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Engineered Nanoparticles May Induce Genotoxicity

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Dramatically increased engineered nanoparticle (ENP) use has resulted in much greater potential for environmental and human exposures to these materials. Although receptor responses to ENP exposure can be low, most of the literature indicates toxicity by a wide range of measures. For plants, the most common toxic responses include reduced germination or growth, membrane damage, impaired photosynthesis, slowed or reduced reproductive development, and mortality. Commonly described toxic responses for animals exposed to ENPs include cytotoxicity by necrosis or apoptosis, tissue or organ-level damage, growth inhibition, impaired reproduction and/or development, and mortality. Although humans may not be exposed to high levels of ENPs occupationally, widespread low dose exposure can occur through a variety of ENP-containing consumer products, including textiles, cosmetics, and food packaging, for which the potential risks are poorly understood.

A "Web of Science" search found 2567 articles with the results Topic=(nanoparticle) AND Topic=(toxicity), while there are only 136 articles with results Topic=(nanoparticle) AND Topic=(genotoxicity). However, mounting evidence shows that ENP exposure can induce genotoxicity in mammalian cells, bacteria, mice,[1] and plants including soybean and radish.[2] These findings suggest potential long-term risk and harm to ecosystems and humans. The reported genotoxic responses range from oxidative DNA damage to point mutations and altered gene expression. The ENPs shown to generate genotoxic responses include metal/metal-oxide nanoparticles (TiO_2 and CuO), fullerenes, and carbon nanotubes.[1,2] Therefore, our viewpoint is that genotoxicity can be induced by ENP exposure and the mechanisms driving this molecular response need to be thoroughly characterized to enable adequate evaluation, prediction, and management of risk.

1. WHAT ARE THE MECHANISMS OF GENOTOXICITY?

The mechanisms of genotoxicity are classified as either direct or indirect. Direct genotoxicity results from physical interactions with DNA, for example, influencing stacking forces among DNA bases, impacting phosphorylation, causing adduct formation, or altering gene expression/regulation. Indirect genotoxicity can result from reduced DNA repair function or from increased production of reactive oxygen species (ROS) upon interaction with other cellular components (e.g., mitochondria, cell membrane), resulting in antioxidant depletion and altered gene expression. In fact, it is currently postulated that ENPs cause nonspecific oxidative damage and that the resulting stress may be the predominant cause of DNA damage and subsequent genotoxicity. However, much of this information is anecdotal and based on detection of oxidative stress by a number of straightforward assays; the mechanisms of toxicity may indeed be more complex. For example, it is unknown why different ENP physiochemical properties elicit specific genetic effects. In addition, carbon nanomaterials and CeO_2 can act as quenching agents against free radicals,[3] making genotoxicity evaluation more complex.

2. WHAT ARE THE HUMAN AND ECOLOGICAL HEALTH RISKS FROM ENP-INDUCED GENOTOXICITY?

An obvious concern over ENP genotoxicity is the long-term risk to sensitive receptors, including humans. Small genetic changes can be cumulative throughout biota life cycles. For

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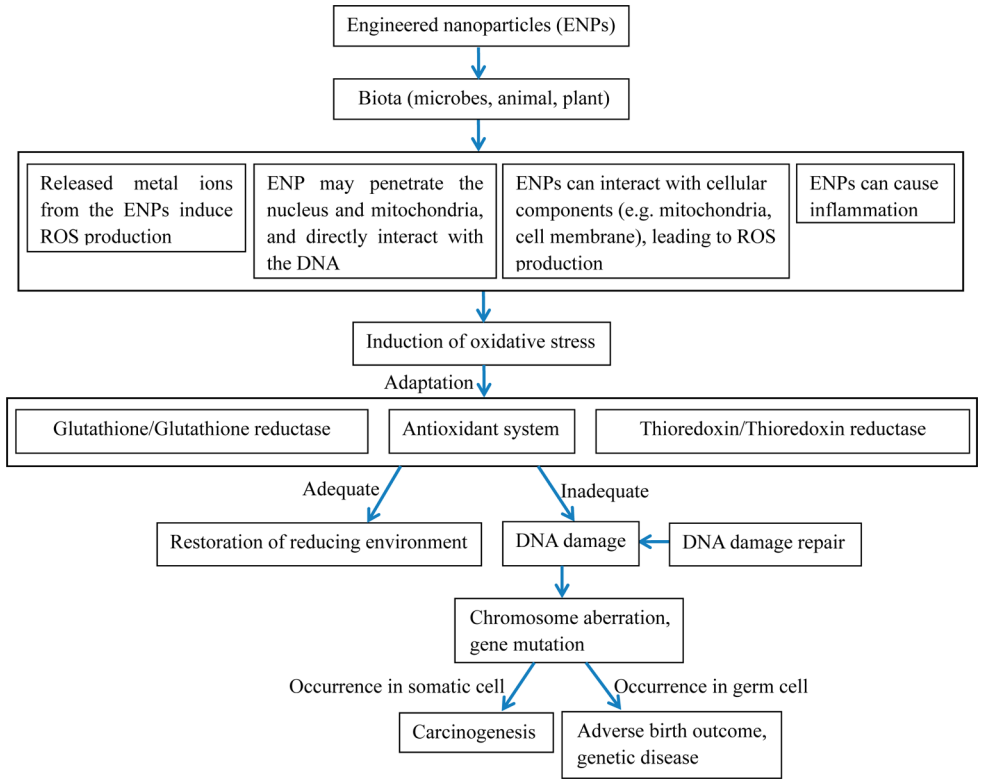

Figure 1. Scheme of potential genotoxicity induced by engineered nanoparticles (ENPs).

humans, molecular changes upon exposure can affect either somatic or germ cells and, historically, changes in the latter are known to lead to adverse birth outcomes and genetic diseases. Importantly, genotoxicity could initiate and promote carcinogenesis or may impact fertility, development, and human lifespans. Last, ENP exposure may compromise health more broadly, making exposure to other genotoxic agents more likely to cause harm. However, no published evidence exists for such phenomena. An additional concern relates to the potential transgenerational nature of genotoxicity. For instance, low concentrations of cadmium-containing quantum dots were sufficient to cause transgenerational genotoxicity in exposed cells.[4] In addition to human concerns, potential ENP genotoxicity can be a risk at the ecosystem level. The transfer and biomagnification of ENPs through food chains under a number of exposure scenarios has been suggested. However, if and how genotoxicity can be induced in higher trophic level organisms through food chain exposure remains unknown. Under extreme conditions, genotoxicity in individual species could affect genetic diversity and evolutionary processes, as well as having implications for ecosystem function. Therefore, integrating considerations across individual, population, and ecosystem levels is needed when investigating and quantifying ENP genotoxicity. See Figure 1

3. WHAT ARE THE KNOWLEDGE GAPS FOR ACCURATE ASSESSMENT OF ENP-INDUCED GENOTOXICITY?

There are at least five significant knowledge gaps regarding ENP-induced genotoxicity (i). There are currently no standardized metrics and experimental conditions for examining ENP genotoxicity. ISO/DTR 16197, which is entitled "Nanotechnologies - Guidance on toxicological screening methods for manufactured nanomaterials",[5] is being developed to offer some information in this area, but many published results are difficult to interpret and often impossible to compare. In addition, the application of current standard genotoxicity test methods to ENPs is frequently problematic. For example, the Ames test is not applicable to bactericidal ENPs or for ENPs that cannot cross the bacterial cell wall. Use of a suite of standardized genotoxicity testing methods covering a range of genotoxic mechanisms is the only viable approach (ii). The actual dose at the site of toxicity mediates biological responses and this will be different from the nominal exposure dose. However, our current understanding of ENP fate and transport in environmental and biological systems is poor and the current literature relies exclusively on nominal exposure (iii). Genotoxic effects under realistic exposure scenarios such as occupational situations and chronic low dose exposure are not considered (iv). To discriminate genotoxicity induced by ENPs from that of other coexposed agents, investigations centering on comprehensive transcriptional activity is warranted (v). The relationships between genetic diseases, carcinogenesis, and genotoxic effects as a function of trophic level are unknown.

There is little information on genotoxicity relative to our understanding of alternative toxicity mechanisms. Yet, there is growing evidence that genotoxicity may be a common biotic response to ENP exposure. Thus, the potential impacts of ENPs may be vastly underestimated without considering genotoxicity. Clearly, resources need to be focused on this critical issue, which is important for safe development and application of nanotechnology, and for the protection of human health and the environment.

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Notes

The authors declare no competing financial interest.

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