A SHORT REVIEW ON COPPER AND METALSKIN ANTIMICROBIAL PROPERTIES

March 2020

Introduction:

The use of copper as a sanitizer has been known for centuries all over the world. The oldest documented report of this usage is in the Smith Papyrus, an Egyptian medical text written between 2600 and 2200 BC, which describes applications of copper to sterilize chest wounds and drinking water [Dolwett and Sorenson 1985].
Phoenicians, Ancient Greeks, Roman, Celts and others have also widely used copper antimicrobial properties for sterilizing drinking water, heal wounds or as antifouling on ship's hulls.
In the 18th and 19th century, doorknob and kitchen accessories were widely used and that is with the appearance of antibiotics that it was almost totally abandoned.

Nowadays, the rise bacteria resistance towards antibiotics and, more dramatically, the current pandemic outbreak of Covid-19, are rewriting the rule

Copper is safe to humans, as demonstrated by the widespread and prolonged use of copper intrauterine devices (IUDs) and, in contrast to the low sensitivity of human tissue (skin or other) to copper [Warnes 2014], microorganisms are extremely susceptible to it. **This make copper a privileged candidate to create self-sanitizing touch surfaces specifically in hospital and healthcare buildings, but not only. As a matter of fact, public places such as hotels, office buildings, nurseries, eldery houses… are all concerned by micro-organisms contamination. So are means of public transportation (buses, tramways, trains, planes…).**

Copper interaction with microorganisms:

Copper is an essential element to life. It acts as a cofactor for enzymes involved in diverse biological processes including respiration, destruction of free radicals, iron homeostasis, and neurological development. However, when in excess, copper is toxic as it generates reactive oxygen species (ROS) via the Fenton reaction, disrupts metal ion binding and homeostasis, and binds macromolecules such as proteins inappropriately [Rensing and Grass 2003].
Several mechanisms to explain and model this have been suggested (figure 1) that involves copper ions to interact with cells membranes (figure 2).

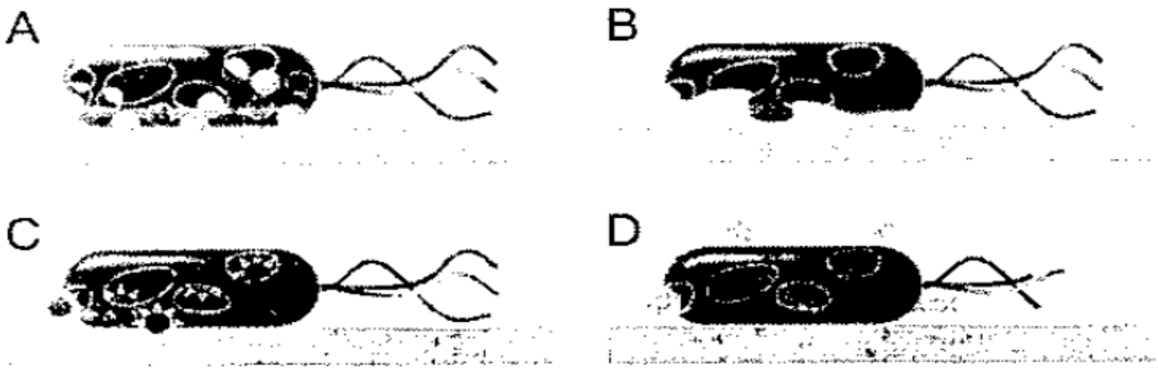


Figure 1. Simplistic tentative scheme in contact killing of bacteria on copper. [Grass 2011]

(A) Copper ions dissolves from the copper surfaces and causes call damages. 5B). The cell membrane ruptures because of copper and other stress phenomena, leading to loss of membrane potential and cytoplasmic content. 5C) Copper ions induce the generation of Reactive Oxygen Species, which cause further, call damage. 5D) Genomic and plasmid DNA becomes degraded.

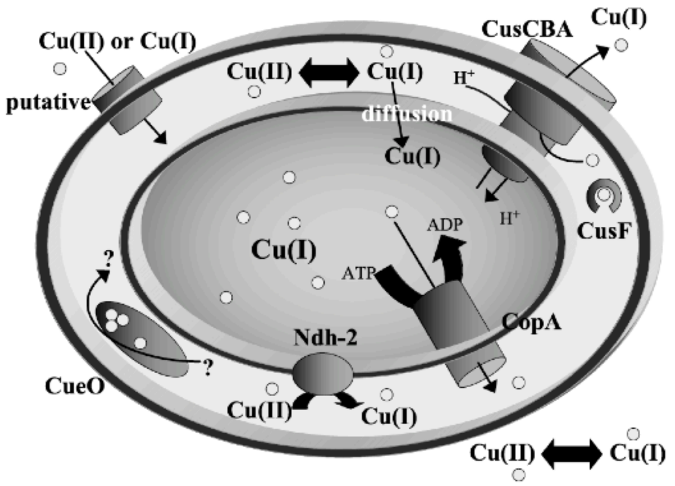


Figure 2. Copper homeostasis mechanisms on E. Coli. [Rensing and Grass 2003].

Only the most relevant elements of the system are represented: CopA (Copper ATPase which is a Cu(I) translocation Ptype ATPase – Ndh-2 a cupric redactase ; CueO a multi-copper oxidase ; CusFBA a four-component copper efflux pump.

However, if the death of bacteria cells is not doubted, the mechanism is still unknown in its details and the ROS involvement via Fenton reaction is still discussed.

Copper efficacy, in vitro studies:

The most recent study was carried out by Dr. van Doremalen, Mr. Bushmaker, and Mr. Morris in the New England Journal of Medicine. This study aimed at comparing the stability of Covid-19 (in red) vs SARS-Cov 1 (in blue) on different surfaces. This study shows that the Covid-19 lives no longer than 4 hours on copper whereas it can survives for days on stainless steel (fig.3)

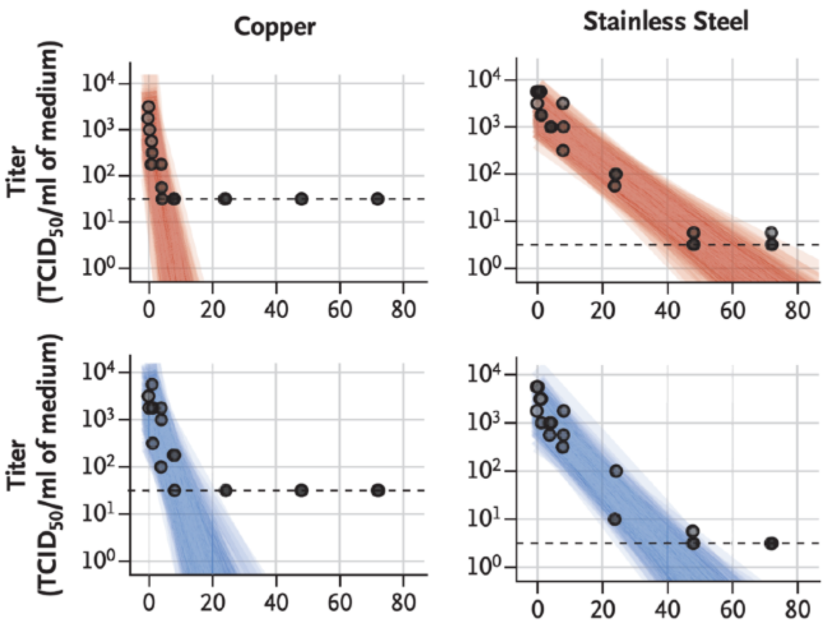


Fig 3- Comparative evolution of the stability of Covid19 and SARS-Cov 1

A new French standard has set the level of efficiency required for a material to claim a bactericidal activity (NF S90-700: method of evaluation of the basic bactericidal activity on non porous surfaces)

This standard defines the killing rate at 99% and the killing time at 1 hour, and this must be obtained on four different strains : Escherishia Coli, Staphilococcus Aureus, Pseudomonas Aeruginosas and Entreociccus Hirae.

This standard is being promoted to the ISO level with the creation of a new technical committee on biocidal surfaces.

MetalSkin was tested following that standard and the results are as below:

		Killing Rate in 1 h	
Escherishia Coli		-3,21 log	passed
Staphilococcus Aureus		-2,76 log	passed
Pseudomonas Aeruginosas		-2,75 log	passed
Enterococcus Hirae		-5,09 log	passed
	Avg	-3,45 log	

Several studies have measured the efficacy of the contact killing property of copper and copper alloys on a wide variety of microorganisms, prior to the release of the NF S90-700. We only report here a summary of results on bacteria of interest in hospitals. Furthermore, we concentrate on experiments for which the methodology was relevant to simulate inoculation of touch surfaces by finger tips in a normal environment (room temperature, normal relative humidity, and natural UV lighting). Complete data, and methodology details are left to the reader to browse through into the references.

species	inoculation level	killing time, RT	reference
Acinetobacter johnsonii DSM6963	10e9 CFU	a few minutes	Espirito Santo and al
Clostribdium difficile ATCC9689	10e6 CFU	6 hours	Weaver and al.
E. ColiW3110	10e9 CFU	1 min	Espirito Santo and al
E. Coli O157	10e7 CFU	75min	Wilks and al.
Listeria monocytegenes Scott A	10e7 CFU	60 min	Wilks and al.
Pantoen Stewartii DSM30176	10e9 CFU	1 min	Espirito Santo and al
Pseudomonas oleovorans DSM1045	10e9 CFU	1 min	Espirito Santo and al
Pseudomnas Aeruginosa UR1156	10e6 CFU	15 min	Ballo and al.
Pseudomonas Aeruginosa ATCC	10e11 CFU	<90 min	Meyer and al.
Staphylococcus warnerii DSM20316	10e9 CFU	a few minutes	Espirito Santo and al
Staphylococcus Aureus ATCC	10e10 CFU	<60 min	Meyer and al.
Bruchybacterium conglomeratum DSM10241	10e9 CFU	a few minutes	Espirito Santo and al

Variations in results are due to initial strains level of concentration (see table above, inoculation level), contact duration between surfaces and strains, humidity level [Espirito Santo 2011] but also by the counting methods employed. Indeed, all authors are reporting a killing time as the time to kill all bacteria cells on the surface. However, intervals between 2 observations are not identical (from a few minutes to the hour) as well as the detection limit of counting methods (from a log 3 to a log 5 reduction).

Keeping in mind the application of copper on touch surfaces in hospitals, one can wonder about the efficacy towards repetitive inoculation; Indeed, doorknobs, tap handles, handrails and other elements are touched several times a day by patients, visitors and staff. Michels and al. [Michels 2008] have run experiments that demonstrate the immediate and lasting killing effect of copper that makes it highly suitable to maintain a sanitized touch surface despite repeated contaminations over time.

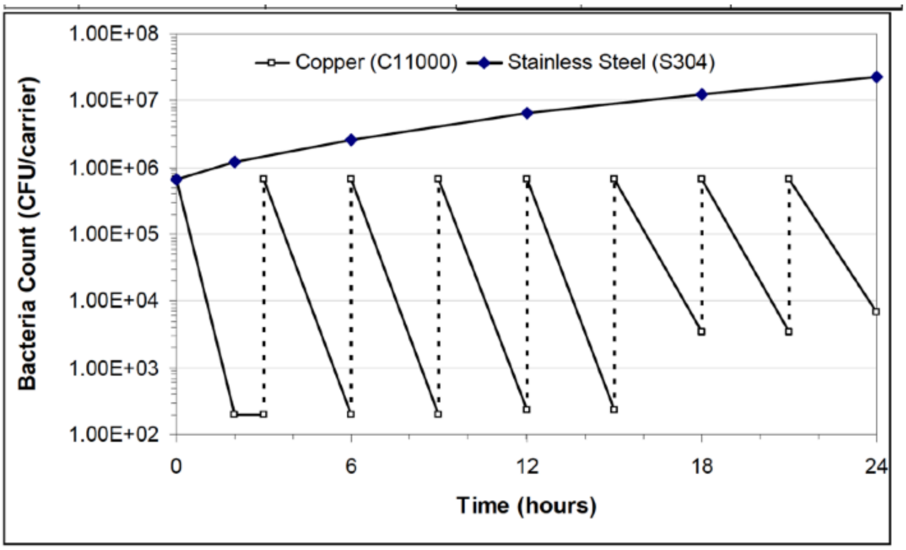
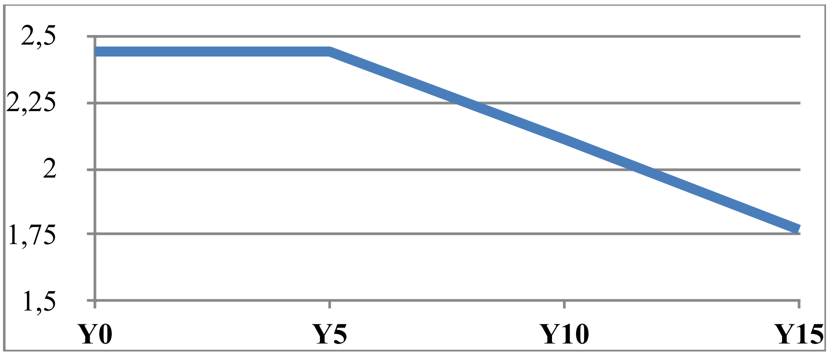


Figure 4. Continuous Reduction test results of MRSA on Copper

A recent measure was carried out in the Fonderephar laboratory in Toulouse on plastic surfaces (ABS). The test was designed following the method of NF S90-700 on Enterococcus Hirae and established a benchmark between: raw surface, surface coated with MetalSkin Medical, and surface coated with metalSkin Medical and aged. The ageing simulation was carried out in a laboratory by applying 100.000 contacts with a plastic pad that was moistured every morning with an acid solution (PH 5) to simulate the action of the human sweat. This protocol simulates a 15 year period of time. The results are as follow

	Killing Rate in 1 h
Uncoated ABS Surface	0
MetalSkin Coated Surface	- 2,44
MetalSkin Coated + Aged Surface	- 1,77

Tests in MetalSkin Laboratories have shown that the bactericidal efficiency sees no decrease within 5 years. Therefore the evolution of the killing rate (in log) of MetalSkin could be modeled as follows:



Copper efficacy, in situ studies:

Casey et al. (21) compared microbial counts between copper-containing and non-copper-containing items in a cross-over study conducted in an acute medical ward. After 5 weeks, the copper-containing and non-copper-containing items were switched (once-weekly sampling at 07:00 and 17:00). Median numbers of microorganisms harbored by the copper-containing items were 50 to 100% lower than their control equivalents at both 07:00 and 17:00, and these differences were statistically significant except for one item.

The cross-over study of Karpanen et al. (22) sampled 14 items in 19 rooms of an acute care medical ward. The study lasted 24 weeks with 12 weeks using the copper items and 12 weeks without. The authors found that 8 of the 14 copper items had significantly lower microbial counts than their non-copper counterparts. The other six copper items had reduced microbial counts compared to non-copper equivalents but the reduction did not reach statistical significance.

The cross over study of JP Daurès, MG Leroy et al. sampled 7 items in 6 rooms of a orthopedic surgery ward. The study lasted 8 weeks with 3 rooms equipped with MetalSkin items and 3 rooms without. The authors concluded that there are significantly less bacterias in rooms equipped with coated items, especially on internal door handle, external door handle (poorly significant), light switch, bedside trail (extremely significant), shower grab rail and tap handle.
Considering its lower cost […], the authors believe that this new product can confer a true benefit in reducing bacterial contamination and transmission in the acute care setting.
The analysis of the microbial counts over time in the 6 rooms led to suggest that the MetalSkin Medical® copper composite, by reducing the number of microorganisms in the treated rooms, could also reduce contamination in untreated rooms through a halo effect.

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About this report :
This document is intended to provide the up to date visibility on copper antimicrobial properties as of April 2020.

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Metalskin data in vitro test: AQMC Laboratories and FONDEREPHAR Laboratories