# Differential Cytotoxic Responses to Polystyrene Micro and Nanoplastics in Human Caco-2, HepG2, and SH-SY5Y Cells

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**ABSTRACT:**
The global escalation of plastic waste has intensified environmental contamination by macroplastics and primary microplastics (MPs). Degradation processes fragment plastics into MPs (1–5000 μm) and nanoplastics (NPs) (<1 μm), which are now detected in water, food, and human biological fluids. Despite growing interest, studies assessing the biological effects of environmentally relevant MNP (micro- and nanoplastic) concentrations and particle sizes remain scarce.

This study evaluated the cytotoxicity of polystyrene (PS) NPs (30 nm, 100 nm) and MPs (1.1 μm) on human HepG2 (hepatocytes), Caco-2 (intestinal epithelial), and SH-SY5Y (neuronal) cell lines. Cells were exposed for 24 hours, followed by multiparametric High Content Analysis (HCA) assessing cell number, nuclear morphology, mitochondrial mass, and membrane potential. Caco-2 cells exhibited no significant cytotoxic effects across PS particle sizes. Conversely, SH-SY5Y and HepG2 cells demonstrated pronounced mitochondrial dysfunction, reduced viability, and altered expression of oxidative stress markers (*SOD*, *COX5A*). Notably, SH-SY5Y cells exposed to 100 nm PS (20 μg/mL) showed elevated interleukin-8 (IL-8) expression, indicating an inflammatory response.

Complementary optical photothermal infrared (O-PTIR) spectroscopy revealed lipid accumulation and structural remodeling in HepG2 and SH-SY5Y cells (Figure 1), correlating spatially with PS particle localization. These results indicate that PS MNPs induce differential cytotoxic responses depending on cell type, with hepatic and neuronal cells particularly susceptible to oxidative stress, mitochondrial impairment, and inflammation. Collectively, the data suggests that MNP exposure could compromise cellular homeostasis, posing potential health risks, and highlight the need for further long-term studies.