Oncogenic effects caused by *in vitro* long-term co-exposure to polystyrene nanoparticles and arsenic

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The widespread and persistent presence of micro- and nanoplastics (MNPLs) in the environment calls for urgent evaluation of their potential risks. These particles have been found to enter the human body, translocate through physiological barriers, and exert a mild yet relevant impact at different levels: cytotoxicity, ROS generation, DNA damage, and secretome and pro-inflammatory response alterations. However, many questions remain to be answered regarding the potential hazard that MNPLs pose to human health, specially at the long-term. Moreover, increasing interest is being directed towards the likely role of MNPLs as carriers for other more hazardous contaminants, resulting in the so-called *Trojan horse* effect; that is, MNPLs may enhance the bioaccumulation and impact of other pollutants of concern.

Hence, in this work we have aimed to examine the interaction and the long-term joint effects of polystyrene nanoplarticles (PSNPs) and arsenic (As^{III}), both being prevailing water pollutants. Interestingly, we could demonstrate a physical interaction between both pollutants using transmission electron microscopy (TEM) coupled with energy dispersive X-ray (EDX). Regarding the effects of the PSNPs and As^{III} mixture, we established a new model in which cells previously transformed by chronic arsenic exposure were further exposed to PSNPs, As^{III}, and the combination PSNPs/As^{III} for 12 weeks. Our results indicate that the continuous co-exposure enhances the DNA damage and the aggressive features of the initial transformed phenotype. Remarkably, when compared to cells exposed to arsenic or PSNPs alone, the co-exposed cells present a higher proportion of spindle-like cells within the culture population, an increased capacity to grow independently of anchorage, as well as enhanced migrating and invading potential.

Therefore, our work reveals the MNPLs' potential to exacerbate arsenic-transforming effects. Besides, this study highlights the need to further explore the long-term effects of MNPLs and the importance of considering their role as carriers for other pollutants to effectively perform risk assessment.