The COVID-19 Pandemic, Part 1: Can Antimicrobial Copper-Based Alloys Help Suppress Infectious Transmission of Viruses Originating from Human Contact with High-Touch Surfaces?

John R. Scully, Technical Editor in Chief

On behalf of all readers, including those in the corrosion community and those visiting our journal, *CORROSION* sends our sincerest heartfelt wishes for your safety and good health to you, your family, and colleagues. Hopefully you are reading this while safe in your home! We also wish to take this opportunity to express our unbounded gratitude to the entire healthcare community and all emergency responders—the real heroes on the front lines of this pandemic. The purpose of this editorial is to share information on the benefits of materials that may function to deactivate viruses and bacteria and thereby offer the possibility of contributing to the overall goal of mitigating disease transmission. It is intended to broach the needs, gaps, and opportunities regarding materials that may mitigate infectivity through corrosion processes.

WHAT IS COVID-19?

World-wide attention concerning public health is focused on a novel human coronavirus disease that causes a severe acute respiratory syndrome (SARS) named SARS-CoV-2. The disease caused by this virus, named COVID-19 by the World Health Organization,[1] has over 2.1 million confirmed infections and over 143,000 related deaths worldwide, with over 665,000 confirmed infections and over 32,000 deaths in the United States alone, as of April 16, 2020.[2] Throughout this editorial this virus is hereafter referred to as the COVID-19 virus.

Human-to-human transmission is believed to spread in the form of infectious droplets (> 5 μm diameter) and aerosols (< 5 μm) which may be acquired by a unique host during casual person-to-person encounters with infected individuals.[3] These hosts shed the virus in the form of droplet and aerosol productions from coughing, sneezing, or, when under hospital care, from episodic excretions or medical procedures.[4] Such aerosols may become lodged in the respiratory tract of a novel host. This direct route of infection is likely augmented by alternative spreading pathways where aerosols settle on other sources such as skin and hands, personal protective equipment (PPE), clothing, and other fomites.[5,(1)] Airborne aerosols remain aloft as a function of size before either evaporating or settling on the surfaces of such inanimate objects as well as novel hosts.[6] According to a recent publication in the *New England Journal of Medicine*, the COVID-19 virus remained viable in the analyzed deposited drops and aerosols with only a slight loss in infectious viability for at least 3 h (the duration of the test).[7] When droplets and aerosols settle from the atmosphere on high-touch surfaces, the remaining viable infectious virus could possibly be transferred to the hand by touch contact, with a possibility of transmission by hand-to-face contact (research on transmission pathways of COVID-19 is ongoing). This can apparently occur with some viruses even on "dry" surfaces.[5,8-9] A novel host with newly acquired hand contamination may touch their face as frequently as 16 to 23 times per hour according to some studies, enabling transfer of the virus to eyes, nostrils, and mouth.[10-11] Unfortunately, the COVID-19 virus appears to be able to remain infectious for days[7-8] on some surfaces.

MITIGATION OF FOMITE-TO-HAND TRANSMISSION BY EITHER CHEMICAL DISINFECTING AND/OR INTRINSICALLY ANTIMICROBIAL SURFACES

One obvious and effective means of mitigation of this transmission route is frequent cleaning of fomites with a biocidal agent that disinfects.[8,12] While cleaning with biocides certainly can help mitigate fomite transmission, there are still some concerns. Continuous host aerosol deposition, frequent touching, as well as accidentally missing infected parts of surfaces during cleaning may leave residuals in spots that continue to infect. Surfaces, in public places especially, can be re-infected easily. Therefore, frequent and effective cleaning is crucial.

Additionally, intrinsic protection could be provided to surfaces through selection and deployment of materials that have properties that enable *intrinsic* antimicrobial functionality. This could either in the form of monolithic objects or impregnation or imbuing of materials with pigments or particles. For example, various metallic materials may have antimicrobial properties; one such example is copper.[13-15] It should be noted that stainless steels look clean because of their thin

(1) "Fomite" is a term used to describe an inanimate object or material that is likely to carry infections and provide a source for further transmission to a novel host.

chromium-rich passive film but have no antimicrobial capabilities. Recent interest in copper well prior to COVID-19 has been substantial, where it has been recognized that copper alloys kill bacteria and viruses and could reduce fomite-related spreading.[7,9,13,15-21] It is also well established that other materials are antimicrobial such as silver[22] and TiO_2 photocatalyst.[23-24]

ANTIMICROBIAL PROPERTIES OF COPPER

Historically, it has been well known that copper is antimicrobial.[13-14] Ancient civilizations used copper for water purification, skin ailments, and wound healing.[14,25] The maritime community knew of these properties hundreds of years ago or more when copper was used for antifouling purposes on ship hulls.[26] Metallurgists optimized copper for ship hulls with alloying elements that promoted ion release necessary for antifouling balanced against excessive metal wastage due to too much corrosion.[26]

Copper and silver[22] possess intrinsic antimicrobial properties that are enabled by corrosion. Ideally, a high-touch surface is corrosive enough to mitigate virus viability through Cu ion release, yet tarnish resistant enough to maintain a tarnish-free surface without porosity that can be cleaned and does not collect dirt, moisture, and other particles.[15] Alloying elements are intentionally added to copper to achieve certain targeted properties superior to those of pure copper. However, commercial off-the-shelf alloys have mostly been considered to date for antimicrobial purposes.[9,13] In many cases, alloying additions were originally aimed toward other purposes such as strength and ductility. In studies of antimicrobial properties conducted to date on commercial alloys, retention of copper at greater than 60 wt% to 70 wt% ensures some antimicrobial function.[9,13] The exact composition of the alloy matters for antimicrobial properties because a balance is usually sought between sufficient release of copper to affect viability and other factors such as color stability, passivity, or excessive tarnishing which could create a porous surface. Many copper alloys may release other elements preferentially with respect to copper by a process known as dealloying or, in contrast, may passivate over time in various environments.

The inactivation of bacteria and viruses on metallic copper occurs by an electrochemical process whereupon copper cations are produced during aqueous corrosion.[9,17,21] Antimicrobial efficacy relies on copper ions (i.e., Cu^+ and Cu^{2+}) in solution distinct from copper sequestering in the oxide layer formed over the surface of the alloy or released 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.[9,17-18,21,27-28] Therefore, Cu ions must be released from the alloy and present at the same spot and in the same local environment as the bacteria or virus, as opposed to just the presence of a copper surface, per se. The release mechanism in humid air occurs by the electrochemical process of metallic corrosion. All such spontaneous metallic corrosion processes involve an anodic reaction. In the case of copper, this is an oxidation half-cell electrochemical reaction which oxidizes elemental copper from the fomite, liberating Cu^+ and Cu^{2+}. This anodic half-cell reaction must be coupled with at least one cathodic electrochemical half-cell reaction such as oxygen reduction. This cathodic reaction must occur at a matched rate to consume the electrons stripped from the outer valence shell of the copper atoms. Corrosion requires both a continuous ionic path and electrical connection between the anode and cathode which could be the same copper surface and even the same location on that surface. This coupled set of anodic and cathodic half-cell reactions sustains spontaneous corrosion process on a fomite material such as copper. Copper ions can also be released from either natural or "engineered" molecular compounds containing previously oxidized Cu^+ or Cu^{2+}. In this case, copper ions are released by a chemical dissolution driven process.[29] This is the approach sometimes used in medical fabrics and other copper impregnated materials such as security trays at airports (to be discussed later in Part II).

Copper is also oxidized in air under dry oxidation at very low relative humidity (RH) by oxygen in the atmosphere. However, surfaces containing debris and/or chemical deposits form a thin film of aqueous solution at most RH levels aided by dew point condensation, capillary condensation, and/or deliquescence of salt deposits. These enable aqueous corrosion processes to proceed even when surfaces appear "dry."[30-33,(2)] The typical cathodic reaction during copper corrosion in sulfide-free environments is the oxygen reduction reaction (ORR). Some ORR mechanisms produce hydrogen peroxide (H_2O_2) as an intermediate. As discussed above, this may result in both the metal ion and hydrogen peroxide at the same or nearby sites.

The subsequent mechanism of bacterial death in the presence of these chemicals brought about by corrosion is complex. However, it is known that more than one of the chemical species produced by these electrochemical and chemical reactions affect virus and bacteria survivability including copper cations, peroxide, reactive oxygen species, and possibly other chemicals.[9] Some literature also posits that the Fenton reaction on metals and/or the Haber-Weiss reaction produce toxic reactive species[9,16] catalyzed by certain metals. Copper cations appear to be the primary chemical for virus inactivation because chelating of copper ions (a form of sequestering) inhibits inactivation and protects coronaviruses, while sequestering of reactive oxygen species has some, albeit less, impact on virus inactivation.[9]

In a study which confirms this, $CuCl_2$ + H_2O_2 or $FeCl_3$ + H_2O_2 was applied to an array of different viruses used as surrogates (this particular investigation was conducted well before COVID-19 but was intended to be representative of various future viruses) and compared to glutaraldehyde (8%).[17] The data indicate the fastest and most severe inactivation of a range of surrogate viruses occurred in the case of Cu^{2+} + H_2O_2, with performance even better than glutaraldehyde. This was evident from both the time needed to inactivate 90% of the virus at a pre-selected concentration and the concentration required to achieve a 90% reduction in a fixed time period.[17] Hence, it can be presumed that copper corrosion yields on-the-spot generation of Cu ions ejected into the thin layer aqueous solution on surfaces as well as other reactive species generated as products

(2) Surface droplet and aerosol deposition are well known to the corrosion community, which has long recognized that that atmospheric corrosion relies on material surface wetting by aerosols and droplets, water condensation, as well as by wetting when the RH exceed the deliquescence RH_{crit} or DRH of a specific deposited hygroscopic chemical species. For instance, see Dante and Kelly[30] and Cole and coworkers.[31-33] The surface may collect chemicals from natural salt deposition or by direct touch where drying perspiration leaves chemicals that also deliquescence at lower RH compared to the wetting of clean surfaces. This enables corrosion of metals.

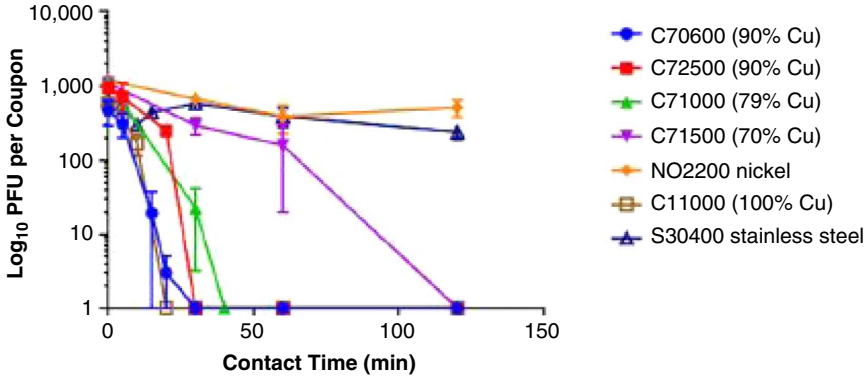

FIGURE 1. *Inactivation of HCoV-229E when 10^3 PFU of HCoV-229E in 20 μL was applied to 1 cm^2 coupons for a range of copper-nickel alloys and monitored over time. Note: results for stainless steel, nickel, and zinc (not shown) exhibited minimal change of less than $-\log_{10}(\Delta PFU/coupon)$ of 1. Reprinted from S.L. Warnes, Z.R. Little, C.W. Keevil,* mBio *6, 6 (2015): article e01697-15, https://creativecommons.org/licenses/by-nc-sa/4.0/.*[9]

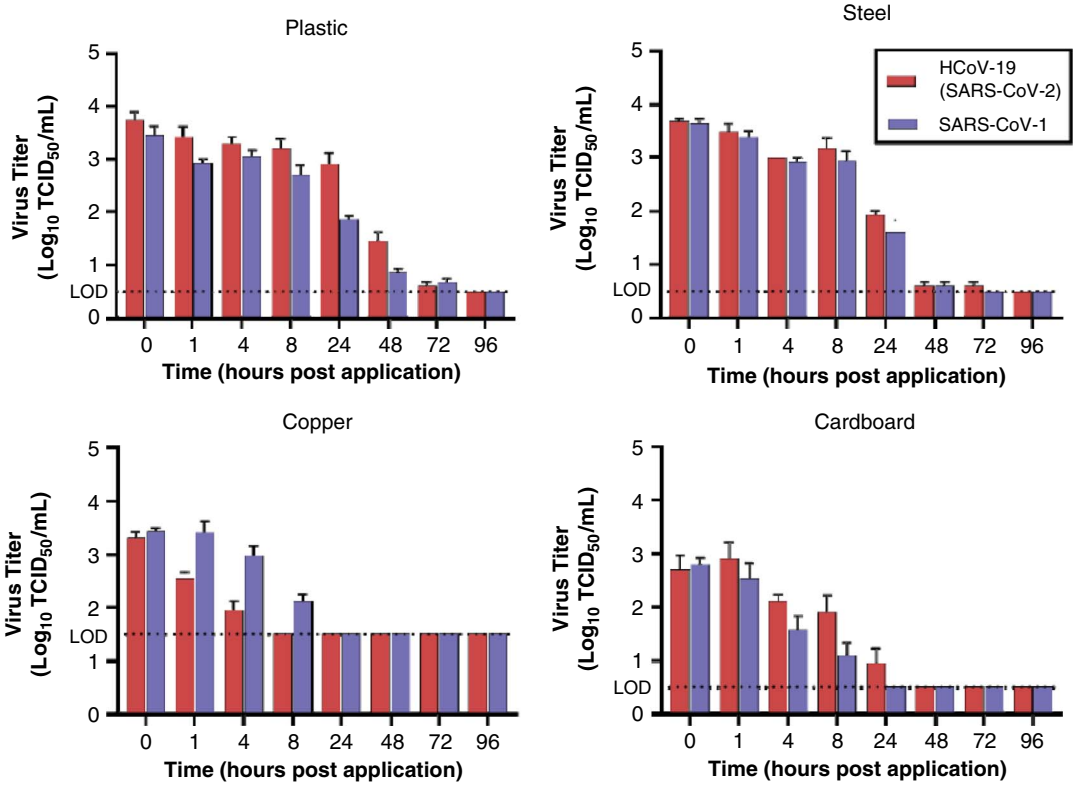

FIGURE 2. *Viability of SAR-Cov-1 and SACR-CoV-2 on various surfaces. Viruses were applied to copper, cardboard, stainless steel, and plastic at 21°C to 23°C and 40% RH over 7 d. Plot shows the means and standard errors. The decays were predicted from this experimental data and an exponential decay was found. $TCID_{50}$ is the point at which 50% of the cells are infected (or 50% tissue culture infectious dose [TCID]). Reprinted from van Doremalen, et al., "Aerosol and Surface Stability of HCoV-19 (SARS-CoV-2) Compared to SARS-CoV-1," medRxiv 2020.03.09.20033217 version 1, https://doi.org/10.1101/2020.03.09.20033217, under CC0 license.*[34]

of the electrochemical corrosion reactions operating. This produces some of the same chemicals, such as peroxides, utilized as synthetic biocides[8] except that in this case they are a natural consequence of the exposure environment and the metal. Moreover, no human intervention is necessary. It relies on the surface not passivating over time, which is a process by which a protective layer forms on the alloy surface limiting Cu ion release and the coupled process of reactive oxygen species generation discussed above.

COPPER AND HUMAN CORONAVIRUSES

In 2015, Warnes and coworkers published a manuscript showing that copper surfaces (including various brass and copper-nickel alloys) destroyed human coronavirus HCoV-229E.[9] Viable

HCoV-229E was effectively reduced with a $-\log_{10}(N_t/N_o)$ reduction of 4 relative to the starting virus concentration.[3] This occurred in less than 50 min on brass and 120 min on copper-nickel alloys with more than 70% copper. Inactivation was more rapid on alloys containing 70% copper or more. Moreover, nickel as well as stainless steel were relatively ineffective (Figure 1).

Recently, the aerosol viability and surface stability of the COVID-19 virus were evaluated on different surfaces.[7] Virus stability varied with the nature of the surface. Surfaces were exposed to a 50 µL inoculum (10^5 $TCID_{50}$/mL) at 40°C and 40% RH with the COVID-19 virus.[7,4] Median half-lives for viable COVID-19 virus were 3.46 h on cardboard, 5.63 h on AISI Type 304 steel, 6.81 h on polypropylene plastic, and only 0.774 h on 99.9% copper (Figure 2[34]).[7] Decay in viable virus levels was then modeled and found to be exponential, implying virus inactivation on copper predicted by a change of $-\log_{10}$(TCID/mL) of >3 in less than 10 h compared to greater than 50 h on stainless steel. Decay was faster on copper in the case of the COVID-19 virus compared to SARs-CoV-1. However, this was not always the case on every material.

SOME THINGS TO CONSIDER IN FUTURE COPPER CORROSION RESEARCH TOWARD IMPROVED ANTIMICROBIAL FUNCTIONALITY

There may be further ways to optimize the corrosion resistance of copper-based alloys for antimicrobial properties than achieved to date. Based on what is known so far, the fate of copper—whether oxidized and retained in the solid oxide, thin water film, or somewhere else—must be tracked to truly understand whether a given copper alloy and environment create the circumstances where antimicrobial properties are operative. There are a few examples of this on copper alloys.[27-28] It is tempting to gauge copper alloy antibacterial properties by utilizing previously reported corrosion rates in seawater, in part because the literature on copper corrosion is more comprehensive in this environment.[25,35] On the other hand, testing for virus and bacteria viability is often conducted in various physiological solutions.[9,17] However, Cu ion release on high-touch surfaces are perhaps best investigated by testing corrosion in human perspiration.[18,21,28] Caution is warranted because corrosion properties of a given alloy may differ between the physiological solution used in antibacterial studies, readily available data in seawater, and human perspiration (from touch) and other realistic solutions on touch surfaces.[18-21,5] Temperature, environment chemistry, pH, and gas solubility all affect Cu corrosion rates and Cu ion destinations. Surface preparation and roughness matter as well. Surface treatments of copper that lower corrosion rates, such as pretreatments promoting formation of a more protective oxide layer, application of lacquers, or corrosion inhibitors all can lower the antimicrobial effectiveness of copper surfaces. Therefore, a range of temperature, surface conditions, and RH must be investigated in order to identify the combinations of conditions where copper alloys are effective. Cleaning solutions capable of refreshing surfaces that might become passivated over time should also be studied. Moreover, the structure, chemistry, and physiology of the microbe play a big role in its survivability. Therefore, understanding the survivability of viruses (i.e., lifetimes) of these different and common bacteria or viruses in a systematic way on different copper alloys in different environments and at various pertinent temperatures is necessary for further antimicrobial alloy development. It is imperative to investigate windows of operation where specific copper alloys are successful in reducing virus viability to the point where human transmission by fomite contact is reduced.

FINAL THOUGHTS

Fomites that are high-touch objects pose a threat to disease transmission and novel host infection by viruses and perhaps COVID-19. Copper alloy surfaces may be capable of suppressing virus transmission through inherent lethality with respect to viable viruses on these fomite surfaces. This is enabled by natural corrosion processes on copper triggered by oxidation in relatively "dry" or humid air, as well as in an infected droplet or aerosol excretion that has settled on fomite surfaces. This process is intrinsic to copper in many environments and can occur without regular human interventions such as daily cleaning. Additional research is needed to confirm the effectiveness of copper alloy surfaces with respect to the COVID-19 virus, but the early research reported[7,34] is promising. Further investigation focusing in detail on materials properties, surface preparation, and environments may uncover additional ways to enhance antimicrobial properties.

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[3] Virus and bacteria survival as a function of time when exposed a biocidal agent or anti-biocidal material capable of deactivation 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, and N_o is the initial concentration. The typical test procedure involves an inoculum of virus or bacteria usually expressed as some 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 plaque forming units per unit volume, colony forming units 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.

[4] $TCID_{50}$ (50% tissue culture infectious dose) is the point at which 50% of the cells are infected.

[5] Caution is warranted as there is no assurance that antimicrobial efficacy toward inactivation or survivability with respect to any particular bacteria can be directly translated into inactivation capabilities with respect to viruses, specifically COVID-19, where data are limited at the time of this publication.

References

1. "Naming the coronavirus disease (COVID-19) and the virus that causes it," World Health Organization, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (April 16, 2020).
2. "COVID-19 Case Tracker," John Hopkins University & Medicine, https://coronavirus.jhu.edu/ (April 16, 2020).
3. "Q&A on Coronaviruses (COVID-19)," World Health Organization, https://www.who.int/news-room/q-a-detail/q-a-coronaviruses (April 16, 2020).
4. S.D. Judson, V.J. Munster, *Viruses* 11, 10 (2019): article 940.
5. M. Ronnqvist, L. Maunula, *Future Virology* 11, 3 (2016): p. 207-217.

6. X. Xie, Y. Li, A.T.Y. Chwang, P.L. Ho, W.H. Seto, *Indoor Air* 17 (2007): p. 211-225.
7. 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, V.J. Munster, "Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1," *New England J. Medicine*, March 17, 2020, http://dx.doi.org/10.1056/NEJMc2004973 (April 16, 2020).
8. G. Kampf, D. Todt, S. Pfaender, E. Steinmann, *J. Hospital Infection* 104, 3 (2020): p. 246-251.
9. S.L. Warnes, Z.R. Little, C.W. Keevil, *mBio* 6, 6 (2015): article e01697-15.
10. M. Nicas, D. Best, *J. Occupational Environ. Hygiene* 5 (2008): p. 347-352.
11. Y.L.A. Kwok, J. Gralton, M.-L. McLaws, *Am. J. Infect. Control* 43, 2 (2015): p.112-114.
12. "Cleaning and Disinfection for Households," Center for Disease Control and Prevention, March 26, 2020, https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cleaning-disinfection.html (April 16, 2020).
13. H.T. Michels, C.A. Michels, *Current Trends Microbio.* 10 (2016): p. 23-45.
14. J. Morrison, "Copper's Virus-Killing Powers Were Known Even to the Ancients," *Smithsonian Magazine*, April 14, 2020, https://www.smithsonianmag.com/science-nature/copper-virus-kill-180974655/ (April 16, 2020).
15. P. Airey, J. Verran, *J. Hospital Infection* 67, 3 (2007): p. 271-277.
16. Y. Fujimori, T. Sato, T Hayata, T. Nagao, M. Nakayama, T. Nakayama, T. Sugamata, K. Suzuki, *Appl. Environ. Microbiol.* 78, 4 (2012): p. 951-955.
17. J.-L. Sagripanti, L.B. Rouston, C.D. Lytle, *Appl. Environ. Microbio.* 59, 12 (1993): p. 4374-4376.
18. L.L. Foster, J.R. Scully, *Corrosion* 72 (2016): p. 1095-1106.
19. Y.-S.E. Lin, R.D. Vidic, J.E. Stout, V.L. Yu, *Water Res.* 30 (1996): p. 1905-1913.
20. C. Molteni, H.K. Abicht, M. Solioz, *Appl. Environ. Microbiol.* 76 (2010): p. 4099-4101.
21. L.L. Foster, M. Hutchison, J.R. Scully, *Corrosion* 72 (2016): p. 51-65.
22. J.L. Clement, P.S. Jarrett, *Metal-Based Drugs* 1 (1994): p. 467-482.
23. M. Cho, H. Chung, W. Choi, J. Yoon, *Water Res.* 38, 4 (2004): p. 1069-1077.
24. M. Cho, H. Chung, W. Choi, J. Yoon, *Appl. Environ. Microbio.* 71, 1 (2005): p. 270-275.
25. "Copper, Pathogens and Disease," Copper Development Association, https://copperalliance.org.uk/knowledge-base/education/education-resources/copper-pathogens-disease/ (April 16, 2020).
26. J.M. Bingeman, J.P. Bethell, P. Goodwin, A.T. Mack, *Int. J. Naut. Archaeol.* 29, 2 (2000): p. 218-229.
27. M.J. Hutchison, P. Zhou, K. Ogle, J.R. Scully, *Electrochim. Acta* 241, 1 (2017): p. 73-88.
28. D.J. Horton, H. Ha, L.L. Foster, H.J. Bindig, J.R. Scully, *Electrochim. Acta* 169 (2015): p. 351-366.
29. M. Pourbaix, *Atlas of Electrochemical Equilibria in Aqueous Solutions* (Houston, TX: NACE International, 1974).
30. J.F. Dante, R.G. Kelly, *J. Electrochem. Soc.* 140, 7 (1993): p. 1890.
31. I.S. Cole, W.D. Ganther, J.D. Sinclair, D. Lau, D.A. Paterson, *J. Electrochem. Soc.* 151 (2004): p. B267.
32. I.S. Cole, D.A. Paterson, W.D. Ganther, *Corros. Eng. Sci. Technol.* 38, 2 (2003): p. 129-134.
33. I.S. Cole, D.A. Paterson, *Corros. Eng. Sci. Technol.* 39, 2 (2004): p. 125-130.
34. 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, V.J. Munster, "Aerosol and Surface Stability of HCoV-19 (SARS-CoV-2) Compared to SARS-CoV-1," medRxiv 2020.03.09.20033217 version 1, https://doi.org/10.1101/2020.03.09.20033217.
35. M. Schumacher, *Seawater Corrosion Handbook* (Park Ridge, NJ: Noyes Data Corp., 1979).