



# Copper Nanoparticles and Antioxidant Stress: Problem Makers or Solvers?



**Michael AB Naafs\***

*Dutch Internist Endocrinologist, Netherlands*

**\*Corresponding author:** Michael AB Naafs, Dutch Internist Endocrinologist, Netherlands

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## Abstract

In this mini-review various aspects of copper nanoparticles are considered with a special emphasis on antioxidant stress. Copper nanoparticles may become a problem maker for the environment but seems a problem solver in wound dressings and potentially in diabetes and cancer. Long-term toxicity of copper nanoparticles is not known. An international registry agency should control the use of copper nanoparticles, especially in food nanotechnology.

## Introduction

The increased use of metal nanoparticles in the food chain is an increasing concern. Nanoparticles (NPs) are used in various areas, including medicine, electronics, cosmetics, oil lubricants and also in the food chain. The extensive use of these NPs allows them to be released into the environment either during production use or disposal. Phytotoxicity of copper NPs has already been reported [1]. Copper NPs are believed to cause oxidative stress by increasing the activity of oxidative stress enzymes as catalase, superoxide dismutase and glutathion-S-transferase [1,2]. Copper NPs cause in this way a dose dependent toxicity via inducing reactive oxygen species (ROS) and nitrous oxide (NO) [3]. Toxicity of copper NPs has been studied mainly in animals and is manifested as hepato- and renal toxicity, splenic toxicity, neurotoxicity, gene toxicity and carcinogenicity at LD 50 values of nano- copper (23.5nm) of 413mg/kg/body/weight [4]. Copper (Cu) is a redox active metal and an essential nutrient in all species. Deficits and excessive amounts can result in human disease and oxidative stress plays a major role in both circumstances. Copper deficiency can contribute to the development and progression of cardiovascular disease and diabetes [5]. Copper NPs showed antidiabetic and antioxidant properties [6]. In addition, copper NPs are used as antibacterial and antifungal agents [7]. So, are copper NPs problem makers or problem solvers? In this mini-review the various aspects of copper NPs will be discussed.

## Synthesis

Copper NPs are very attractive due to their high thermal conductivity and relatively low costs compared to e.g. gold and silver nanoparticles. They can be synthesized by physical, chemical and green techniques. Vacuum vapor deposition, pulsed laser ablation, pulsed wire discharge and mechanical wiring are physical

techniques. Chemical reduction, microemulsion techniques, sonochemical reduction, electrochemical, microwave assisted and hydrothermal are chemical approaches for the synthesis of copper nanoparticles [4,5,8]. Green synthesis of copper NPs is using different plants, bacteria and fungi [9,10].

## Characteristics

The properties of copper NPs depend largely on size, structure, shape, surface properties, particle aggregation, agglomeration and optical characteristics. Their catalytic activity increases with the decrease in size of copper NPs [11].

## Catalytic activity

Catalysts are substances that promote and accelerate chemical reactions without being consumed. Catalysis based on copper NPs may benefit for example the synthesis of methanol or the production of hydrogen on an industrial scale [11-13].

## Antibacterial/Antifungal action

It has been known for a long time that copper and copper alloys have antimicrobial properties [14]. Copper has two key properties that are exploited in consumer products and medical devices. Copper has potent biocidal properties and is critical for most tissues including the skin. In the skin, copper is involved in the synthesis and stabilization of extracellular matrix skin proteins and angiogenesis [14]. It is therefore not surprising these properties are leveraged of copper-oxide NPs impregnated wound dressings [14-17].

Copper has antimicrobial activities against Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, vancomycin-

resistant enterococci (VRE) and ESBL-producing species as well as adenoviruses, Influenza A and fungi [14,18].

### Cytotoxicity

Elevated copper levels result in the loss of membrane integrity, which causes essential nutrients, including potassium and glutamate to leak from cells and cause apoptosis [14]. Shafagh et al. [19] studied cytotoxicity and apoptosis of copper oxide NPs on a chronic myeloid leukemia (CML) K562 cell line. CuO NPs showed selectivity towards the K562 cell line and are potentially a good anti-cancer drug since it does not kill healthy cells. Apoptosis is mediated through reactive oxygen species (ROS) production in cancer cells, starting with P53 up-regulation [19]. Copper NPs also induced apoptosis in a human skin melanoma cell line [20]. Similar findings have been reported in a glial cancer cell line by Kukia et al. [21].

### Antioxidant activity

Copper oxide (CuO) NPs have higher toxic effects than Cu NPs due to its oxidative property. CuO NPs stimulate photosynthesis at low concentrations (<0.25mg/L) but suppression of photosynthesis was observed at 1mg/L concentration. CuO NPs have been shown to enhance the production of reactive oxygen species (ROS). At low copper concentrations these ROS' are protective in plants, but at high Cu concentrations they may be cytotoxic and lead to apoptosis, as mentioned before [4,22]. In addition, phytohormones were also observed to be altered as a response to CuO NPs [23]. Most studies of the antioxidant effects of Cu NPs have been done in animals [4]. The effect of antioxidant stress on cytochrome P450 and liver disease has been studied in rats and in cancer cell lines [24,25]. In humans, curcumin Cu NPs have been studied mostly for their potential anti-cancer activity [26,27]. Although curcumin has been strongly advocated as a natural antioxidant in vitro, in vivo and clinical studies are not able to provide evidence for a significant role in the prevention of cancer. Even with modern curcumin nano-formulations poor curcumin bioavailability could not be overcome [28].

### Metabolic disease

Nanotechnology has been used in diagnosing and monitoring of diabetes by sensor technology [29,30]. Ghosh et al. [6] suggested an antidiabetic effect of copper NPs by inhibiting the enzyme alpha-glucosidase. Javed et al. [31] believe that copper NPs can have hypoglycemic properties. Recently, it has been reported that patients with metabolic syndrome need more vitamin C to break the cycle of antioxidant depletion [32]. It is very well possible that the antidiabetic effects of copper NPs are achieved by restoring vitamin C mediated antioxidant depletion in the metabolic syndrome. Therefore, it is interesting to know that CU NPs can be prepared with ascorbic acid (vitamin C) by an aqueous solution reduction method [33]. It has also been known that vitamin C depletion lowers the uptake of copper [34].

### Conclusion

It is obvious that the widespread use of copper NPs in all kind of sectors can lead to large environmental problems. The

use of these NPs has not been regulated and toxicity is not known for the long term. Accumulation in the environment has clear toxic effects on plants when these NPs are used in pesticides and fertilizers. Detection of Cu NPs in the environment is extremely difficult [35] and therefore copper NPs could be problem makers in the long term. Long-term toxicity in humans is not known and an international registry agency covering the use of NPs and Cu NPs should be instituted therefore, especially for food nanotechnology [28]. On the other hand, the use of Cu NPs in wound dressing and diabetes sensor technology, as well as their antimicrobial spectrum are of proven benefit [14-18,30]. So, they are problem solvers, too. The anti-cancer activity still has a potential future in nanomedicine and has been explored not enough, yet. So, there has to be done still much more research in the ecological effects of NPs, in nanomedicine and especially in food nanotechnology.

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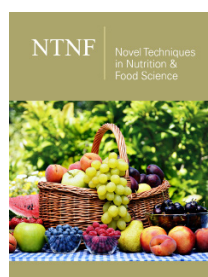
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