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Preface

Carbon nanotubes in medicine and biology — Safety and toxicology☆

Current production of carbon nanotubes has reached several thousand tons per year. CNTs used as bulk powder have already been incorporated in various commercial products, from sporting goods, batteries to water filters and concrete alloys. Future applications include field emission displays, supercapacitors, chemical sensors and in the longer term, as components for biomedical devices. With increased production expected to fulfil such needs and the widespread use of the material, exposure of workers, consumers and patients needs to be investigated.

Almost exactly 10 years ago, the first primary research reports were published to raise awareness of the potential risks from CNT exposure at the occupational health setting. These early studies almost exclusively focused on the pulmonary route of exposure to nanotubes. At the same time, other scientists – including some of us – were reporting the first data to demonstrate the possibility of using CNTs for intracellular delivery purposes, expanding the promise of these materials in medicine. For a few years, these two communities of researchers worked almost independently with little interaction. As a consequence, results from the evaluation of the toxicological profile of carbon nanotubes were commonly contradicting among reports showing deleterious effects and others demonstrating complete biocompatibility. More recently, it has become apparent that most studies that were seemingly conflicting were using a common generic name to describe the nanomaterials used ('carbon nanotubes'), but were in fact experimenting on very different materials. Moreover, it is critical to underline that even within each community of toxicologists and biomedical scientists, almost each group has been using their own materials, modified, prepared and used in a specific manner. The physicochemical characteristics of any nanomaterial, including CNT, are of utmost importance regarding compatibility with the biological milieu, and interestingly almost each report available in the literature can be specific only to the materials used.

With the above considerations as a backdrop, we aimed to assemble the latest knowledge and understanding with regard to what has been proven during the last few years one of the most contentious issues in the development of nanotechnology, summarised in a simple question: Are carbon nanotubes safe?

The safety and toxicological profile of CNTs and the definition of criteria to allow safer by-design materials are discussed in this Special Issue. Thanks to a continuing body of important research efforts that helped us understand the origins of CNT toxicity, we have now identified some critical physicochemical characteristics that can make CNTs either toxic or biocompatible nanoscale entities as described by Lanone et al. (http://dx.doi.org/10.1016/j.addr.2013.07.019). One of the latest and most important determinants of toxicity is probably the 'biological identity' of the CNTs (e.g. how protein surface coverage will influence the interaction with cells and the eventual biological response). A review on computational approaches for understanding the interactions between carbon nanomaterials and cellular nanobiosystems (Yanamala et al. http://dx.doi.org/10.1016/j.addr.2013.05.005) illustrates the emerging interest of nanotoxicology towards more computational modelling and system biology approaches. These aim to reveal all toxicological aspects associated with a single type of nanomaterial in a comprehensive approach and also how it can be extrapolated to the many compounds available.

Pulmonary exposure is considered as the most probable route of entry of CNTs (at least in the occupational context) by which nanotube production workers and researchers may be exposed to powders of CNTs. The fibrous shape of CNTs has raised serious concerns regarding the induction of unwanted effects similar to those of asbestos fibres. Donaldson et al. (http://dx.doi.org/10.1016/j.addr.2013.07.014) benchmark CNT lung pathogenicity against the fibre pathogenicity paradigm and try to predict the likelihood of specific CNT characteristics that could be involved in carcinogenesis in the long term. Early investigations have revealed that CNTs induced inflammation followed by fibrosis and granulomas in the lungs, considered as early onsets that might lead to lung cancer. Bhattacharya et al. (http://dx.doi.org/10.1016/j.addr.2013.05.012) describe progress in the understanding of the role of inflammation in CNT toxicity and fate, while Toyokuni (http://dx.doi.org/10.1016/j.addr.2013.05.011) discusses the genotoxicity and carcinogenicity of CNTs in a systematic manner.

One of the key questions to address when investigating the potential consequences of exposure to a nanomaterial is to understand their kinetics in the body. Studies on the fate of CNTs at the whole body level are relatively scarce. As for other nanomaterials, depending on the route of exposure, CNTs can circulate the blood stream, be excreted or accumulate in tissues for long periods of time. Ali-Boucetta et al. (http://dx.doi.org/10.1016/j.addr.2013.10.004) discuss how different types of CNT will have a different biokinetic fate. The physicochemical features of the starting material and transformations that may take place during their residency time will dramatically influence their overall toxicokinetic profile and therefore their toxicological burden. Besides the pulmonary system, the interaction of CNTs with the immune system, in the blood compartment or in the tissue, is a central question. The possible activation of the immune cells can induce distant or systemic responses, as the review article by Dumortier (http://dx.doi.org/10.1016/j.addr.2013.09.005) discusses. Indeed, over the last few years, some unexpected beneficial modulations of immune cells by CNT have also been demonstrated. Lastly, another important and related question is the interaction of CNTs with other blood components, such as the complement system, the coagulation system, blood proteins or red blood cells. Indeed, after unintended (occupational, environmental) or intentional exposure (injection for biomedical purposes), nanotubes can

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reach the blood compartment where they will interact with its protein or cellular components. The last review of the Issue by Bussy et al. (http://dx.doi.org/10.1016/j.addr.2013.10.008) illustrates the multiplicity and complexity of such interactions.

It is interesting to note that after 10 years of scientific research, a lot of which is explained and discussed in this Special Issue, the regulatory framework around the health and safety governing the production and use of nanomaterials has started to adopt some of the knowledge generated. Guidance notes both in Europe and the USA related to carbon nanotube exposure at the workplace have been updated and released in 2013 by various agencies around the world.

Most of these are in relation to the use of nanomaterials at the workplace (including carbon nanotubes and other biopersistent high aspect ratio nanomaterials), with recommendations for occupational exposure limits to carbon nanotubes and carbon nanofibres. In the biomedical field, the toxicity risk will need to be balanced over the clinical benefit offered for a specific pathological condition as with any other medical device or pharmaceutical agent. In the meantime, a lot of further knowledge will need to be generated in order to draw more systematic relationships between nanotube structure and the ensuing biological activities that will determine toxicological burden.

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