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Advancing Nanotoxicology: High-Throughput Screening for Assessing the Toxicity of Nanoparticle Mixtures

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ABSTRACT

The widespread application of nanoparticles (NPs) in fields ranging from consumer products to industrial processes has led to increased concerns about their potential toxic effects on human health and the environment. While traditional toxicological studies often evaluate the effects of individual nanoparticles, real-world exposure scenarios typically involve mixtures of nanoparticles, where interactions between particles can significantly alter their toxicological profiles. This study focuses on addressing this critical gap by employing high-throughput screening (HTS) to evaluate the combined effects of nanoparticle mixtures under various exposure conditions. Our research investigated metal oxide nanoparticles, which have advancement in commercial applications, for their cytotoxic, genotoxic, and oxidative stress-inducing effects. By leveraging HTS platforms, we rapidly screened multiple mixture ratios and exposure durations using human lung epithelial cells and zebrafish embryos as model systems. The results revealed a range of interactions, from synergistic effects, where the combined toxicity exceeded the sum of individual toxicities, to antagonistic effects, where toxicity was mitigated. Mechanistic analyses showed that oxidative stress and metal ion release were key drivers of toxicity, particularly in ZnO dominant mixtures. This study highlights the importance of integrating HTS into nanotoxicology research to provide a more comprehensive understanding of nanoparticle mixtures' behavior. The large datasets generated through HTS enable predictive modeling, allowing researchers to anticipate toxicological outcomes and guide the development of safer nanomaterials. Furthermore, the findings emphasize the need for regulatory frameworks to incorporate mixture effects into nanoparticle risk assessments, moving beyond the current single-particle-focused approaches.

NANOPARTICLES & NANOTOXICOLOGY

Nanoparticles (10-100 nm) are a revolutionary class of materials where their immense surface area and quantum effects create properties distinct from bulk matter. This unique reactivity drives innovation across disciplines but also defines their potential biological interactions. Consequently, traditional mass-based dose metrics are often inadequate for predicting their toxicity. Their risk is instead governed by complex physicochemical properties like infiltrate cells, generate oxidative stress, and trigger inflammation. Their toxicological impact is driven by size, shape, and surface chemistry rather than dose alone.

Nanomaterials & Exposure

- Metal NPs, Carbon-based Quantum dots
- Inhalation Ingestion Dermal, injection

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Cellular Uptake & Mechanism

- Endocytosis / Diffusion / Phagocytosis
- Oxidative stress -ROS Inflammation Damage DNA & Protein

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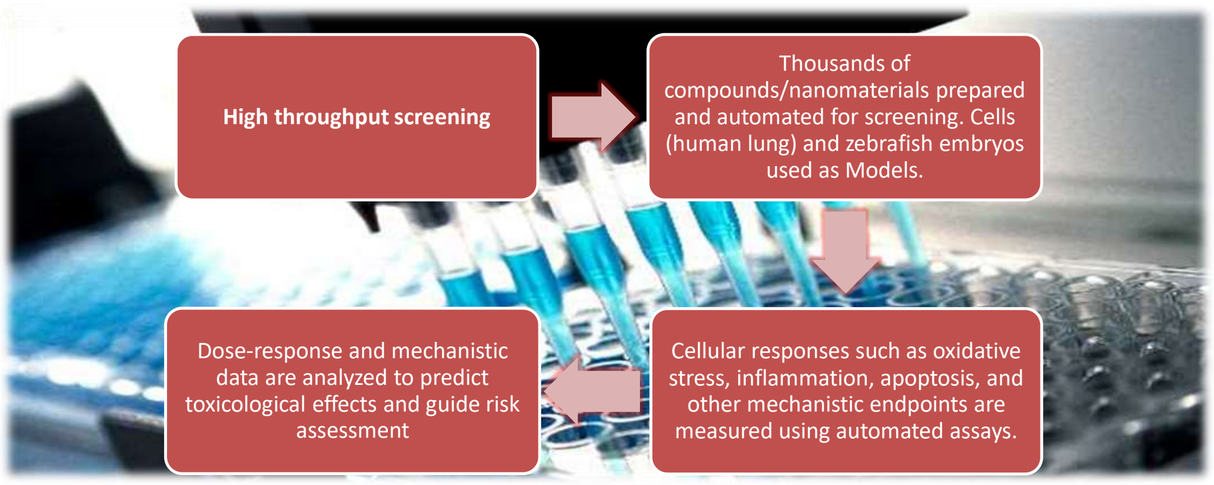
Biological Effects & Risk

- Cytotoxicity: Apoptosis, Necrosis.
- Genotoxicity: DSBs, SSBs, Organ/Systemic damage

HIGH THROUGHPUT SCREENONG FOR ADVANCED RISK ASSSESSMENT

High-throughput screening (HTS) uncovers toxic mechanisms by evaluating thousands of compounds in automated cell- and organism-based assays. Human lung cells and zebrafish embryos reveal how nanoparticles trigger oxidative stress, inflammation, and cellular damage. ZnO nanoparticles, for example, activate proinflammatory pathways paralleling pulmonary toxicity. Mechanistic endpoints and dose-response data, validated by rigorous quality control, make HTS essential for predictive toxicology.

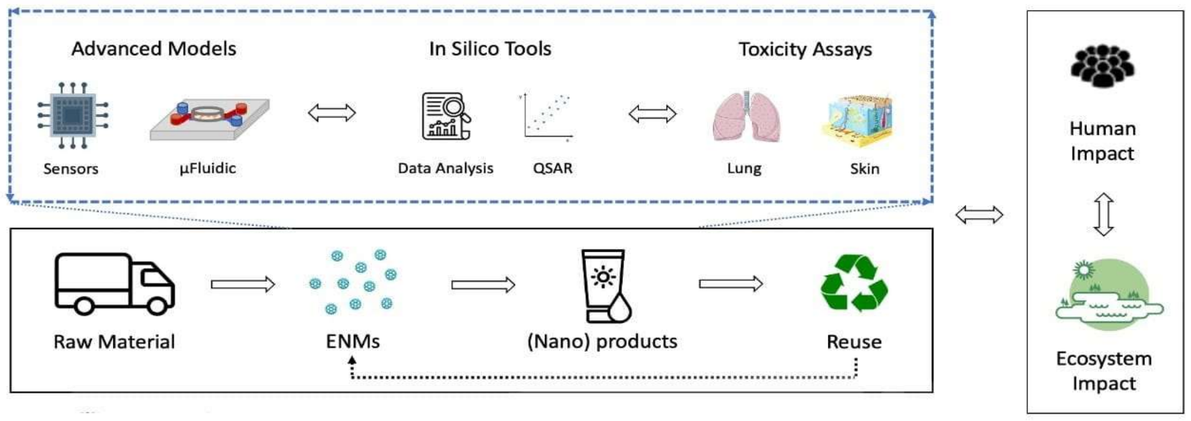


OXIDATIVE STRESS AND EFFECTS OF METAL IONS

Nanoparticles	Nanoparticles property associated with toxicity	Toxicological phenomenon observed/mode of action
Metal	Shedding heavy metal (e.g. Ag, Cu, Pt)	DNA cleavage and damage leading to genotoxicity and mutation; heavy metal ions induced oxidative stress and inflammatory responses
Metal Oxide	Dissolution and heavy metal release (e.g. ZnO)	Heavy metal ions induced oxidative stress and inflammatory responses
Silica Particles	Surface defects	Blood platelet, vascular endothelial and clotting abnormalities
Metal Chalcogenide	Heavy metal release	Blood platelet, vascular endothelial and clotting abnormalities
Fullerenes and CNTs	Heavy metal contamination	Fibrogenesis and tissue remodeling injury, oxygen radical production, GSH depletion, bio-catalytic mechanisms

PREDIACTIVE MODELING FOR SAFER NANOPARTICLES USE

Predictive modeling integrates high-throughput screening (HTS) data to assess the toxicity of metal oxide nanomaterials. HTS evaluates cellular and organismal endpoints, including oxidative stress, inflammation, DNA damage, and protein dysfunction. Mechanistic correlations between physicochemical properties—size, shape, and surface chemistry—and biological responses are established. Machine learning and in silico approaches predict dose-response relationships and potential adverse effects. Such predictive frameworks enhance model reliability, guide safer nanomaterial design, and support regulatory risk assessment.



CONCLUSION

High-throughput screening (HTS) enables rapid assessment of nanoparticle mixtures, revealing cytotoxic, genotoxic, and oxidative stress effects, especially in ZnO-dominant combinations. Synergistic and antagonistic interactions highlight the limitations of single-particle toxicology. Predictive modeling of HTS datasets facilitates anticipation of adverse outcomes and guides the design of safer nanomaterials. Integrating mechanistic insights and mixture effects provides a robust framework for accurate, translational nanotoxicity assessment.

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