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PUBLICATION PORTFOLIO

Biocidal Effects of Copper Products

Reference	Conclusion	Link
Borkow, G., and Gabbay, J. (2005) **Copper as a biocidal tool.** Current Medicinal Chemistry. 12(18): 2163-2175.	Copper displays potent anti-bacterial, anti-fungal and anti-viral activities. The biocidal mechanism includes denaturation of nucleic acids; alteration of proteins; plasma membrane permeabilization; and membrane lipid peroxidation. Today copper is used as a water purifier, algaecide, fungicide, nematocide, molluscicide, and as an anti-bacterial and anti-fouling agent.	http://www.bentham-direct.org/pages/content.php?CMC/2005/00000012/00000018/0005C.SGM
Borkow, G., and Gabbay, J. (2004) **Putting copper into action: copper impregnated products with potent biocidal activities.** *FASEB Journal.* 18: 1728-1730.	A platform technology was developed that binds copper-oxide to textile fibres from which woven and non-woven fabrics can be produced. Copper may be integrated into latex and other polymers during manufacture. These products possess broad-spectrum anti-microbial properties. This technology, for example, enables the production of anti-viral gloves and filters, anti-bacterial self-sterilizing fabrics, anti-fungal socks, and anti-dust mite mattress-covers. No skin sensitization or irritation is observed in animal studies.	http://www.fasebj.org/cgi/reprint/04-2029fjev1
Zatcoff, R.C. **HealthStrides™ Socks—Footwear to a Higher Standard.** Podiatry Management, November/December 2005, pages 202-203.	A study with 56 patients demonstrate statistical improvement or resolution of several attributes related to athlete's foot by the sole use of socks containing copper-oxide impregnated fibers.	http://www.cupron.com/Articles/healthstrides.pdf
Borkow, G., Sidwell, R.W., Smee, D.F., Barnard, D.L., Morrey, J.D., Lara-Villegas, H.H., Shemer-Avni, Y., and Gabbay, J. (2007) **Neutralizing viruses by copper oxide based filters.** Antimicrobial Agents and Chemotherapy, 51(7): 2605-2607.	Copper oxide-containing filters reduce infectious titers of a wide panel of viruses (including enveloped; non-enveloped; RNA and DNA viruses). This work suggests the possibility of using copper oxide-containing devices to deactivate a wide spectrum of infectious viruses found in filterable suspensions.	http://aac.asm.org/cgi/content/full/51/7/2605?view=long&pmid=17470650
Borkow, G., Gabbay, J. and	Copper plays a key role in wound healing. We hypothesized that	http://linkinghub.elsevier.com/retrieve/pii/S0306-

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Zatcoff, R. (2007) **Could chronic wounds not heal due to too low local copper levels?** Medical Hypotheses, 70(3): 610-613	in individuals with compromised circulation to the wound site, part of the incapacity of the wounds to heal is due to low local copper levels. Wound dressings with copper would i) reduce the risk of contamination; and ii) stimulate faster wound repair directly.	9877(07)00412-4
Borkow, G., Gabbay, J. (2007) **Biocidal textiles can help fight nosocomial infections.** Medical Hypotheses, 70, 990–994.	Contaminated textiles in hospitals are an important source of microbes contributing to nosocomial infections. The use of antimicrobial textiles, especially in those textiles that are in close contact with the patients, may significantly reduce bioburden in clinical settings and consequently reduce the risk of nosocomial infections.	http://linkinghub.elsevier.com/retrieve/pii/S0306-9877(07)00568-3
Mumcuoglu, K.Y., Gabbay, J., and Borkow, G. (2008) **Copper oxide impregnated fabrics for the control of house dust mites.** International Journal of Pest Management. 54(3), 235- 240.	The acaricidal efficacy of copper-oxide containing fabrics on the common house dust mite, *Dermatophagoides farinae* is demonstrated in this manuscript. The acaricidal effect is via direct toxicity to the mites. The usage of fabrics containing copper oxide may thus be an important avenue for killing the house dust mite and reducing the load of dust mite allergens.	http://www.ingentaconnect.com/content/tandf/ttpm/2008/00000054/00000003/art00006
Borkow, G., Lara, H.H., Covington, C.Y., Nyamathi, A., and Gabbay, J. (2008) **Deactivation of HIV-1 in Medium by Copper-Oxide Containing Filters.** Antimicrobial Agents and Chemotherapy. 52(2):518-525.	Filtration of HIV-1 through filters containing copper-impregnated fibers resulted in viral deactivation of all 12 wild-type or drug-resistant laboratory or clinical, M- or T-tropic, clades A, B, or C, HIV-1 isolates tested. Viral inactivation was not strain specific. Thus, a novel means to inactivate HIV-1 in medium has been developed.	http://aac.asm.org/cgi/content/full/52/2/518?view=long&pmid=18070974
Zatcoff, R.C., Smith, M.S., and Borkow, G. (2008) **Treatment of tinea pedis with socks containing copper impregnated fibers.** The Foot. 18:136-41	Tinea pedis, known as Athlete's foot, is a common fungal infection of the feet. The effectiveness in using copper oxide impregnated socks in treating the common manifestations of tinea pedis, is demonstrated in the clinical study described in this manuscript.	http://linkinghub.elsevier.com/retrieve/pii/S095825920800028X

Manufacturing

Reference	Conclusion	Link
Borkow, G., and Gabbay, J. (2006) **Endowing textiles**	Bactericidal and anti-fungal activities of fabrics containing copper-oxide treated fibres are demonstrated also after 50 industrial washes and use,	http://www.cupron.com/Articles/Journal_of_Textile_and_Apparel,_Technology_

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with permanent potent biocidal properties by impregnating them with copper oxide. Journal of Textile & Apparel, Technology & Management.	indicating that the biocidal properties of the copper-oxide containing fibers are retained for the life of the products.	and_Management.pdf
Gabbay, J., Mishal, J., Magen, E., Zatcoff, R., Shemer-Avni, Y., and Borkow, G. (2006) **Copper oxide impregnated textiles with potent biocidal activities.** Journal of Industrial Textiles. 35(4):323-335.	Two durable platform technologies enabling the mass production of woven and non-woven fabrics, without the need of altering any industrial procedures or machinery, are detailed. Additionally, data showing i) that anti-fungal socks containing copper impregnated fibers alleviate athlete's foot; ii) antimicrobial fabrics (sheets) containing copper impregnated fibers decrease bacterial colonization in a clinical setting, and iii) these fabrics do not cause any adverse reactions in volunteers, is given.	http://jit.sagepub.com/cgi/content/abstract/35/4/323

NON-CUPRON PUBLICATIONS SUPPORTING TECHNOLOGY

Anti Microbial Effects of Copper Products

Reference	Conclusion / Abstract	Link
Sagripanti, J. L. (1992) **Metal-based formulations with high microbicidal activity.** *Appl.Environ.Microbiol* 58:3157-3162.	Abstract: Substances were evaluated for their relative potencies in inactivating Junin virus, Escherichia coli, and spores of Bacillus subtilis. Under the conditions of our test, glutaraldehyde was the most efficient agent among all substances currently recommended for disinfecting and sterilizing medical devices. Either copper or iron ions by themselves were able to inactivate virus with an efficiency similar to that of substances currently used for disinfection and sterilization…	http://aem.asm.org/cgi/reprint/58/9/3157?view=long&pmid=1332611
Faundez, G., M. Troncoso, P. Navarrete, and G. Figueroa. (2004) **Antimicrobial activity of copper surfaces against suspensions of Salmonella enterica and Campylobacter jejuni.** *BMC.Microbiol* 4:19-25.	CONCLUSIONS: Results [of this study] shows that metallic copper surfaces have an antibacterial activity against S. enterica and C. jejuni and suggest its potential application as an inhibitory agent in the various stages of the food processing operations.	http://www.biomedcentral.com/1471-2180/4/19

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Cioffi, N., N. Ditaranto, L. Torsi, R. A. Picca, E. De Giglio, L. Sabbatini, L. Novello, G. Tantillo, T. Bleve-Zacheo, and P. G. Zambonin. (2005) **Synthesis, analytical characterization and bioactivity of Ag and Cu nanoparticles embedded in poly-vinyl-methyl-ketone films.** *Anal.Bioanal.Chem.* 382:1912-1918.	Abstract: The electrosynthesis of copper and silver core-shell nanoparticles (NPs) by the sacrificial anode technique, employing tetraoctylammonium (TOA) salts as base electrolyte for the first time, is described…..On the basis of these stability and bioactivity results, it is clear that Cu-NPs and Ag-NPs are suitable for application in disinfecting or antifouling paint and coating formulations	http://www.springerlink.com/content/q61l12w114848834/
Hofer, D. (2006) **Antimicrobial textiles, skin-borne flora and odour.** *Curr.Probl.Dermatol.* 33:67-77.	Abstract: Along with climate and physical activity, textiles have an effect on sweating and the development of odours. Accordingly, textiles inadequately optimized in terms of clothing technology as a result of poorly cut structures or poor materials result in increased sweating and odour. However, the development of body odour itself cannot be avoided, even with optimally designed clothing. Therefore new textiles, 'treated with antimicrobial agents', have been developed, with the aim of reducing odour by decreasing the number of germs on the skin. From the scientific point of view, the interactions between textiles, sweat, skin and skin flora are extremely complex. For this reason, this article explains in more detail the basic principles of odour formation resulting from sweat and how this can be influenced by textiles treated with antimicrobial agents.	http://www.ncbi.nlm.nih.gov/pubmed/16766882
http://www.copper.org:80/about/pressreleases/2008/pr2008_March_25.html	The U.S. Environmental Protection Agency (EPA) has approved the registration of antimicrobial copper alloys, with public health claims. These public health claims acknowledge that copper, brass and bronze are capable of killing harmful, potentially deadly bacteria. Copper is the first solid surface material to receive this type of EPA registration, which is supported by extensive antimicrobial efficacy testing. Cupron has received an official permit to sale copper oxide impregnated fibers.	http://www.copper.org:80/about/pressreleases/2008/pr2008_March_25.html
Noyce JO, Michels H, Keevil CW. (2006) **Potential use of copper surfaces to reduce survival of epidemic meticillin-resistant Staphylococcus aureus in the healthcare environment.** J Hosp Infect.63:289-97.	The results of this study demonstrate a potent antimicrobial effect of copper surfaces against MRSA in contrast to the widely used stainless steel, supporting the notion of using copper surfaces in hospital settings for reducing microbial contamination and nosocomial infections.	http://linkinghub.elsevier.com/retrieve/pii/S0195-6701(06)00037-5

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Noyce JO, Michels H, Keevil CW. (2007) **Inactivation of influenza A virus on copper versus stainless steel surfaces.** Appl Environ Microbiol. 73:2748-50.	This study demonstrates the capacity of copper surfaces to effectively reduce infectious titers of Influenza A, as opposed to stainless steel, supporting the notion of using copper surfaces in hospital settings for reducing the risk of viral infections.	http://aem.asm.org/cgi/content/full/73/8/2748?view=long&pmid=17259354
Weaver L, Michels HT, Keevil CW. (2008) **Survival of Clostridium difficile on copper and steel: futuristic options for hospital hygiene.** J Hosp Infect. Feb;68(2):145-51.	*Clostridium difficile* is rapidly becoming a major cause of hospital-acquired infections worldwide, due in part to transmission of the faecal pathogen between contaminated hands and contact surfaces. All *Clostridium* spores were killed by the copper surfaces within 24-48hr, while no significant death rate was observed on stainless steel even after 168 h. This study further supports using copper surfaces in hospital settings for reducing the risk of nosocomial infections.	http://linkinghub.elsevier.com/retrieve/pii/S0195-6701(07)00417-3
Mehtar S, Wiid I, Todorov SD. (2008) **The antimicrobial activity of copper and copper alloys against nosocomial pathogens and Mycobacterium tuberculosis isolated from healthcare facilities in the Western Cape: an in-vitro study.** J Hosp Infect. Jan;68(1):45-51.	Clinical isolates of meticillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Acinetobacter baumannii, Candida albicans* and *Mycobacterium tuberculosis* (MTB) were all killed by copper containing alloys. In contrast, stainless steel and polyvinylchloride (PVC) surfaces showed poor antibacterial activity.	http://linkinghub.elsevier.com/retrieve/pii/S0195-6701(07)00374-X
Noyce JO, Michels H, Keevil CW. (2006) **Use of copper cast alloys to control Escherichia coli O157 cross-contamination during food processing.** Appl Environ Microbiol. 72(6):4239-44.	As opposed to stainless steel, this study demonstrates potent kill of *Escherichia coli*, one of the most notable microbes that contaminates food products, by copper.	http://aem.asm.org/cgi/content/full/72/6/4239?view=long&pmid=16751537
E.A. Abou Neela, I. Ahmeda, J. Prattenb, S.N. Nazhata, J.C. Knowles. (2005) **Characterisation of antibacterial copper releasing degradable phosphate glass fibres.** Biomaterials 26: 2247–2254.	The effect of the diameters of two glass fibres containing copper oxide on short-term (3 h) killing against *Staphylococcus epidermidis* were investigated. The kill rate was related to their rate of degradation in deionised water, as well as copper ion release measured using ion chromatography.	http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TWB-4DCMHGN-2&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_version=1&_urlVersion=0&_userid=10&md5=ddeba31c82b7b726324b3bdd0c30edb7

C. Espı´rito Santo,N. Taudte, D.H. Nies, and G. Grass. (2008) **Contribution of Copper Ion Resistance to Survival of *Escherichia coli* on Metallic Copper Surfaces.** Applied and Environmental Microbiology, 74: 977–986.	Data presented in this study suggest that bacteria are killed rapidly on dry copper surfaces. Several factors, such as copper ion toxicity, copper chelators, cold, osmotic stress, and reactive oxygen species, but not anaerobiosis, influenced killing rates.	http://aem.asm.org/cgi/content/abstract/AEM.01938-07v1
J. J. Harrison, R.J. Turner, D.A. Joo, M.A. Stan, C.S. Chan, N. Allan, H.A. Vrionis, M.E. Olson, and H. Ceri. (2008) **Copper and Quaternary Ammonium Cations Exert Synergistic Bactericidal and Antibiofilm Activity against *Pseudomonas aeruginosa*.** Antimicrobial Agents and Chemotherapy, 52: 2870–2881	By using a high-throughput method for testing combinations of antimicrobials for synergistic activity against biofilms, it was identified that Cu^{2+} works synergistically with quaternary ammonium compounds (QACs) to kill *Pseudomonas aeruginosa* biofilms, a microorganisms involved in nosocomial infections. In some cases, adding Cu^{2+} to QACs resulted in a 128-fold decrease in the biofilm minimum bactericidal concentration compared to that for single-agent treatments. In combination, these agents retained broad-spectrum antimicrobial activity that also eradicated biofilms of *Escherichia coli*, *Staphylococcus aureus*, *Salmonella enterica* serovar Cholerasuis, and *Pseudomonas fluorescens*. To investigate the mechanism of action, isothermal titration calorimetry was used to show that Cu2_ and QACs do not interact in aqueous solutions, suggesting that each agent exerts microbiological toxicity through independent biochemical routes. Additionally, Cu^{2+} and QACs, both alone and in combination, reduced the activity of nitrate reductases, which are enzymes that are important for normal biofilm growth. Collectively, the results of this study indicate that Cu2_ and QACs are effective combinations of antimicrobials that may be used to kill bacterial biofilms.	http://aac.asm.org/cgi/content/abstract/52/8/2870?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fulltext=%C2%B5g&searchid=1&FIRSTINDEX=1220&resourcetype=HWFIG
Salam A. Ibrahim a,*, Hong Yang b, Chung W. Seo. (2008) **Antimicrobial activity of lactic acid and copper on growth of Salmonella and Escherichia coli O157:H7 in laboratory medium and carrot juice.** Food Chemistry 109: 137–143.	The effect on the survival and growth of 38 Salmonella spp. and six E. coli O157:H7 strains were of either lactic acid (0.2%) alone, copper sulfate (50 ppm) alone or the combination of the two was studied. The growth inhibition was negligible when copper sulfate was added alone. Lactic acid (0.2%) retarded the growth of bacterial strains. However, the growth of bacterial strains was significantly inhibited when both lactic acid and copper were combined.	http://74.125.45.104/search?q=cache:WDCxh2Rm39YJ:www.aseanfood.info/scripts/count_article.asp%3FArticle_code%3D11023135+Antimicrobial+activity+of+lactic+acid+and+copper+on+growth+of+Salmonella+and+Escherichia+coli+O157:H7+in+laboratory+medium+and+carrot+juice&hl=en&ct=clnk&cd=1&gl=us

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M. Horie, H. Ogawa, Y. Yoshida, K. Yamada, A. Hara, K. Ozawa, S. Matsuda, C. Mizota, M. Tani, Y. Yamamoto, M. Yamada, K. Nakamura and K. Imai. (2008) **Inactivation and morphological changes of avian influenza virus by copper ions.** Arch Virol 153:1467–1472.	The infectivity of the H9N2 virus to MDCK cells was time-dependently inhibited by Cu^{2+} at concentrations of 2.5–250 μM. In 25 μM Cu^{2+} solution, the virus titer decreased by approximately 3 and 4 log within 3 and 6 h, respectively. Compared to Cu^{2+}, Zn2+ was much less effective in virus inactivation.	http://www.springerlink.com/content/3234874542k7075x/
Nan L, Liu Y, Lü M, Yang K. (2008) **Study on Antibacterial Mechanism of Copper-bearing Austenitic Antibacterial Stainless Steel by Atomic Force Microscopy** J Mater Sci Mater Med. 19(9):3057-62.	The antibacterial mechanism of copper-bearing austenitic antibacterial stainless steel by a series of methods such as atomic force microscopy (AFM) observation, force-distance curves and inductively coupled plasma mass spectrometer test were investigated. It was observed by AFM that the structure of the outer cell membrane responsible for the cell permeability was substantially changed for the bacteria after contacting with the antibacterial stainless steel, showing that cell walls were seriously damaged and a lot of contents in the cells leaked. It was also found that the adhesion force of bacteria to antibacterial stainless steel was considerably greater than that to the contrast steel, indicating that the electrostatic forces by Cu^{2+} being an important factor for killing bacteria.	http://www.springerlink.com/content/771h15n33676t285/
Gant VA, Wren MW, Rollins MS, Jeanes A, Hickok SS, and Hall TJ. (2007) **Three novel highly charged copper-based biocides: safety and efficacy against healthcare-associated organisms.** Journal of Antimicrobial Chemotherapy 60, 294–299.	Three copper-based inorganic formulations were tested for their activity against clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA), Legionella pneumophila, Acinetobacter calcoaceticus/baumannii (ACCB), glycopeptide-resistant Enterococcus and spores of Clostridium difficile in time-kill assays; for their ability to decontaminate ultramicrofibre (UMF) cloths; and (iii) for their cytotoxicity to human skin and intestinal epithelial cells. All three copper-based formulations were potently biocidal down to concentrations of 1 ppm for both stationary- and log-phase organisms, and they were all active against C. difficile spores. At 150 ppm, they achieved a complete (>6 log10) kill of MRSA and ACCB mostly within 1 h. This biocidal activity was not achieved by copper sulphate or the inorganic binders used in the formulations. All three copper-based formulations completely decontaminated UMF cloths containing MRSA, ACCB or C. difficile spores. All three copper-based formulations and copper sulphate were not cytotoxic to human epithelial cells up to concentrations of 100-200 ppm.	http://jac.oxfordjournals.org/cgi/content/abstract/dkm201v1

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H.M. Yates, L.A. Brook, I.B. Ditta, P. Evansa, H.A. Foster, D.W. Sheel, and A. Steele. (2008) **Photo-induced self-cleaning and biocidal behaviour of titania and copper oxide multilayers**. Journal of Photochemistry and Photobiology A: Chemistry 197: 197–205.	This paper describes the deposition of films of titania and copper oxide by atmospheric pressure chemical vapour deposition (CVD). The films were investigated as part of multilayer systems to assess their potential to offer the dual functionality of self-cleaning and biocidal films. The multilayer systems were achieved by deposition of copper oxide with subsequent titanium dioxide deposition and vice versa. It is shown that by careful choice of the experimental growth conditions, multilayers can be formed with both biocidal and 'self-clean' functionality under UV photo-induced conditions.	http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TGY-4RHFVG2-3&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=fafa279b8f2e3378a875762c3b50c3c7

Copper Safety

Reference	Conclusion / Abstract	Link
Hostynek, J. J. and H. I. Maibach. (2003) **Copper hypersensitivity: dermatologic aspects--an overview**. *Rev.Environ.Health* 18:153-183.	Abstract: Reports of immune hypersensitivity reactions of both the immediate and the delayed type following cutaneous or systemic exposure to copper are reviewed here in an endeavor to draw a comprehensive profile of the immunogenic potential of that metal and its compounds... ...considering the widespread use of copper intrauterine devices (IUDs) and the importance of copper in coinage, items of personal adornment and industry, unambiguous reports of sensitization to the metal are extremely rare, and even fewer are the cases that appear clinically relevant. Most reports of immune reactions to copper describe systemic exposure as a cause--predominantly to intrauterine devices and to prosthetic materials in dentistry--implicitly excluding the induction of hypersensitivity from contact with the skin as a risk factor	http://www.ncbi.nlm.nih.gov/pubmed/14672513
Cheng D. (2000) **The intrauterine device: still misunderstood after all these years.** South Med J. 93(9):859-64.	The copper intrauterine device (IUD) is one of the most effective, safe, and economic methods of contraception today. It is used by more women worldwide than any other reversible method of birth control.	http://www.ncbi.nlm.nih.gov/pubmed/11005342
Bilian X. (2002) **Intrauterine devices.** Best Pract Res Clin Obstet Gynaecol. Apr;16(2):155-68.	Copper IUD are efficacious for even 10 years of usage without significant adverse effects.	http://www.ncbi.nlm.nih.gov/pubmed/12041959

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Microbial Resistance to Silver

Reference	Conclusion / Abstract	Link
Silvestry-Rodriguez, N., E. E. Sicairos-Ruelas, C. P. Gerba, and K. R. Bright. (2007) **Silver as a disinfectant.** *Rev.Environ.Contam Toxicol.* 191:23-45.	Abstract: Silver has been used as an antimicrobial for thousands of years. Over the past several decades, it has been introduced into numerous new venues such as in the treatment of water, in dietary supplements, in medical applications, and to produce antimicrobial coatings and products…Many mechanisms of the antibacterial effect of silver have been described, but its antiviral and antiprotozoal mechanisms are not well understood. Both microbial tolerance and resistance to silver have been reported; however, the effect of silver has been observed against a wide variety of microorganisms over a period of years. Further research is needed to determine the antimicrobial efficacy of silver in these new applications and the effects of its long-term usage	http://www.springerlink.com/content/tg6315643164271t/
Silver, S., l. T. Phung, and G. Silver. (2006). **Silver as biocides in burn and wound dressings and bacterial resistance to silver compounds.** *J.Ind.Microbiol.Biotechnol.* 33:627-634.	Abstract: Silver products have been used for thousands of years for their beneficial effects, often for hygiene and in more recent years as antimicrobials on wounds from burns, trauma, and diabetic ulcers. Silver sulfadiazine creams (Silvazine and Flamazine) are topical ointments that are marketed globally. In recent years, a range of wound dressings with slow-release Ag compounds have been introduced, including Acticoat, Actisorb Silver, Silverlon, and others. While these are generally accepted as useful for control of bacterial infections (and also against fungi and viruses), key issues remain, including importantly the relative efficacy of different silver products for wound and burn uses and the existence of microbes that are resistant to Ag+. These are beneficial products needing further study, although each has drawbacks. The genes (and proteins) involved in bacterial resistance to Ag have been defined and studied in recent years	http://www.springerlink.com/content/e66l0g6125655482/

Cosmetic Effects

Reference	Conclusion / Abstract	Link
http://www.smartskincare.com/treatments/topical/copper.html	Copper and cosmetic effects.	http://www.smartskincare.com/treatments/topical/copper.html

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Ahmed, Z., B. D. Idowu, and R. A. Brown. (1999). **Stabilization of fibronectin mats with micromolar concentrations of copper.** *Biomaterials* 20:201-209.	Abstract: …The aim of this study was to examine means of increasing the stability of Fn-mats using a novel treatment with micromolar concentrations of copper ions which may be used to improve wound healing/nerve repair. Cytotoxicity of incorporated copper was determined using rat Schwann cells, rat tendon fibroblasts and human dermal fibroblasts. Dissolution of protein from the Fn-mat showed that treatment with the lowest concentration of copper used (1 microM) increased the stability of mats by 3-4 times at room temperature relative to control mats and twofold at 37 degrees C. Copper mediated increase in stability was dose dependent. Orientation of the Fn-fibres (within mats), monitored by scanning electron microscopy was retained with 1 microM copper but disappeared with higher concentrations. Schwann cells grew in culture with mats stabilized by 1 microM copper treatment without reduction in cell number but growth was inhibited at 10-200 microM Cu. All types of fibroblasts were unaffected by copper treatment upto 200 microM. Fn-mats can be successfully stabilized by this technique producing longer survival in vitro. The differential effects of copper on these cell types suggests that CuFn-mats may be used to select the type of cells which colonize these materials	http://www.ncbi.nlm.nih.gov/pubmed/10030596

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Simeon, A., F. Monier, H. Emonard, P. Gillery, P. Birembaut, W. Hornebeck, and F. X. Maquart. (1999) **Expression and activation of matrix metalloproteinases in wounds: modulation by the tripeptide-copper complex glycyl-L-histidyl-L-lysine-Cu2+.** *J Invest Dermatol.* 112:957-964.	Abstract: We investigated the expression and activation of matrix metalloproteinases in a model of experimental wounds in rats, and their modulation by glycyl-L-histidyl-L-lysine-Cu(II), a potent activator of wound repair. Wound chambers were inserted under the skin of Sprague-Dawley rats and received serial injections of either 2 mg glycyl-L-histidyl-L-lysine-Cu(II) or the same volume of saline. The wound fluid and the neosynthetized connective tissue deposited in the chambers were collected and analyzed for matrix metalloproteinase expression and/or activity. Interstitial collagenase increased progressively in the wound fluid throughout the experiment. Glycyl-L-histidyl-L-lysine-Cu(II) treatment did not alter its activity. Matrix metalloproteinase-9 (gelatinase B) and matrix metalloproteinase-2 (gelatinase A) were the two main gelatinolytic activities expressed during the healing process. Pro-matrix metalloproteinase (pro-form of matrix metalloproteinase)-9 was strongly expressed during the early stages of wound healing (day 3). In the wound fluid, it decreased rapidly and disappeared after day 18, whereas in the wound tissue, matrix metalloproteinase-9 expression persisted in the glycyl-L-histidyl-L-lysine-Cu(II) injected chamber until day 22. Pro-matrix metalloproteinase-2 was expressed at low levels at the beginning of the healing process, increased progressively until day 7, then decreased until day 18. Activated matrix metalloproteinase-2 was present in wound fluid and wound tissue. It increased until day 12, then decreased progressively. Glycyl-L-histidyl-L-lysine-Cu(II) injections increased pro-matrix metalloproteinase-2 and activated matrix metalloproteinase-2 during the later stages of healing (days 18 and/or 22). These results demonstrate that various types of matrix metalloproteinases are selectively expressed or activated at the various periods of wound healing. Glycyl-L-histidyl-L-lysine-Cu(II) is able to modulate their expression and might significantly alter wound remodeling	http://www.nature.com/jid/journal/v112/n6/abs/5603188a.html

Maquart, F. X., G. Bellon, B. Chaqour, J. Wegrowski, L. M. Patt, R. E. Trachy, J. C. Monboisse, F. Chastang, P. Birembaut, P. Gillery, and . (1993) **In vivo stimulation of connective tissue accumulation by the tripeptide-copper complex glycyl-L-histidyl-L-lysine-Cu2+ in rat experimental wounds.** *J Clin Invest* 92:2368-2376.	Abstract: The tripeptide-copper complex glycyl-L-histidyl-L-lysine-Cu2+ (GHK-Cu) was first described as a growth factor for differentiated cells. Recent in vitro data showed that it possesses several properties of a potential activator of wound repair. We investigated the effects of GHK-Cu in vivo, using the wound chamber model described previously (Schilling, J.A., W. Joel, and M.T. Shurley, 1959. Surgery [St. Louis]. 46:702-710). Stainless steel wire mesh cylinders were implanted subcutaneously on the back of rats. The animals were divided into groups that received sequential injections into the wound chamber of either saline (control group) or various concentrations of GHK-Cu. At the end of the experiments, rats were killed, wound chambers were collected, and their content was analyzed for dry weight, total proteins, collagen, DNA, elastin, glycosaminoglycans, and specific mRNAs for collagens and TGF beta. In the GHK-Cu-injected wound chambers, a concentration-dependent increase of dry weight, DNA, total protein, collagen, and glycosaminoglycan contents was found. The stimulation of collagen synthesis was twice that of noncollagen proteins. Type I and type III collagen mRNAs were increased but not TGF beta mRNAs. An increase of the relative amount of dermatan sulfate was also found. A control tripeptide, L-glutamyl-L-histidyl-L-proline, had no significant effect. These results demonstrate that GHK-Cu is able to increase extracellular matrix accumulation in wounds in vivo	http://www.jci.org/articles/view/116842
Raju, K. S., G. Alessandri, M. Ziche, and P. M. Gullino. (1982) **Ceruloplasmin, copper ions, and angiogenesis.** *J Natl.Cancer Inst.* 69:1183-1188.	Abstract: The ability to induce new formation of capillaries in the cornea was tested for ceruloplasmin, the copper carrier of serum, for fragments of the ceruloplasmin molecule with and without copper, for heparin, and for glycyl-L-histidyl-L-lysine, bound or not bound to copper ions. Male or female 2- to 3-kg New Zealand White rabbits were used. These experiments were prompted by the previous observation of copper accumulation in the cornea during angiogenesis and by the inability of copper-deficient rabbits to mount an angiogenic response. The results showed that the three different molecules were all able to induce angiogenesis provided that they were bound to copper. Fragments of the ceruloplasmin molecule also induced angiogenesis but only when copper was bound to the peptides. The data are interpreted to indicate that copper ions are involved in the sequence of events leading to angiogenesis and that the carrier molecules may be of quite a different nature	http://www.ncbi.nlm.nih.gov/pubmed/6182332

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Essential element for Human Body

Reference	Conclusion / Abstract	Link
Tapiero, H., D. M. Townsend, and K. D. Tew. (2003) **Trace elements in human physiology and pathology. Copper.** *Biomed.Pharmacother.* 57:386-398.	Abstract: Copper is a trace element, important for the function of many cellular enzymes. Copper ions can adopt distinct redox states oxidized Cu(II) or reduced (I), allowing the metal to play a pivotal role in cell physiology as a catalytic cofactor in the redox chemistry of enzymes, mitochondrial respiration, iron absorption, free radical scavenging and elastin cross-linking…	http://www.ncbi.nlm.nih.gov/pubmed/14652164
Olivares, M. and R. Uauy. (1996) **Copper as an essential nutrient**. *Am.J Clin.Nutr.* 63:791S-796S.	Abstract: Animal and human studies have shown that copper is involved in the function of several enzymes. Studies have also shown that copper is required for infant growth, host defense mechanisms, bone strength, red and white cell maturation, iron transport, cholesterol and glucose metabolism, myocardial contractility, and brain development. Copper deficiency can result in the expression of an inherited defect such as Menkes syndrome or in an acquired condition….	http://www.ncbi.nlm.nih.gov/pubmed/8615366
Uauy, R., M. Olivares, and M. Gonzalez. (1998) **Essentiality of copper in humans**. *Am.J Clin.Nutr.* 67:952S-959S.	Abstract: The biochemical basis for the essentiality of copper, the adequacy of the dietary copper supply, factors that condition deficiency, and the special conditions of copper nutriture in early infancy are reviewed. New biochemical and crystallographic evidence define copper as being necessary for structural and catalytic properties of cuproenzymes…	http://www.ajcn.org/cgi/reprint/67/5/952S
Barceloux, D. G. (1999) **Copper.** *J.Toxicol.Clin.Toxicol.* 37:217-230.	Abstract: Copper is an essential trace element, which is an important catalyst for heme synthesis and iron absorption. Following zinc and iron, copper is the third most abundant trace element in the body…..The average daily intake of copper in the US is about 1 mg Cu with the primary source being the diet. The bioavailability of copper from the diet is about 65-70% depending on a variety of factors including chemical form, interaction with other metals, and dietary components... Chronic copper toxicity is rare and primarily affects the liver.	http://www.ncbi.nlm.nih.gov/pubmed/10382557

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Environmental or Adverse Effects

Reference	Conclusion / Abstract	Link
Weir, F. W. (1979) **Health hazard from occupational exposure to metallic copper and silver dust**. *Am.Ind.Hyg.Assoc.J.* 40:245-247.	Abstract: This review of the toxicity and occupational hazard from exposure to metallic copper and silver dust was undertaken to examine the bases for the current standards and to suggest an alternative approach to controlling potential occupational hazard in conditions where exposures are limited to the prime metals. There are no data to suggest that exposure to silver or copper metal dust has produced remarkable disease in man. Further, there is no reason to consider the dust from either of these metals to be anything but nuisance particulate as defined by the ACGIH. They should, therefore, be regulated as such at the recommended level of 10 mg/m3	http://www.ncbi.nlm.nih.gov/pubmed/495463
http://www.washingtonpost.com/wp-dyn/content/article/2006/11/22/AR2006112201979_2.html	Nanosilver and environment - EPA concerns of nanosilver effects on the environment.	http://www.washingtonpost.com/wp-dyn/content/article/2006/11/22/AR2006112201979_2.html
Toxicology Data	Based on the Toxicological Profile for Silver and Toxicological Profile for Copper reports written by the U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Agency for Toxic Substances and Disease Registry.	http://www.seagrant.umn.edu/water/report/chemicalsofconcern/copper/copper.pdf

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Chen, X. and H. J. Schluesener. (2008) **Nanosilver: a nanoproduct in medical application.** *Toxicol.Lett.* 176:1-12.	Abstract: Nanotechnology is a most promising field for generating new applications in medicine. However, only few nanoproducts are currently in use for medical purposes. A most prominent nanoproduct is nanosilver… At nanoscale, silver exhibits remarkably unusual physical, chemical and biological properties. Due to its strong antibacterial activity, nanosilver coatings are used on various textiles but as well as coatings on certain implants. Further, nanosilver is used for treatment of wounds and burns or as a contraceptive and marketed as a water disinfectant and room spray. Thus, use of nanosilver is becoming more and more widespread in medicine and related applications and due to increasing exposure toxicological and environmental issues need to be raised. In sharp contrast to the attention paid to new applications of nanosilver, few studies provide only scant insights into the interaction of nanosilver particle with the human body after entering via different portals. Biodistribution, organ accumulation, degradation, possible adverse effects and toxicity are only slowly recognized and this review is focusing on major questions associated with the increased medical use of nanosilver and related nanomaterials	http://www.ncbi.nlm.nih.gov/pubmed/18022772