

Impact of Advanced Materials on Human Health: Dissolution Control of Copper Oxide Nanoparticles for Therapeutic Applications

Arianna Borgers¹, Karolia Edlund¹, Rosemarie Marchan¹, Suman Pokhrel², Christoph van Thriel¹

¹ Department of Toxicology, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany

² Department of Process Engineering, Leibniz Institute for Materials Engineering IWT, Bremen, Germany

Copper is an essential micronutrient that is required as a cofactor for numerous copper-containing enzymes and transcription factors and thereby contributes to several physiological processes. However, due to the toxic potential of copper, its homeostasis is tightly regulated through copper-binding importers, chaperones, and exporters ^[1]. Copper oxide nanoparticles (CuO NPs) are known to release Cu²⁺ ions. However, the excessive release of these ions can cause a series of downstream effects, ultimately leading to cell death ^[1,2]. Using a safe-by-design approach, Naatz et al. ^[2] prepared CuO NPs that were doped with different degrees of iron. Thereby, they were able to attenuate the dissolution of Cu²⁺ ions and reduce the cytotoxicity of the particles. Moreover, they achieved a selective targeting of cancer cells with the iron-doped NPs ^[3]. However, the exact mechanism behind these observations needs to be further elucidated. The goal of this project is to further investigate the responses of relevant cell types to the different, iron doped CuO NPs and to study how they are absorbed, distributed, metabolized, and eliminated in human cells. The cytotoxicity of the NPs will be studied *in vitro* using a range of human (cancer) cell lines. Using Raman-Spectroscopy, the uptake and distribution will be investigated. To identify particle-induced cell responses and molecular signatures of the different treatments, RNA-sequencing will be performed. Since copper dyshomeostasis is also known to be associated with several neurodegenerative diseases, models assessing the neurotoxicity of the NPs will be included as well. Last, we want to identify further model systems to simulate the routes of exposure and thereby predict the safety of other advanced materials in the future.

Key messages:

1. Copper contributes to several physiological processes but can have toxic effects.
2. Iron-doping changes the dissolution kinetics and thereby the toxicity of CuO NPs.
3. Our first results indicate a lowered toxicity of the higher doped CuO NPs *in vitro*.

[1] Chen, L., Min, J., & Wang, F. (2022). Copper homeostasis and cuproptosis in health and disease. *Signal Transduction and Targeted Therapy*, 7(1), 1-16.

[2] Naatz, H., Lin, S., Li, R., Jiang, W., Ji, Z., Chang, C. H., Köser, J., Thöming, J., Xia, T., Nel, A. E., Mädler, L., & Pokhrel, S. (2017). Safe-by-Design CuO Nanoparticles via Fe-Doping, Cu-O Bond Length Variation, and Biological Assessment in Cells and Zebrafish Embryos. *ACS nano*, 11(1), 501–515.

[3] Naatz, H., Manshian, B. B., Rios Luci, C., Tsikourkitoudi, V., Deligiannakis, Y., Birkenstock, J., Pokhrel, S., Mädler, L., & Soenen, S. J. (2020). Model-Based Nanoengineered Pharmacokinetics of Iron-Doped Copper Oxide for Nanomedical Applications. *Angewandte Chemie (International ed. in English)*, 59(5), 1828–1836.