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Understanding the mechanism of toxicity of carbon nanoparticles in humans in the new millennium: A systemic review

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Abstract

Manmade nanoparticles range from the well-established multi-ton production of carbon black and fumed silica for applications in plastic fillers and car tyres to microgram quantities of fluorescent quantum dots used as markers in biological imaging. While benefits of nanotechnology are widely publicized, the discussion of the potential effects of their widespread use in the consumer and industrial products are just beginning to emerge. Acceptance of nanoparticle toxicity led to wide acceptance of the fact that nanotoxicology, as a scientific discipline shall be quite different from occupational hygiene in approach and context. Understanding the toxicity of nanomaterials and nano-enabled products is important for human and environmental health and safety as well as public acceptance. Assessing the state of knowledge about nanotoxicology is an important step in promoting comprehensive understanding of the health and environmental implications of these new materials. Very limited data exist for health effects secondary to inhalation of very fine respirable particles in the occupational environment. Nanomaterials may have effects on health due to their size, surface, shape, charge, or other factors, which are not directly predictable from mass concentration measurements. Numerous epidemiological studies have associated exposure to small particles such as combustion-generated fine particles with lung cancer, heart disease, asthma and/or increased mortality. The omnipresence of nanoparticles shifts focus of research toward efforts to mitigate the health effects of nanoparticles. Newer health assessment methods and newer techniques need to be developed for diagnosing sub-optimal health in populations exposed to carbon nanoparticles.

Keywords: Environment, health and safety, literature review, nanotoxicology

INTRODUCTION

Discovery of carbon nanoparticle (NP) in 1980s was perhaps most important discovery of the last century. It was observed quite early that there is a radical alteration of physical and chemical properties of matter when it exists at nanoscale. Manmade NPs range from the well-established multi-ton production of carbon black and fumed silica for applications in plastic fillers and car tyres to microgram quantities of fluorescent quantum dots used as markers in biological imaging. Nanomaterials—substances smaller than 100 nm in size—have been added in recent years to an increasing numbers of consumer products used in day-to-day life: in food packaging, medical devices, pharmaceuticals, cosmetics, odor-resistant textiles and household appliances. The extensive application of nanomaterials in a wide range of products for human use poses a potential for toxicity risk to human health and the environment. Such adverse effects of nanomaterials on human health have triggered the development of a new scientific discipline known as "nanotoxicity"—the study of the toxicity of nanomaterials.^[1-7]

Discovery of NPs sounded the last death knell for the occupational hygiene movement. In 1990s it was accepted almost by consensus that statistical models of dose-response on which legislative limits are based may not be correct. While benefits of nanotechnology are widely publicized, the discussion of the potential effects of their widespread use in the consumer and industrial products are just beginning to emerge.[5] Acceptance of NP toxicity led to wide acceptance of the fact that nanotoxicology, as a scientific discipline shall be quite different from occupational hygiene in approach and context.

Understanding the toxicity of nanomaterials and nano-enabled products is important for human and environmental health and safety as well as public acceptance. The scientific literature is a primary source of information about nanomaterial toxicology and thus plays a role in the emerging dialogue about the safety of nano-enabled products. American Heart Association's scientific statement concludes that short-term exposure to elevated particulate matter concentrations in outdoor air significantly contributes to increased acute cardiovascular mortality, particularly in certain at-risk subsets of the population. Long-term exposure to air pollution increases the risk of dying from coronary heart disease. Respiratory exposure can result in inflammatory reactions and release of pro-coagulatory cytokines into the circulatory system and may result in cardiovascular effects.[2] The inflammatory nature of particulate matter has been convincingly confirmed, and there is an increasing appreciation of the adverse effects of particulates on endothelial function, fibrinolysis, and thrombogenesis.

Very limited data exist for health effects secondary to inhalation of very fine respirable particles in the occupational environment. Nanomaterials may have effects on health due to their size, surface, shape, charge, or other factors, which are not directly predictable from mass concentration measurements. Evidence exists for disproportionately higher toxicity of nano-sized particles measured on mass basis. [8-12]

The methods characterizing exposure and translocation of NPs in the body are still experimental and there are reports of NPs clearing from airways readily and gaining access to circulation and simultaneously reports are claiming that NPs do not readily clear from peripheral airways and exert their effects mediated through inflammatory cytokines released into circulation. However, there are reports of acute impairment of vascular and myocardial function as a consequence of respiratory exposure of elemental carbon. The observed effects on cardiovascular function may be secondary to direct or indirect effects of carbon NPs.

DISCUSSION

The International Life Sciences Institute Research Foundation/Risk Science Institute convened an expert working group to develop a screening strategy for the hazard identification of engineered nanomaterials. The working group report presents the elements of a screening strategy rather than a detailed testing protocol. Based on an evaluation of the limited data currently available, the report presents a broad data gathering strategy applicable to this early stage in the development of a risk assessment process for nanomaterials. Oral, dermal, inhalation, and injection routes of exposure are included recognizing that, depending on use patterns, and exposure to nanomaterials may occur by any of these routes. The three key elements of the toxicity screening strategy are physicochemical characteristics, *in vitro* assays (cellular and non-cellular), and *in vivo* assays. There is a strong likelihood that biological activity of NPs will depend on physicochemical parameters not routinely considered in toxicity screening studies. Physicochemical properties that may be important in understanding the toxic effects of test materials include particle size and size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge, and porosity. Numerous epidemiological studies have associated exposure to small particles such as combustion-generated fine particles with lung cancer, heart disease, asthma and/or increased mortality.[11-12] Both Donalson *et al*, and Oberdorster concluded in their reviews that ultra-fine particles of low solubility and low toxicity materials are more inflammogenic in the rat lung than larger particles of the same material.[11] Additionally, NPs are able to penetrate deeply into the respiratory tract. Once deposited in the alveolar region, they may translocate to blood and to sites

distant from their portal of entry such as the liver, spleen, kidney and brain. Their migration to distant sites is an important issue with regard to their toxicity. The kidney is particularly susceptible to xenobiotics owing to its high blood supply and ability to concentrate toxins. Few studies have examined the impact of NPs in kidney, while both glomerular structures during plasma ultra-filtration and tubular epithelial cells may be exposed to NPs.

There are two types of NPs to be considered in hygiene science; one is the environmental NP emitted from automobiles and the other is the manufactured NP. In general NPs (less than 100 nm) are reported to be permeable through the cell membrane and tissues and their large surface area is responsible for the greater toxicity compared to larger particles. However, there are contradictory reports on the health effects of NPs. Recent reports suggest that carbon nanotubes, fiber-shaped biopersistent NPs, resemble asbestos in the pathogenesis of granuloma and mesothelioma. Literature search describes a limited number of toxicological studies, but that all conclude that there are some health risks following exposure to NPs. For a given substance, the toxicity is much greater when the substance is of nanometric dimensions than when it is of micrometric dimensions. Since these particles are very small, they could have significant toxic effects on workers' health. Due to the many unknowns related to NPs and their potential health effects, caution and stringent prevention procedures are required for exposed people. There are no accepted standards for assessment of exposure to NPs. All the techniques to assess NPs are in a nascent and experimental state. The biggest hurdle is the practical impossibility of measuring NPs' exposure on mass basis. All the exposures are so small on mass basis that they are negligible.

CONCLUSIONS

NPs are omnipresent and exist almost always as a mixture. Except for occupational setting where only one type of NP is manufactured, exposure to a single type of NP cannot be found. Thus, it becomes very difficult to ascertain health effects of NPs. Taking cue from the studies in the arena of occupational medicine, it is being proposed that study of toxicity of asbestos may provide the models for NP toxicity as chrysotile asbestos is a nanofiber. There is almost a consensus that asbestos fiber has surface properties quite different from the chemical properties of its constituents and it has been conclusively proven that only asbestos fibers in nanorange produce health effects.

Asbestos fiber toxicity is being hypothesized as a model for toxicity of nanofibers.[4] "Carbon nanotube" is another nanofiber and workers involved in grinding operations are chiefly exposed to this type of nanofiber. It was found that carbon nanotubes have higher inflammatory potential as compared to another type of carbon NPs fullerenes. Echocardiographic assessment of cardiac functions and actual measurement of left atrium and other chamber in three dimensions shall provide insights into the mechanisms of cardiovascular toxicity of carbon NPs.

Diagnoses of diseases are dependent upon accepted protocols. Health in contrast is not well categorized. A practical demarcation of healthy and diseased state is mainly the word of mouth of the patient hearing which a doctor starts formulating his diagnosis. Public health in the 21st century attempts to characterize markers for the incipient states of disease or sub-optimal health. Unlike disease states, sub-optimal health is a community diagnosis, and a well-accepted marker of sub-optimal health is lower average life span of population. There is an urgent need for the identification of clustering of "established risk factors" in a given population and devising interventional strategies.

Epidemiological evidence links cardio-respiratory end points to outdoor air pollution. Recent studies indicate that target organ for carbon NP toxicity might be heart. The further study should plan in which established biomarkers for sub-optimal health shall be correlated with statistically determined exposure averages. Simultaneously, indicators like CIMT, LAE shall be used to assess the target organ damage. Exposure to nano-sized particles cannot be contained much by engineering controls. The omnipresence of NPs shifts focus of research toward efforts to mitigate the health effects of NPs. Newer health assessment methods and newer techniques need to be developed for diagnosing sub-optimal health in populations exposed to carbon NPs. At present there exist no reliable and

validated standards for measurement of aerosolized nanomaterials and there is considerable debate how nanomaterials gain access to different organ systems. The observed health effects can be thought to be due to the exposure to engineered nanomaterial in accordance with "precautionary principle" and "uncertainty-based decision making". The occupational environments may be the places to look for high exposure to engineered nanomaterials and to assess their health effects. Furthermore, the potential use of new high throughput "predictive" toxicity" strategies, such as that envisioned in the recent NRC report "Toxicity Testing in the 21st century," have emerged as possible solutions to deal with the issue of how to assess the safety of the thousands of chemicals to which humans are potentially exposed.

Footnotes

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Conflict of Interest: None declared

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