The COVID-19 Pandemic, Part 2: Understanding the Efficacy of Oxidized Copper Compounds in Suppressing Infectious Aerosol-Based Virus Transmission

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In *CORROSION'S* June 2020 editorial,[1] we explored the COVID-19[2] pandemic and the antimicrobial function of copper and silver enabled by corrosion. Since that editorial was written, we have gone from 2.1 million confirmed infections and over 143,000 related deaths worldwide[3] to 114,582,356 cases and 2,541,808 deaths as of March 1, 2021, according to the John Hopkins University COVID-19 Dashboard.[3]

A cause of this large increase is the high rate of the spread of SARS-CoV-2 (the virus that causes the coronavirus disease COVID-19), which is 40-fold greater than that of SARS-CoV-1.[4] Recently, a more highly contagious mutation has been reported which makes this virus (referred to as the COVID-19 virus throughout this editorial) even more transmittable.[5] This makes the COVID-19 virus even more difficult to control[4] than SARS-CoV-1. Human-to-human transmission is now confirmed to be a dominant form of spread especially by inhalation of aerosols (< 5 μm) and infectious droplets (> 5 μm diameter) which may be acquired by a unique host during casual person-to-person encounters with infected individuals.[6]

While Part 1[1] of this editorial series focused on copper and, to a lesser extent, silver corrosion when utilized as a high-touch surfaces in humid air and perspiration, Part 2 explores incorporating copper oxidation products as antiviral agents into "protective gear," such as face masks, air filters, fabrics, and clothing. Given the increased airborne transmittability of the virus,[6] this topic is of significant importance.

In order to contribute to the public dialogue regarding the important role of protective gear, we seek to present some of the "science behind it" or "how it works" of the antiviral properties of copper and its compounds. As the science surrounding the inactivation of the COVID-19 virus by copper is still emerging, we discuss the factors controlling Cu ion availability when Cu, its oxides, and other chemical compounds are utilized as particles impregnated in personal protective equipment (PPE) or related components. Additionally, some of the corrosion- and chemical-related aspects that should be considered when discussing the potential for virus inactivation are illuminated. So, how does an oxidized metal work as a disinfectant when embedded in PPE? Let us begin our discussion by briefly reviewing transmission mitigation by face masks.

COVID-19 VIRUS AEROSOL TRANSMISSION AND MITIGATION OF TRANSMISSION BY ACTIVE AND PASSIVE FILTRATION STRATEGIES

Airborne transmission is a highly virulent and dominant route for the spread of the COVID-19 virus[6] (see Figure 1[a]). One way to mitigate this spread is to use "passive" physical barriers, such as face masks and other related equipment like gloves, face shields, and protective suits.[4] Face coverings prevent airborne transmission of viruses by blocking atomization and inhalation of virus-bearing aerosols as well as also altering contact transmission pathways by hindering viral shedding of droplets[4,6] from sneezing, etc., onto high-touch surfaces which might then enable hand-to-hand transfer (Figure 1[a]). Protection can be provided by physically isolating virus-laden aerosols using masks. Surgical masks are often made of three different fiber layers to prevent the entry of viruses: the outside layer is designed to stop liquids from traveling inwards towards the face, mouth, and nose without encountering an obstacle; an interlayer acts as a barrier against viruses and bacteria; and an inner layer absorbs moisture exhaled by the wearer.[7,8] Different materials can be synthesized to act as protective coatings where the fabric can be designed to control pore size relative to airborne aerosol and particulate dimensions,[4] as well as function in other ways such as by electrostatic attraction of aerosol particles.

A number of strategies for improving face masks beyond serving as "passive" physical barriers have been reported because of the high airborne transmission of the COVID-19 virus, along with previous SARS events.[4] These strategies all involve materials science principles,[4] with a few governed by electrochemical corrosion processes. What if incoming aerosols with viruses were inactivated upon contact and exhaled atomized saliva was also disinfected when landing on the inner layer? Or, if self-cleaning functions were "built in" such that PPE can be self-sanitized during a pause in use for a certain time and then reused?

Materials that lead to oxygen radical production by photocatalysis or photothermal materials could be envisioned.[9] Disinfection methods using silver[10] and TiO_2 photocatalysts are fairly mature technologies.[11,12] New ideas have been reported concerning materials that disinfect "on the spot" or provide self-cleaning functionality.[13-15] In this discussion, we direct our focus towards oxidized copper-impregnated face mask. Approaches have been developed for placing copper oxides on textile fibers, latex, and other polymer products[16,17] to function as antiviral agents. For example, a face mask with functional copper oxide is shown in Figure 1(b).[18] But how does a copper compound deployed as a disinfectant actually work? Let us briefly review the antiviral effects of copper first in metallic form and then as an oxidized compound.

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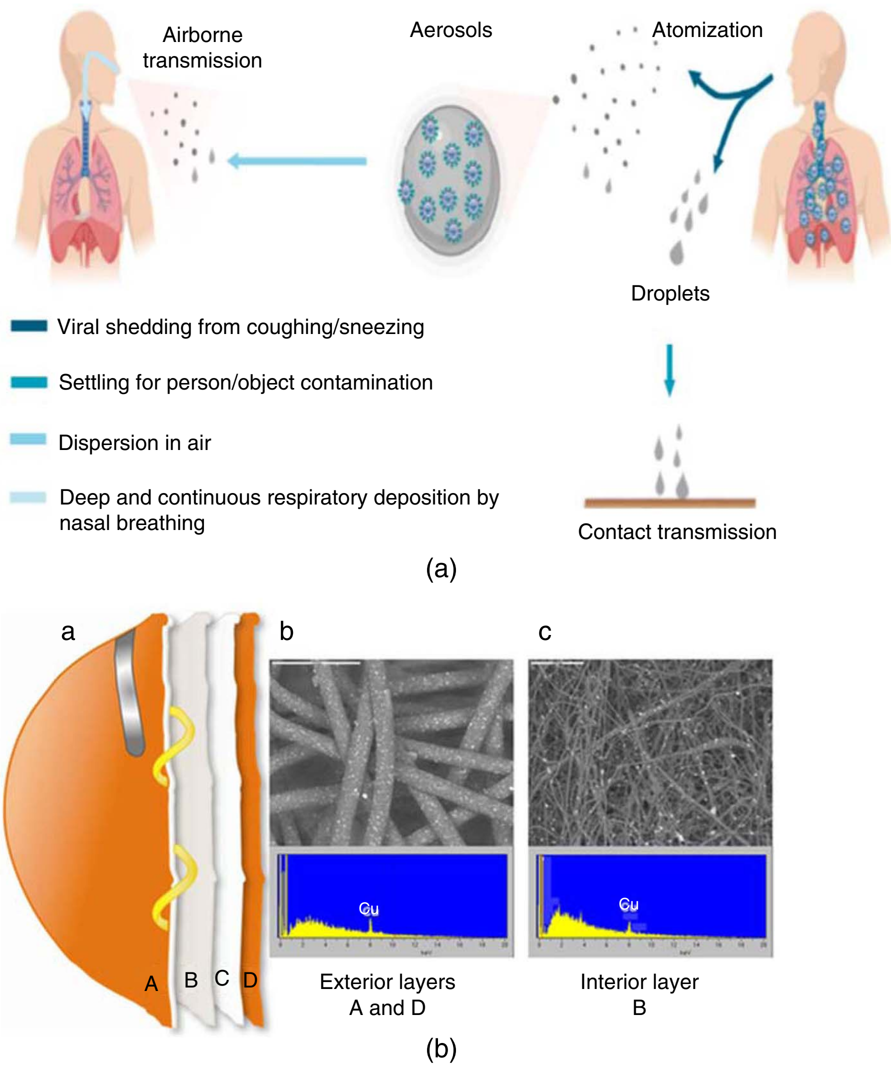

FIGURE 1. *(a) Possible pathways for transmission of the COVID-19 virus involving human atomization of viruses during the coughing or sneezing of an infected person. These events produce virus-containing droplets (>5 μm) and aerosols (<5 μm). Virus transmission from person to person may be enabled by airborne aerosol/droplet routes. Inhaled airborne viruses may deposit directly into the human respiration tract without functional face gear. Large droplets mainly settle out of air to cause person/object contamination, while aerosols are efficiently dispersed in air. Reprinted from R. Zhang, et al.,[6] licensed under CC BY 4.0, http://creativecommons.org/licenses/by/4.0/. (b) Schematic of copper oxide arranged on mask fibers. Reprinted from G. Borkow, et al.,[18] licensed under CC BY 3.0, https://creativecommons.org/licenses/by/3.0/.*

ANTIMICROBIAL AND ANTIVIRAL PROPERTIES OF COPPER

Copper's antimicrobial properties[19,20] have been used by ancient civilizations for water purification, skin ailments, and wound healing.[20,21] Over time, additional uses for copper were discovered. Copper alloys were optimized for ship hulls using elements that promoted the ion release necessary for anti-fouling balanced against undesired levels of metal wastage due to excessive corrosion.[22] More recently, numerous scientific articles have emerged regarding copper-based functional materials. In laboratory tests, copper has been found to interfere with the viability of bronchitis virus,[23] poliovirus,[24] herpes simplex virus,[25,26] human immunodeficiency virus (HIV),[16,27-29] and influenza viruses.[30,31]

Antimicrobial and antiviral efficacy relies on "free" copper ions (i.e., dissociated Cu^{+} and Cu^{2+} ions) in solution. Figure 2 shows the inactivation times (>99.9% reduction) for *E. coli*[32] and *L. pneumophila*[(1)] as a function of the free copper cation concentrations. The strong effect of copper ion concentration on inactivation time is evident.[32,33] However, data linking the sensitivity of the COVID-19 virus and other coronaviruses to inactivation as a function of free Cu ions concentration are not yet available. Elemental copper and silver[10] possess intrinsic antimicrobial properties that are enabled by corrosion which releases free metal cations.[25,32,34] The free ions are distinct from copper ion sequestering in the oxide layer formed over the surface of the alloy or dissolved but chelated (to form a compound usually with an organic species in the environment, whereupon the organic is bonded to the copper ion) with some molecular species in solution.[25,32,34-37]

Copper surfaces have also been found to destroy human coronavirus HCoV-229E.[34] These types of studies often report log reduction in plaque forming units (PFU) or some other unit describing the concentration of the pathogen such as the human

[(1)] *Escherichia coli* (HCB1) and Legionella pneumophila bacteria.

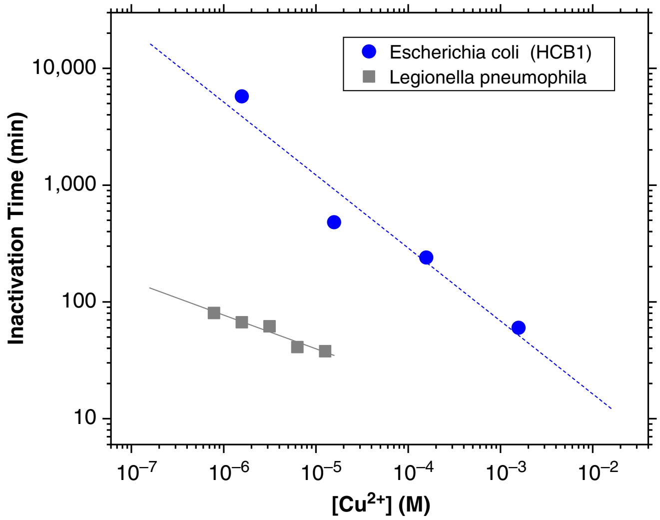

FIGURE 2. *Inactivation time (>99.9% reduction) of* Escherichia coli *(HCB1) and* Legionella pneumophila *bacteria in various soluble $[Cu^{2+}]$ concentrations. Data from Foster, et al.,[32] and Lin, et al.[33] Trend line indicates a regression fit.*

coronavirus. Viable HCoV-229E was effectively reduced with a $-\log_{10}(N_t/N_o)$ reduction of 4 relative to the starting virus concentration[(2)]. In 2020, the aerosol viability and surface stability of the COVID-19 virus were evaluated on different surfaces. A reduced COVID-19 virus viability on copper was observed over a period of hours.[38] In another very recent study, exposure of 1 μL inoculum of the COVID-19 virus to copper, stainless steel, copper-coated stainless steel, and polyethylene resulted in log(2.74) reduction (note that a log(3) reduction is equal to 99.9% killed).[39] The reported inactivation time was 1 min in the case of the copper surfaces. Surface temperature and relative humidity were not reported. As can be observed, there is a large difference in the inactivation time period reported in the two studies.[38,39] The author of one of these papers attributed this to the specific inoculum used.[39] This raises an important point and sends a cautionary message. Because the corrosion thermodynamics, kinetics, and the stability of the oxidized products formed can all differ with the molecular identity of the product, inoculum, saliva,[40] and perspiration "solution chemistry,"[32] these considerations need to be evaluated carefully to fully understand the efficacy of both Cu as a surface disinfectant and Cu compounds as disinfecting agents impregnated in PPE.

Materials containing impregnated oxidized copper oxide or other compounds possess antimicrobial properties[16,17] including antiviral properties.[16,29,41] The concept relies on copper ions which are stored and released from either natural or "engineered" molecular compounds containing oxidized Cu^+ or Cu^{2+}. As in the case of metallic copper after corrosion, copper ions in this form would also be available "on the spot" and are released by chemical dissolution when aerosols and droplets are exhaled and land near the Cu particle.[42] This is the approach that may be considered in medical masks, fabrics, as well as other copper-impregnated materials such as security trays at airports and glass touch screens.[43] Corrosion oxidation is not required when a suitably soluble oxidized copper compound serving as a reservoir of the copper ions is utilized. A recent study has demonstrated the benefit of copper oxide particles on glass and stainless steel in inactivating the COVID-19 virus.[44] In some formulations, the oxidized copper compound is coated with a "leaky" polymer layer, which regulates dissolution.

Numerous patents exist that describe the use of various copper compounds for antibacterial and antiviral function.[43,45-47] However, these patents focus on demonstration of performance often quantified as described above[(2)]. Rarely, if ever, is the "science behind it" illuminating the governing factors explained in the supporting literature or the patent itself. Chemical stability diagrams (shown in Figure 3) are a useful way to illustrate the thermodynamic principles behind copper release from copper compounds.[48]

DECIPHERING HOW IMPREGNATED PRODUCTS CONTAINING CHEMICAL COPPER SPECIES FUNCTION: HOW DOES IT WORK?

Let us examine how such an impregnated oxidized copper compound on a high-touch surface, mask, glove, or air filter might behave when contacted by a "sweaty" hand or a virus-laden droplet or aerosol. The chemical stability diagrams developed in the corrosion field and elsewhere can be of assistance here.[42,48,49] The chemical stability of copper compounds as a function of total soluble Cu ion concentration (including free copper Cu^{2+} and Cu^+ and also "bound" or chelated copper $Cu(L^n)_x^{2-nx}$ and $Cu(L^n)_x^{1-nx}$, where L is the binding ligand) and pH is given for some common chemicals in Figure 3 (see Supplemental Material).[50] In the case of metal oxides or soluble halide-based compounds, the copper ion concentration in the arriving droplet deposited near the particle is likely below its equilibrium solubility at first (the "X" in Figure 3 indicates the initial solution chemistry of simulated human perspiration containing no copper ions initially). The copper-based compound starts to dissolve, obeying some dissolution law, and the concentration increases towards its equilibrium solubility (as shown by the dashed trajectory curve for each compound) when copper ion concentration increases sufficiently into the droplet. The concentration is then likely relatively constant once equilibrium is satisfied (indicated by the solid dots) for whichever compound can most readily be established (for example, $Cu_4OH_6Cl_2$ may dissolve [shown by blue dashed line] to establish equilibrium between Cu^{2+} and CuO [intersection of blue dashed line with first available solid line, in this case the black solid line for CuO], Figure 3[b]). Equilibrium solubility depends on the thermochemical properties of the particular compound. The solubility of the copper cations will also depend on ligands such as hydroxide, lactate, ammonia, chloride, etc., which can themselves depend on pH. Finally, the valence state of copper (Cu^+ vs. Cu^{2+}) also affects solubility and is largely determine by the oxidizing power of the solution (represented here by the different electrode potentials, 0 V_{SHE} and 1 V_{SHE}).

(2) Virus and bacteria survival as a function of time when exposed a biocidal agent or anti-biocidal material capable of inactivation are often expressed as $\log_{10}(N_t/N_o)$, where N is the unit representing the "concentration" of virus particles or bacteria express as the number of colonies, particles, or units of virus/mL; N_t is the concentration at a given point in exposure time t; while N_o is the initial concentration. The typical test procedure involves an inoculum of virus or bacteria usually expressed as concentration. The units for this concentration can vary but may be colony forming units (CFU), plaque forming units (PFU), and tissue culture infectious dose (TCID). Viability is often determined by assessing the rate of reduction of PFU per unit volume, CFU per unit volume, etc., deposited on a surface or just by monitoring N_t over time. The threshold surviving that is still infectious depends on each specific virus and infectivity as well as the surface chemistry which regulates copper release.

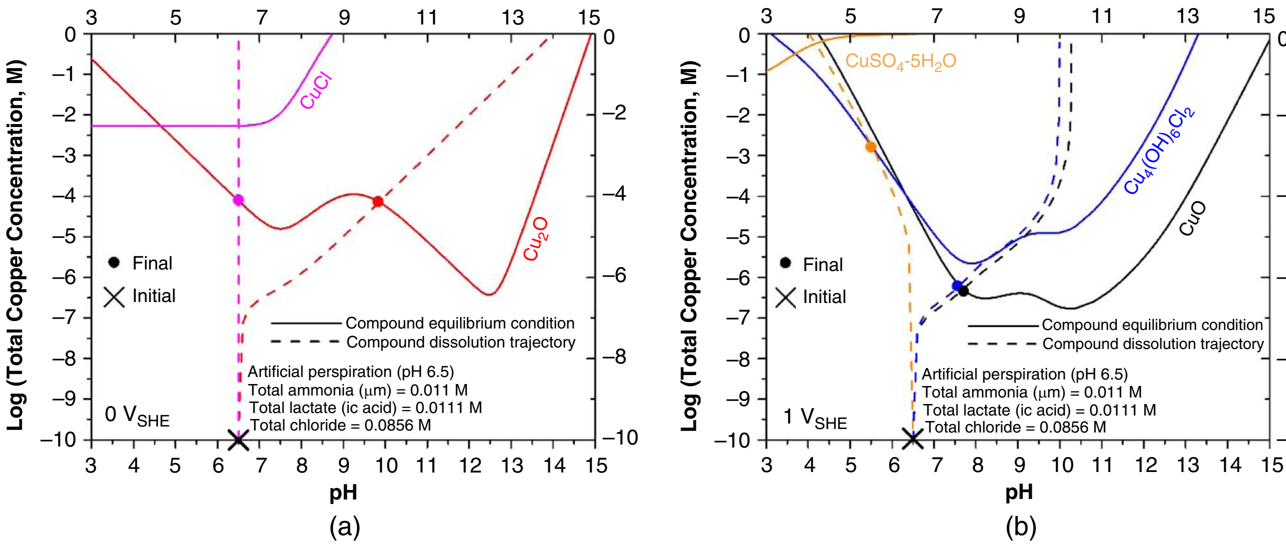

FIGURE 3. *Chemical stability diagrams of select copper compounds calculated in artificial perspiration.[50] Solid lines express the thermodynamic equilibrium conditions necessary for compound stability, in terms of pH and total copper concentration. As the various compounds dissolve, copper ions are released and the pH generally changes, as expressed by the dashed trajectory lines. The solution chemistry will progress from the initial condition (marked by the X) to the final equilibrium condition (marked by the solid dots) uniquely for each compound. Part (a) indicates a less oxidizing condition centered on Cu^+, while part (b) considers Cu^{2+}. See Supplemental Material for more details.*

The pH-dependent solubility of Cu hydroxide or oxide compounds (Figure 3) leads to different equilibrium ion concentrations in solutions, and the solution chemistry of the saliva or perspiration is therefore critical to antiviral function. Viruses and bacteria also have different sensitivity to free Cu ions and the treatment method must reflect that fact. As seen in Figure 2, copper ion dissolution from the oxide to a 100 ppm (~1 mM) level kills *E. coli* in about 40 min in terms of a log(3) or 99.9% reduction. In contrast, *Legionella* was killed within the same time but using 100 times less soluble Cu. Based on the equilibrium Cu concentrations given by the intersections illustrated in Figure 3, and neglecting any complications due to chelators or ligands, an estimate can be made of the amount of time a given compound may take to kill or inactivate various infectious agents from the Cu sensitivity data presented in Figure 2. The estimated effectiveness of several Cu-based compounds and mixtures under certain assumptions are shown in Figure 4[(3)]. While the specific sensitivity of a given virus or bacteria to Cu may be different, the relative rankings and chemical thermodynamics of Cu compounds are the same.

Although in-depth results for the COVID-19 virus are pending, the implications of this are clear: inactivation of viruses and bacteria by some compounds may have longer or shorter disinfection time and will be a function of both dissolved and free copper concentration and the sensitivity of the pathogen to free Cu. Therefore, actively dissolving compounds (or compound mixtures) with relatively high solubility (i.e., less stable in water) are preferable to maintain effective antimicrobial function within a practical timeframe. A balance between speed and durability may be necessary. A highly dispersed, quickly dissolving compound may be effective, but might deplete itself within a short time or be lost by washing, etc. These factors serve as design considerations and some products may take these into account.

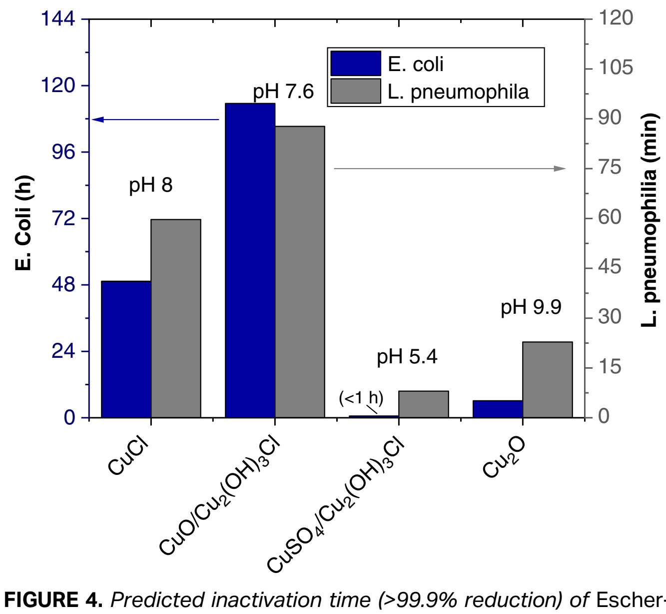

FIGURE 4. *Predicted inactivation time (>99.9% reduction) of* Escherichia coli *(HCB1) and* Legionella pneumophila *resulting from chemical dissolution of Cu-based compounds and mixtures in artificial perspiration. Data obtained from regression fit of Figure 2. Chemical equilibria between compounds considered and Cu cation concentration calculated from Figure 3. Equilibrium pH is indicated for each. Note difference in time scale from left and right axis. Time required to inactivate a bacteria or virus is estimated from the equilibrium Cu ion concentrations and their associated disinfection kinetics. Inactivation is assumed to follow kinetics from viability experiments of planktonic bacteria in suspension with dissociated $CuCl_2$ in artificial perspiration* (E. coli) *and deionized water (*L. *pneumophila).*

(3) The times shown here do not provide an indication of inactivation times for the COVID-19 virus but serve as an example.

SOME THINGS TO CONSIDER ABOUT COPPER ION RELEASE IN ORDER TO BETTER UNDERSTAND THE ANTIVIRAL FUNCTIONALITY OF COPPER

There may be further ways to optimize the chemical dissolution of copper-based compounds for virus inactivation than achieved to date. Based on what is known so far, the fate of copper—whether oxidized and retained in the solid oxide, dissolved in a droplet deposited on a mask, or somewhere else—must be tracked to truly understand whether a given copper compound and environment create the circumstances where antiviral properties are operative in the time desired for the given PPE and application. For instance, overnight cleaning might permit an inactivation time as long as 12 h. However, an aerosol residing on a mask fabric layer for a limited period of time before inhalation (if and when dislodged) might demand a faster inactivation time.

Understanding whether the copper cation concentration supplied would inactivate various viruses in a given time in a given environment is important to consider. Standard test methods could be developed. Such knowledge will help clarify differences in early reports on copper alloy surfaces whereupon one researcher reports 4 h for copper to kill the COVID-19 virus,[38] while another reports less than 1 min.[39] A range of temperatures, surface conditions, and relative humidity must be investigated in order to identify the key combinations of conditions where copper alloys and oxidized copper compounds are effective towards the COVID-19 virus inactivation. Cleaning and wash solutions applicable to PPE should also be studied. It is imperative to investigate and define windows of effective operation where metallic cations are successful in reducing virus viability to the point where human transmission by aerosols and droplets is reduced by a significant amount.

In closing, it seems most efficacious to pursue further developments in the science and technology of copper-based systems for antimicrobial functionality. Moreover, designers should consider the factors governing the desire to attain certain copper concentrations quickly and the efficacy of that concentration in terms of the time required for substantial inactivation. The societal benefits are well worth the investments into further research and understanding.

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