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Systems toxicology used in nanotoxicology: Mechanistic insights into the hepatotoxicity of nano-copper particles from toxicogenomics

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In some studies, nano-copper particles have been found to be acutely toxic to exposed mice, with the liver being the target tissue. However, the characteristics of subacute toxicity from repeated nano-copper exposure in rats and the molecular mechanism of its hepatotoxicity at the genomic level remain unclear. We investigated the mechanisms of nano-copper-induced hepatotoxicity at the genomic level. Male Wistar rats were administered nano-copper or micro-copper at different doses for five days. Subsequently, we examined conventional toxicological parameters (body weight, clinical chemistry, and histopathology), and also used microarrays to identify gene expression changes in rat liver. High dose nano-copper induced increases in alanine aminotransferase, aspartate aminotransferase, triglyceride, total bile acid levels, and a decrease in body weight. Histopathological studies of the liver indicated scattered, dotted hepatocytic necrosis in all rats in the high dose nano-copper group. Identified genes from the group receiving the high dose were functionally categorized, and results showed that genes related to oxidoreductase activity, metabolism, and signal transduction were involved in the development of the observed phenotypes. The results also suggest that altered gene expression patterns induced by exposure to a low, subtoxic dose of nano-copper may reveal signs of cell stress or subtle cell injury indicative of overt toxicity at higher doses. Results in this study provide new insights into the toxicology of nano-copper particles and illustrate how toxicogenomic approaches are providing an unprecedented amount of mechanistic information on molecular responses to nano-copper, as well as how they are likely to impact hazard and risk assessment.

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Systemic distribution of amorphous nanosilica following topical application

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Purpose: Currently, nanomaterials (NMs) with particle sizes below 100 nm have been successfully employed in various industrial applications in medicine, cosmetics and foods. On the other hand, NMs can also be problematic in terms of eliciting a toxicological effect by their small size. However, biological and/or cellular responses to NMs are often inconsistent and even contradictory. In addition, relationships among NMs physicochemical properties, absorbency, localization and biological responses are not yet well understood. In order to open new frontiers in medical, cosmetics and foods fields by the safer NMs, it is necessary to collect the information of the detailed properties of NMs and then, build the prediction system of NMs safety. *Methods*: amorphous nanosilica of particle size 70 nm (nSP70; 250 mg/ear/day) and QD (1.2 pmol/ear/day) suspension supplemented with 10% isopropyl myristate were applied to the inner side of both ears of BALB/c mice for 28 days. After 24 h of last administration, skin, lymph node and brain from each mouse were analyzed by Transmission Electron Microscopy. *Results*: The present study was designed to examine the skin penetration, cellular localization of the well-dispersed amorphous silica particles of diameters ranging from 70 nm to 1000 nm. Our results suggested that the well-dispersed nSP70 penetrated the skin barrier and caused systemic exposure in mouse. Our information indicated that further studies of relation between physicochemical properties and "systemic" biological responses are needed for the development and the safer form of NMs.

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Chromosomal aberration for colloidal silver nanoparticles (AgNPs)

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Purpose: Silver nanoparticles (AgNPs) are broadly used in commercial products, cosmetics, electronics, medical products, and textiles, and in the food industry for its antibacterial properties. Thus, large populations are increasingly exposed to AgNPs through skin contact, food intake, and breathing. However, information regarding the genotoxicity of AgNPs is still lacking. Therefore, in this study, we evaluated the cytotoxic and genotoxic effects of AgNPs (5–20 nm). *Methods*: For the cytotoxicity of AgNPs, we examined the intracellular intake of AgNPs with transmission electron microscopy and analyzed morphological changes in Chinese hamster lung (CHL/IU) cells. The cell viability of AgNPs was confirmed with the WST-1 assay using CHL/IU cells. Then, the genotoxicity of AgNPs was tested with the bacterial reverse mutation test (Ames test) using four *S. typhimurium* and one *E. coli* strains, the chromosomal aberration (CA) test using CHL/IU cells, and the micronucleus (MN) test using ICR mice according to the OECD test guidelines. *Results*: As a result, AgNPs was agglomerated within the nuclear membrane and cytoplasm of CHL/IU cells. In the morphological test and the WST-1 assay, the CHL/IU cells showed distinct unhealthy changes and significantly inhibited cell growth ($p < 0.001$) at 1 μg/ml or more. And, as the results of the genotoxicity tests, the Ames test and the MN test were negative for all groups. Meanwhile, in the CA test, AgNPs significantly increased the numerical chromosome aberration at high dose ($p < 0.001$). Most of the numerical chromosome aberrations induced by AgNPs were endoreduplication.

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