PERSPECTIVE

CAN COPPER HELP FIGHT COVID-19?

Experts on copper and microbiology recommend the expanded use of copper alloys in public spaces to reduce the spread of COVID-19 and minimize future pandemics.

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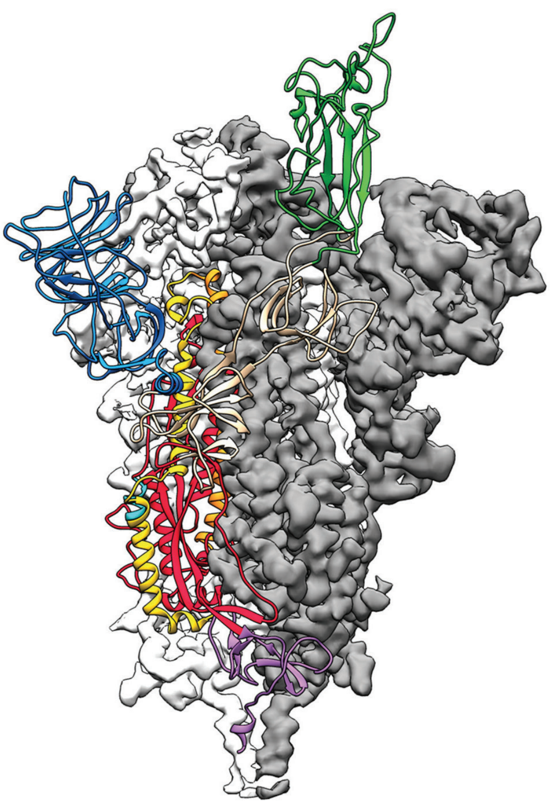
Copper can be a powerful weapon in the fight against COVID-19 and future pandemics, but we have to use it. Throughout history, copper was recognized for its antimicrobial activity[1]. With the advent of antibiotics, the value of copper as a medical treatment was pushed aside and lost from our collective knowledge base. While the world focuses on treating those with COVID-19 and developing testing kits and vaccines, prevention will soon take greater prominence. An ever-increasing body of research indicates that copper alloys have the potential to control the spread of infectious disease and blunt the impact of future pandemics. "An ounce of prevention is better than a pound of cure."

INACTIVATION STUDIES

A recent, highly publicized New England Journal of Medicine article authored by van Doremalen et al.[2] reported that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the newly emerged strain of coronavirus that causes COVID-19 infections, retains infectivity in aerosols and on a variety of common surfaces for extended periods of time. Most significantly, while the virus remained infective on plastic and 304 stainless steel for up to 48-72 hours, inactivation was observed in 4 hours on a 99.9% copper alloy. This finding was largely overlooked by media reports.

Another coronavirus, Human Coronavirus 229E (Hu-CoV-229E) causes a broad spectrum of lung disorders. An article published in 2015 authored by Warnes et al.[3] showed that Hu-CoV-229E remained infectious following exposure to polytetrafluoroethylene (PTFE or Teflon), polyvinyl chloride (PVC), ceramic tile, glass, silicone rubber, and stainless steel, but was rapidly inactivated on copper and on a range of copper-zinc and copper-nickel alloys. Complete loss of infectious activity was reached after as little as a five-minute exposure, depending on the particular alloy tested. Not only was the inactivation rapid but it was accompanied by the irreversible destruction of viral RNA and massive structural damages.

Figure 1, taken from Warnes et al.[3], is rich in content and calls for a detailed explanation. In the experimental protocol, a small sample of a suspension of virus particles was spread onto a 1 cm^2 coupon of metal of the indicated composition. After a designated time, the virus particles were washed from the surface of the coupon and the number of infectious viruses remaining was determined. This number is expressed as the number of plaque forming units (pfu) per coupon. Figure 1 plots the number of pfu (on a logarithmic scale) versus the time of exposure to the alloy surface.



A 3D atomic scale map, or molecular structure, of the 2019-nCoV spike protein. The protein takes on two different shapes, called conformations—one before it infects a host cell, and another during infection. This structure represents the protein before it infects a cell, called the prefusion conformation. Courtesy of Jason McLellan/University of Texas at Austin.

COPPER ALLOY PERFORMANCE

Figure 1a shows a series of brasses ranging from 60 to 95% Cu (balance Zn), C110 (100%), Z130 (100% Zn), and S304

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Stainless Steel (18% Cr – 8% Ni), which served as the experimental control. Both S304 and Z130 displayed no significant loss in infectious viral particles, while C110 (100% Cu) and C210 (95% Cu) showed the fastest reduction, followed by increasing time for complete inactivation in the following order: C210 (95% Cu), C220 (90% Cu), C230 (85% Cu), C260 (70% Cu), and C280 (60% Cu). Note the inverse correlation between decreasing copper content and increasing time for inactivation in brass. Figure 1b is a plot of the data from the first 30 minutes of Fig. 1a. It shows a gradual decline, followed by rapid inactivation. Figure 1c shows a series of copper-nickel alloys ranging from 70%Cu to 90%Cu, N022 (100% Ni), and S304. N022 and S304 showed no significant loss in virus particles. The copper-nickel alloys displayed increasing complete inactivation time with decreasing copper content in the following order: C110 (100% Cu), C706 (90%), C725 (88% Cu), C710 (80% Cu), and C715 (70% Cu). Again, note the inverse correlation between decreasing copper content and increasing time for inactivation in copper-nickel alloys. In Fig. 1d, a very small amount of inoculum, which dried immediately, was placed on the metal samples to simulate a finger touch of the surface. Inactivation of Hu-CoV-229E was complete in 2.5 minutes on C110 (100% Cu) and 5 minutes on cartridge brass C260 (70% Cu) while S304 stainless steel displayed only a modest reduction, most likely due to evaporation. These results strongly support the conclusions that copper alloys rapidly inactivate Hu-CoV-229E virus and that the copper in the alloy is responsible for the inactivation.

These two articles[2-3] used different strains of coronavirus but this is unlikely to be the source of the observed differences in inactivation times. The anti-coronavirus activity of copper alloys probably extends to all strains of coronavirus because this class of virus is essentially structurally identical. We have all become familiar with the spherical shape of coronavirus with its protruding spikes. The virus' RNA (its hereditary information) is contained inside a spherical "envelope" that protects the RNA. The envelope is a thin sphere of lipid molecules (fatty acids) arranged in a double layer or a lipid bilayer. Embedded within this lipid bilayer are two viral proteins, E and M. A third protein, S, or spike protein, is anchored at one end into the lipid layer and projects outward from the surface as radial spikes. These spikes give this group of viruses their name because they look like a "corona" when viewed at high magnification.

Minor variations in the hereditary information (RNA) produce slight variations in the proteins exposed at the outer surface. These proteins, particularly S, are responsible for attaching to and gaining entrance into respiratory cells where the RNA uses the metabolic machinery of the host cell to produce more viruses. Variations in these proteins do not produce significant variation in the overall structure and function of the virus. Thus, one can surmise with a reasonable degree of confidence that the efficacy of copper alloys against Hu-CoV-229E should also be observed when tested with the newly emerged SARS-CoV-2 and SARS-CoV-1, the causative agent in the SARS epidemic of 2003.

Scientists believe that the differences in exposure times observed by van Doremalen et al.[2] and Warnes et al.[3] result from technical differences in the experimental protocols and not from inherent differences among the viral strains. Figure 1d demonstrates that small sample sizes, in this case 1 microliter or 1/50th of a drop, were inactivated in 5 minutes or less. Similar results from a variety of laboratories studying copper alloy killing of bacteria found quite clearly that the volume of the inoculum placed onto the metal coupon contributes significantly to the speed of inactivation. Killing was very slow during the time the sample was drying on the surface but, once it dried, a precipitous decrease in the number of survivors was observed[4]. Another laboratory

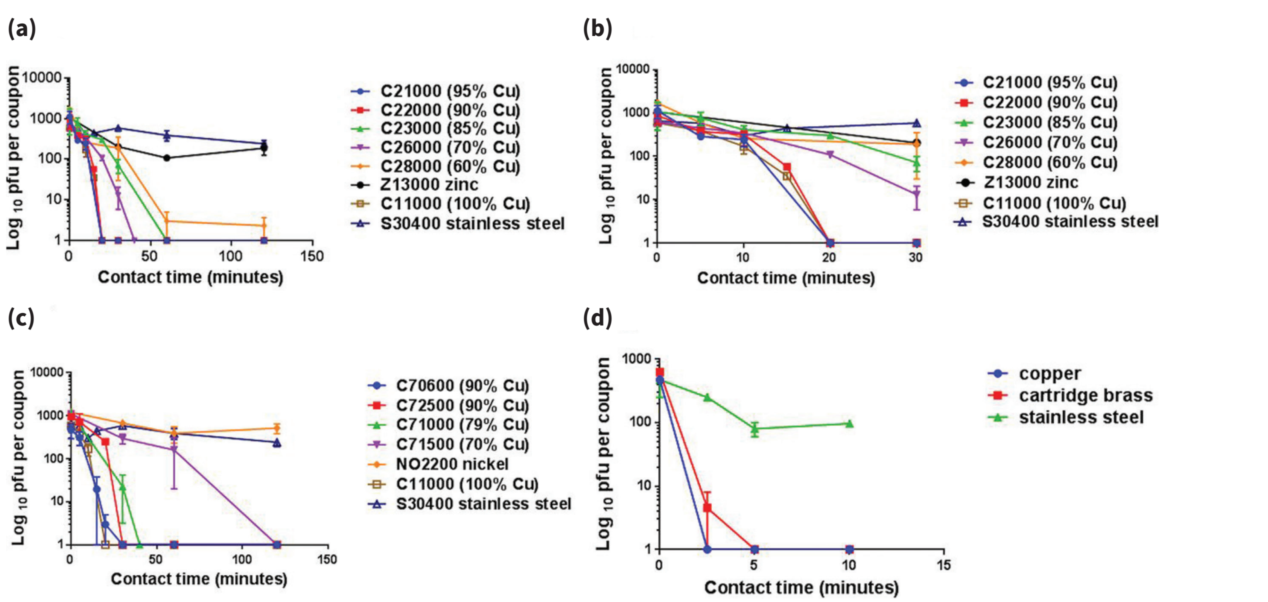

Fig. 1 — Inactivation of Human Coronavirus 229E by copper-zinc and copper-nickel alloys. Reproduced with permission from Warnes et al., 2015[3].

developed a "dry" technique of applying bacteria to the coupon with a cotton swab[5]. They found complete bacterial killing occurred in a minute or less using this method. Samples of 50 microliters were used by van Doremalen et al.[2] but no information on drying time, surface preparation, or sample distribution is provided. Preparation of the metal surface can be a critical factor. An insoluble organic coating, like benzotriazole, is typically present on copper sheet when it leaves the mill. This coating increases surface tension, and, thus, would inhibit inoculum distribution, slow evaporation, and most likely inhibit copper ion release from the surface. These two factors, drying time of the inoculum and surface preparation, are the most likely factors affecting the inactivation time.

PROTECTING PUBLIC SPACES

Small dry inoculums of infectious agents closely simulate what happens when a contaminated hand or a droplet from a cough or sneeze contacts a surface, making these results particularly relevant to the spread of disease in public spaces. Copper alloy inactivation is not limited to coronaviruses and works on viruses with different structures. Reports from the Keevil laboratory have shown that copper alloys inactivate murine norovirus[6] and Influenza A virus[7]. As in their Hu-CoV-229E study, the rate of norovirus inactivation was found to be inversely correlated with copper concentration in both the copper-nickel and copper-zinc alloys, the common theme in all of the studies of antimicrobial copper alloy surfaces.

Longevity of the antimicrobial activity of copper alloys is another very important consideration when selecting materials for components for deployment in public spaces. This is really a three-part question: How long will the copper alloy maintain its ability to kill/inactivate a disease organism; will disease organisms become resistant to killing/inactivation by copper alloys; and what type of maintenance/cleaning is required? Antimicrobial activity of copper alloys appears to be long-lasting. The brass and adjacent wood surfaces in Grand Central Terminal in New York City were used to answer this question. This beautiful Beaux-Arts building is lavishly decorated with marble and brass, an antimicrobial alloy, and opened to the public over a century ago. Defined areas were sampled with a sterile cotton swab and the total number of bacteria picked up by the swab determined. No information was collected on the cleaning history of the surface sampled or frequency of touching. The results are shown in Fig. 2. Bacterial count is expressed in CFU/100 cm^2, or colony forming units per 100 square centimeters. The brass surfaces, with 88 and 51 CFU/100 cm^2, had a significantly lower bacteria count relative to the adjacent wood, with 563 and 1866 CFU/100 cm^2. This finding confirms that the brass components have retained antimicrobial capabilities after decades of hand touching.

Viral inactivation by copper alloys has been largely unstudied but the reports mentioned here show the rapid irreversible destruction of viral particles[3,6,7]. Since viral structure, of necessity, is largely constant, resistance is unlikely to be an issue. In the case of bacteria, the simplest mechanism of killing that is consistent with the data is the Membrane Target theory[4]. In this theory, an essential component of the bacterial membrane, unsaturated fatty acids, are modified by exposure to Cu^+/Cu^{++} ions in a manner that causes complete loss of membrane integrity and cell rupture. Resistance to copper alloy surface exposure has not been found in the over tens of trillions of bacteria tested in laboratory studies. Thus, at least for bacteria, the heritable change required for resistance is highly improbable or lethal, making the organism inviable[1,4].

Cleaning and maintenance are another important consideration. Most of the antimicrobial copper alloys that have U.S. Environmental Protection Agency (EPA) approval tarnish to some degree, but some are tarnish resistant, making them more useful for inclusion in public spaces. The Antimicrobial Copper Action Network website is a resource where one can read the EPA-approved cleaning protocols (amcopper.com) and obtain information about commercially available antimicrobial copper components. It is important to note that the EPA required extensive independent third-party laboratory testing, as described by Michels and Anderson[8]. The testing results demonstrate that the antimicrobial response of copper is powerful and enduring.

RECOMMENDATIONS

Everywhere we go we touch surfaces that are likely to be contaminated with bacteria, viruses, and other disease-causing microorganisms. Think about the last time you were in an airport, a shopping center, or a hospital. You touched doorknobs, push plates, handles, stair railings, shopping cart handles, restroom faucets, and more. Any one of these surfaces in any of these public environments has the potential to transmit disease-causing microbes to your hands that could result in an infection. Your first line of defense is frequent hand washing, but, what if these common touch surfaces were an antimicrobial copper alloy? They would be working all day, every day of the year to kill the bacteria, viruses, and fungi

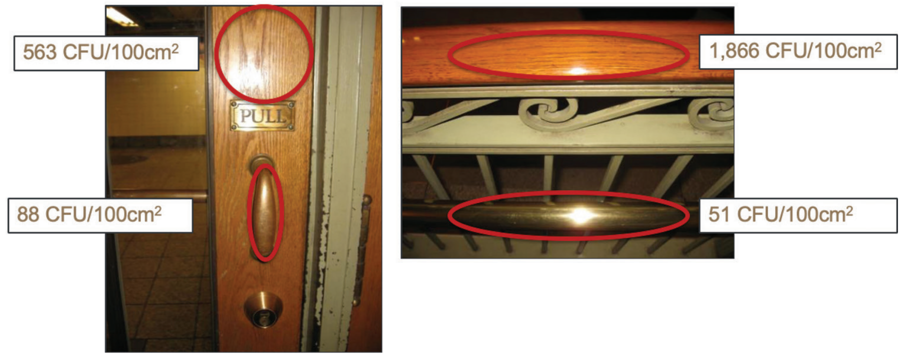

Fig. 2 — Bacterial levels found on brass and adjacent wood surfaces in Grand Central Terminal, New York City.

Fig. 3 — The interior of a Ronald McDonald House in Charleston, South Carolina, retrofitted with copper alloy components.

that cause infectious disease. Over 500 alloys have been approved by the EPA and a large number of alloy producers and component manufacturers have signed on to making the types of items needed.

The world is currently fighting a COVID-19 pandemic. In recent years we have seen HIV, SARS, MERS, and several different strains of influenza each year, not to mention the 1918 flu pandemic. All cause large numbers of fatalities, but, fortunately, only a few spread as rapidly as COVID-19. The COVID-19 pandemic will not be the last. Novel infective agents will continue to emerge and spread worldwide due, in large part, to high global mobility. We must use every weapon available to fight this never-ending battle.

Antimicrobial copper alloys are potentially powerful weapons. These alloys must be widely deployed in public spaces on common touch surfaces, especially in places with high levels of human traffic. Mass transit systems, airports, cruise ships, military bases and ships, shopping centers, schools, hotels, entertainment facilities, sports stadiums, large office buildings, hospitals and healthcare facilities, and more must be retrofitted to include the appropriate placement of antimicrobial copper components such as doorknobs, stair railings, push plates, handles and drawer pulls, electrical switch plates, plumbing fixtures and sinks, and elevator floor buttons. **~AM&P**

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References

1. H.T. Michels and C.A. Michels, The New 'Old' Weapon in the Fight Against Infectious Disease, *Curr. Trends Microbiol.,* Vol 10 p 23-45, 2016.

2. N. van Doremalen, T. Bushmaker, D.H. Morris, M.G. Holbrook, A. Gamble, B.N. Williamson, A. Tamin, J.L. Harcourt, N.J. Thornburg, S.I. Gerber, J.O. Lloyd-Smith, E. de Wit, and V.J. Munster, Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1, *N. Engl. Jour. Med,* 2020, DOI: 10.1056/NEJMc2004973.

3. S.L. Warnes, Z.R. Little, and C.W. Keevil, Human Coronavirus 229E Remains Infectious on Common Touch Surface Materials, *mBio, American Soc. Microbiology,* Vol 6, e01697-15, 2015.

4. R. Hong, T.Y. Kang, C.A. Michels, and N. Gadura, Membrane Lipid Peroxidation in Copper Alloy-Mediated Contact Killing of *Escherichia coli, Appl. Environ. Microbiol.,* Vol 78, p 1776-1784, 2012.

5. C. Espirito Santo, E.W. Lam, C.G. Elowsky, D. Quaranta, D.W. Domaille, C.J. Chang, and G. Grass, Bacterial Killing by Dry Metallic Copper Surfaces, *Appl. Environ. Microbiol.,* Vol 77 p 794-802, 2011.

6. S.L. Warnes, E.N. Summergill, and C.W. Keevil, Inactivation of Murine Norovirus on a Range of Copper Alloy Surfaces is Accompanied by Loss of Capsid Integrity, *Appl. Environ. Microbiol.,* Vol 81, p 1085-1091, 2015.

7. J.O. Noyce, H. Michels, and C.W. Keevil, Inactivation of Influenza A Virus on Copper versus Stainless Steel Surfaces, *Appl. Environ. Microbiol.,* Vol 73, p 2743-2750, 2007.

8. H.T. Michels, and D.G. Anderson, Antimicrobial Regulatory Efficacy Testing of Solid Copper Alloy Surfaces in the USA, *Metal Ions in Biology and Medicine,* Vol 10, edited by C.I. Maymard, T. Theophanides, L. Khassanova, and T. Collery, published by John Libbey Eurotext, Paris, p 185-190, 2008.