *Klebsiella pneumoniae*[1], and also *Clostridium difficile*[2]. These germs may cause with the sick infections of the urinary tract (25%), lower airways (23%),

[1] *Klebsiella pneumoniae* occurring very often in the respiratory- and alimentary tracts is the reason for pneumonia, infection in the area of the alimentary tract, bones, joints, or urinary system (which may lead to sepsis); for infants it is the etiologic factor for meningitis [16].

[2] The bacteria causing necrosis – destruction of the intestine tissues, ulcerations, secretion of fluids and development of the inflammatory status, produces toxins: toxin A (enterotoxin) and toxin B (strong citotoxin), albeit pathogenic may be strains producing toxin B only.

infections of the surgical wounds (11%), skin infections (10%), and blood flow disturbances (6%).

Germs causing infections may survive on surface in the environment of the hospital ward for several days and even months, where the personnel, patients and also visitors may get in touch with them. Therefore, items with which people are in contact, like door handles light switches, trolleys, beds, tables, bedsidecabinets, handrails, stairs , etc. may be easily made from copper and its alloys taking advantage of their antibacterial properties. To be protected optimally from the possibility of infection in hospitals fabrics should be used containing copper fibre for production of bed-clothes, coats of patients and clothing of health service staff.

On 1 cm² of pure copper 10 million *Staphylococcus aureus* germs die within 90 minutes. According to [17] yearly cost of treatment of the hospital-acquired infections in Great Britain, being incurred because of that by NHS (National Health Service) is estimated at about 1 billion pounds. Due to infections the patient's average stay was extended by 11 days andat least 5000 patients die because of complications. It is estimated that employing the antibacterial properties of copper one may reduce the number of infections by 15% yearly, which leads to savings of about 150 million pounds a year [18].

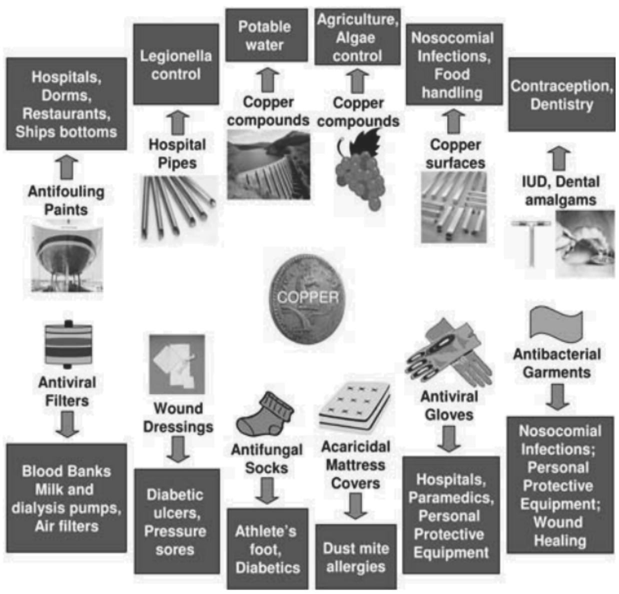

Fig. 1. The current and potential future applications of copper and its compounds in various areas are based on the biocidal properties of copper [19]

Examples mentioned above attest to the fact that before the microorganisms were discovered, the ancient Egyptians, Greeks, Romans, and the Aztecs used copper to cure, among others, sore throat and rash, and also used it to maintain the daily hygiene. Therefore, oddly enough, the antibacterial properties of copper are the fact hardly known by engineers, especially referring to the current and potentially future applications taking advantage of these unique properties (Fig. 1).

2. Material and methods

Copper is the chemical element with the atomic number 29 and electron configuration $1s^2 2s^2 2p^6 3s^2 3p^6 4s^1 3d^{10}$, therefore, the total number of electrons in once Cu atom is 29. However, electrons with the negative charge on the completely filled orbitals are much closer to the atomic nucleus with the positive charge than their equivalents in the incompletely filled orbitals. Therefore, the completely filled orbitals represent the low energy state, and the real electron configuration of the copper atom is Ar4s13d10 with completely populated orbital 3d [20].

Copper is the trace element indispensable in most living organisms, which occurs in more than types of copper containing proteins. The most important of them are first of all: lysine oxidase (protein – in humans LOX gene), which is engaged in collagen reticulation, tyrosinase, required for synthesis of melanin, β-hydroxylase dopamine, cytochrome oxidase – the big protein complex of the mitochondrion and bacteria internal membrane, and also the superoxide dysmutase required for protection from the oxidizing damage - consists from the protein part and from the prosthetic catalytic group in the form of a metal atom playing the role of the active centre (one of the three types is the cytoplasmic *SOD-1* containing copper (Cu) and zinc (Zn) *CuZnSOD-1*).

In these enzymes copper plays a role of the donor of electrons/acceptor by change of the oxidation state from Cu(I) to Cu(II) in the redox type reaction [21].

The reactive hydroxylic radicals may be generated in the Fenton's reaction:

$$Cu^{+} + H^{2}O^{2} \rightarrow Cu^{2+} + OH^{-} + OH \quad (1)$$

Very reactive hydroxylic radical may participate in many reactions harmful for molecules, like oxidation of proteins and lipides [22]. Copper ions may also lead to depletion of the sulfhydryl group (it plays two different roles: stabilisation of the protein particles structure by development of the so called sulphur bridges, the second one: cell detoxication mechanisms), just like in cysteine (organic chemical compound counted to the group of the endogenous coded amino acids, occurs in many proteins).

The molecular mechanisms of the antibacterial activity of copper result from its atomic structure, and especially from the structure of its external electronic shell, and also of the possibility to give (Cu^{2+}) or receive (Cu^{1+}) the electron easily. This is the reason for many useful copper properties, among others, its electrochemical properties used in biological systems. Capability of copper to give or receive the electron is enormous, which means that it has the high electrochemical potential [23].

Microorganisms are based on enzymes using copper to make the important life chemical reactions easier. Thanks to the electrochemical potential the free copper ion interacts with the bacteria proteins, which results in suppressing their activity and gives copper its antibacterial character. One should mention, however, that the antibacterial mechanism are very complex and are realised in many ways, both inside of cells and in the intercellular spaces [23, 24].

Investigation results prove that copper alloys which have the antibacterial properties may be used in places exposed to human touch or contact with food and may add to reducing the hazard connected with transferring the potentially infectious human pathogens.

Keevil with associates [25] demonstrated that copper may be successfully used to control *Clostridium difficile* – bacterium which causes epidemic of the hospital diarrhoea, especially with the elderly people, weakened and patients treated with antibiotics before. However, investigation on the effect of copper on *Clostridium difficile* are still ongoing.

Copper may also play an important role in fight with the avian flu epidemic. The latest Keevil's results [25] indicate that copper may feature the effective barrier against spread of the avian flu. After exposure of 2 million active H5N1 virus units on the sheet copper, its number was reduced after six hours by 99.9%. This effect is connected with the fact that copper violates integrity of viruses.

In this aspect the particular use of copper and its alloys results from their bactericidal properties [23, 26-28]. In 2003 Wilks and Keevin published [29] the bactericidal research results for 28 different alloys, among which 7 were the copper alloys. It was found that the inactivation indices of the *Listeria monocytogenes* bacterium[3] were much higher on copper alloys (Fig. 2). As an example, the alloy called new silver (65% Cu, 18% Ni, 17 Zn) inactivated all bacteria after 90 minutes. Further research of Noyce and Keevil proved beyond doubt that copper may suppress development of the methicillin-resistant Staphylococcus aureus (MRSA) called the "superbacterium" (Fig. 3) being immune in fact to all β-lactam antibiotics (penicillins, ampicillins, cephalosporins). Also investigations made with the colibaccili demonstrated unambiguously that copper alloys feature an important barrier for spread of the bacterium [30].

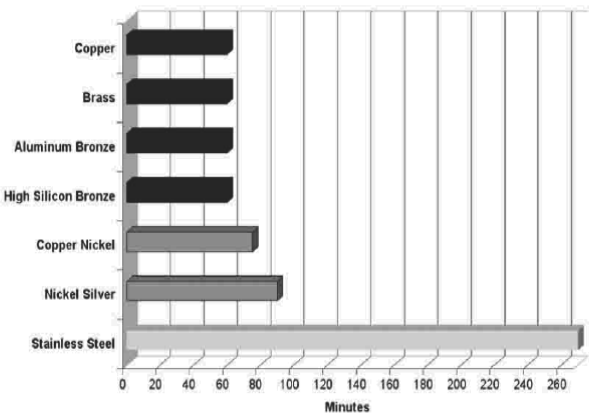

Fig. 2. Life span of *Listeria monocytogenes* bacteria on selected copper alloys and stainless steel at ambient temperature

Therefore, copper alloys are used in production, of, among others, sanitary installation tubes, fittings, door handles, knobs and handrails, and as a material for production of hospital equipment and utensils [23].

[3] A bacterium, very dangerous for humans, infection *Listeria monocytogenes,* causes listeriosis, whose symptoms are most often: septicaemia, spinal meningitis, encephalitis, corneal ulcer, and pneumonia, and also may be the reason for miscarriages or fatal death [31-34].

Fig. 3 presents the life span of Staphylococcus aureus on various substrates. The investigation results show that bacteria survival rate decreases along with the growth of copper content in substrate material. For C19700 (99% Cu) alloy the survival rate is reduced to 1.5 h; for C24000 (80% Cu) alloy the significant reduction of the survival rate occurs after 3 hours and the complete lack of survival capacity after 4.5 hours, and on C77000 (55% Cu) alloy Staphylococcus aureus has significant and lasting reduction of survival rate after 4.5 hours. However, the survival rate on stainless steel was as long as up to 72 hours [23].

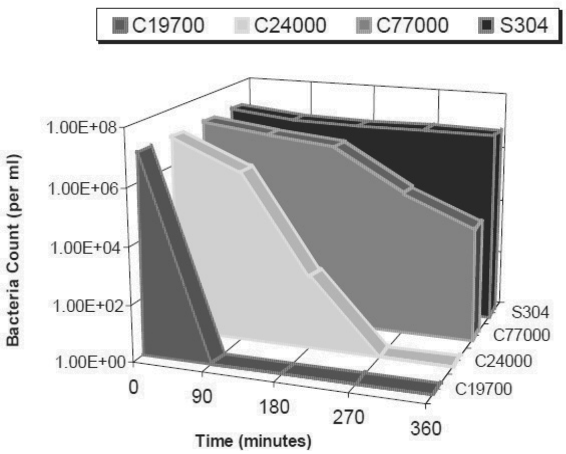

Fig. 3. Survival rate of the methicillin-resistant Staphylococcus aureus (MRSA) on three copper alloys: C19700 (99% Cu), C24000 (80% Cu), C77000 (55% Cu) and stainless steel (S304) at room temperature [30]

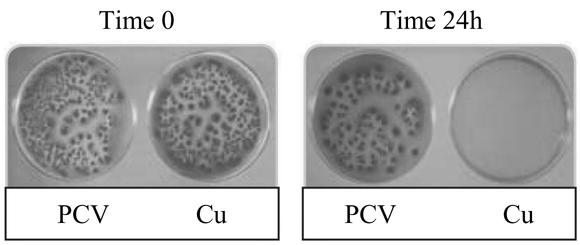

Fig. 4. Behaviour of the bacterial colony from *Escherichia coli* strain after 24 h contact on Petri dishes containing copper and PCV [35]

Results of the many scientific research projects (312 publications from 1892-1973 period) indicate the antimicrobial copper activity which suppresses development of microorganisms, and especially of:

- *Escherichia Coli* [23] – cobacillus (Fig. 4),
- *Legionella Pneumophila* – and bacterial flora occurring in the water environment [36] are the cases of Legionellosis – a group of the respiratory system diseases, first of all – pneumonia,
- *Actinomuicor elegans* [37],
- *Bacterium linens* [37],
- *Tuorolopsis utilis* [38],
- *Acromobacter Fischeri*, *Photobacterium Phosphoreum* [39],
- *Mercenaria mercenaria* [40],

- *Polio virus* [41],
- *Paramecium Caudatum* [42],
- *Compylobacter jejuni* [43],
- *Salmonella Entrica* [43], is pathogenic both for the humans and for the animals - causing the acute food poisonings. They can live outside of a living organism for several months in propitious conditions (warm, humid, presence of protein).

Currently, the antibacterial activity of copper is explained with three mechanisms:

- increased concentration of copper inside the cell causes oxidizing stress (the condition of a lack of equilibrium between activity of the reactive forms of oxygen and the biological capability to quick detoxication of the reactive by-products or repair of damage made) and generation of the hydrogen peroxide; in these conditions copper takes part in the so called Fenton's reaction[4] – chemical reaction causes oxidizing damages of cells;
- excess of copper causes decrease of the membrane integrity of microorganisms, which leads to leak of the particular cell nutritional elements, like potassium and glutamate, which leads to desiccation, and next to the cell death;
- albeit copper is required for many functions, occurring in proteins, however, copper in excesscombines with proteins which do not require its presence for their functioning. This „improper" bonding leads to atrophy of protein functions and/or decay of proteins to the dysfunctional components.

The examples above demonstrate that copper suppresses reproduction of bacteria. It is, therefore, the very good material, e.g., in housing industry. Plastics, albeit much cheaper than copper, are the environment propitious to reproduction of pathogens.

Results of the investigations carried out revealed that on surfaces of copper alloys (with mass concentration of min 65% Cu) as much as 99.9% of bacteria were destroyed already after 2 hours of exposure. Therefore, is made clear that copper is the ideal material for the bactericidal surfaces not only in health service and public spaces, but also, for example, in the food industry.

In [44] the antibacterial susceptibility constants were defined and specified and used for assessment of the antibacterial properties of nanoparticles of silver and copper in respect to *Escherichia coli* and *Bacillus subtilis* bacteria. Constant Z (mL/μg) defining susceptibility of nanoparticles is calculated using the relationship:

$$Z = \frac{-\ln\left(\frac{N}{N_0}\right)}{C} \qquad (2)$$

where:
N – units forming the bacterial colony (CFUs) on agar dish containing nanoparticles (Ag or Cu),
N_0 – CFU on pure agar dish,
C – concentration of nanoparticles (μg/mL).

It turns out from equation (2) that the higher Z value demonstrates the higher susceptibility of bacteria to nanoparticles of metals, which suggests that nanoparticles are more effective fighting the bacteria.

[4] Fenton's reaction takes place with ions of the transition metals (Cu^+ lub Fe^{2+}), resulting with the most reactive oxygen forms.

Reaction of copper nanoparticles with the particle size of 100 nm with *Bacillus subtilis* bacterium revealed the highest susceptibility (Z=0.0734 ml/μg), whereas the reaction with silver nanoparticles with the size of 40 nm with *Escherichia coli* bacterium revealed lower susceptibility (Z=0.0236 ml/μg). However, the authors indicate that the size of nanoparticles may influence their antibacterial activity, therefore further investigations have to be carried out, which results will make it possible to determine the effect of the size of nanoparticles on their antibacterial susceptibility (Figs. 5 and 6).

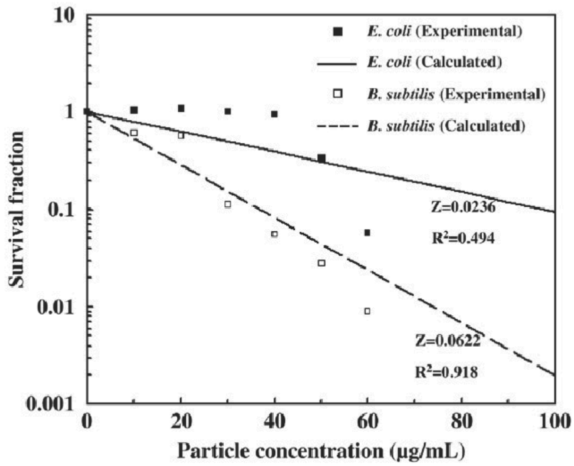

Fig. 5. Antibacterial results of silver nanoparticles [44]

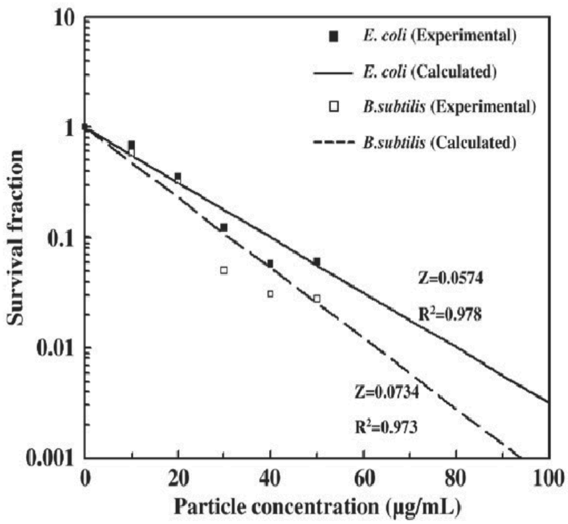

Fig. 6. Antibacterial results of copper nanoparticles [44]

Next, in [45] investigations were made of growth of various strains of microorganisms in presence of copper and silver nanoparticles, determining their effect on the growth profile. It was demonstrated that nanoparticles of silver and copper are very good antibacterial agents against *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* bacteria. Investigation results of MIC (Minimum Inhibitory Concentration), MBC (Minimum

Bactericidal Concentration) and diffusion test suggest that for all strains of *Escherichia coli* and *Staphylococcus aureus* bacteria, the antibacterial activity of silver nanoparticles is more effective and copper nanoparticles are more effective fighting *Bacillus subtilis*bacterium. Based on that, the authors assumed that copper nanoparticles have bigger affinity to the active surface of bacterium from *Bacillus subtilis* group, which might cause the more effective bactericidal activity. The authors suggest that, albeit the activity mechanisms are still not fully known for the copper and silver nanoparticles, yet their merging may lead to the more complete bactericidal activity against the mixed population of bacteria.

In another experiment [46] the bactericidal activity was compared of equipment items in the hospital ward made from copper, with which people have contact (most often by skin touch). This pertained to, among others, sets of handles and taps at the washing basins, metal plates (mounted vertically on the door) for opening the door to the hospital ward. Samples were taken from each element for testing presence of bacteria and presence of bacteria were compared on the same elements in the ward, which did not contain copper. It turned out that the drop of the average number of microorganisms present on copper surfaces exceeded 90%.

One of the most severe disease risks in HVAC systems is *legionella pneumophila* bacterium causing Legionellosis [36] (Legionnaire's disease, Pontiac fever), moulds like *Aspergillus Flavus,* parasite which, thanks to production of aflatoxin, one of the strongest poisons known, destroys human health, and fungi like *Aspergillus niger*. Use of copper and its alloys install to biologically neutral materials in the central heating systems, heat transfer installations, A/C installations, filters, or sewage tubes makes control possible of the amount of bacteria, fungi, and moulds in the dark and humid elements of the HVAC system. It may also turn out to be an effective protection agent because of the economic reasons.

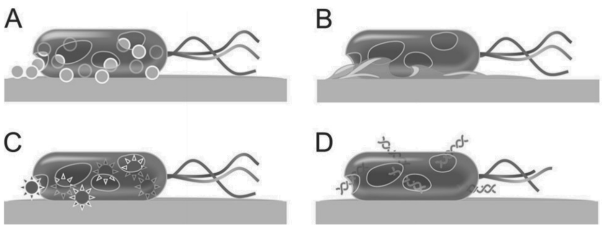

Fig. 7. Schema describing the first stages of destroying the bacteria cells: (A) copper dissolves on surface and causes damages penetrating in the bacteria cells; (B) breakages of cell membrane, due to stresses caused by copper atoms and other phenomena leading to loss of membrane potential and cytoplasmic contents (C) copper ions stimulate development of reactive oxygen forms which causes further damages of cells; (D) genome and plasmid DNA is subject to degradation [47]

Silver cations are more toxic for bacteria than copper cations [48]. However, silver is unstable at the oxidation state Ag(II) and should not catalyse w the Fenton type reactions. It was found, as a result of investigations carried out by Mikolay and associates [49] that silversurfaces do not kill bacteria. However, it was confirmed that copper alloys were really much more bactericidal than materials containing silver. Examinations were made at the temperature and humidity typical for the closed spaces like those that occur, e.g., in hospitals.

Mikolay [49] proved also that bacteria whose genes are coded with copper cations, like, e.g. *Pseudomonas aeruginosa* died very quickly on copper surface just like *E. coli* bacterium. Thus it was confirmed that copper cations released form the copped surfaces were responsible for the bacteria annihilation process (Fig. 7).

3. Conclusions

Nowadays, in the modern building engineering the risk of exposing people to the toxic activity of microorganisms forced improvement of the hygienic conditions in the air conditioning, ventilation and heating (HVAC) systems.

On the other hand, there is a possibility, making use of the physical properties of copper (thermal conductivity), to increase the power effectiveness of systems in which it is installed, and also the mechanical one (operation at the elevated temperature), there is a possibility to fight bacteria and other pathogenic organisms using high temperature of media required in the thermal disinfection process.

Usually the potable water is free from the pathogenic organisms, however, in the public potable water systems presence of viruses, bacteria, fungi, and parasites is possible. Therefore, using copper may also help in fighting the pathogenic organisms in the potable water. Copper sanitary pipes may ensure in this case the additional protection from presence of these organisms and reduce the disease risk.

Currently copper is used in the entire pharmaceutical branch of business, beginning from the antiseptic and antifungal products for health protection, and also for production of personal hygiene items, e.g., creams containing the trace elements.

In the USA, the Environmental Protection Agency, approved copper in March 2008 as an antibacterial agent which fights the particular bacteria causing the potentially lethal infections. As an effect of the investigations carried out on a large scale in the USA, 275 copper alloys were awarded the mark of the "antibacterial materials" in the US. Copper and its alloys are the first solid materials which have acquired such status. So far, the register of the sanitary and disinfecting means included only liquid substances (or sprays) and gas materials.

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