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Recent advances, and unresolved issues, in the application of computational modelling to the prediction of the biological effects of nanomaterials☆

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ABSTRACT

Nanomaterials research is one of the fastest growing contemporary research areas. The unprecedented properties of these materials have meant that they are being incorporated into products very quickly. Regulatory agencies are concerned they cannot assess the potential hazards of these materials adequately, as data on the biological properties of nanomaterials are still relatively limited and expensive to acquire. Computational modelling methods have much to offer in helping understand the mechanisms by which toxicity may occur, and in predicting the likelihood of adverse biological impacts of materials not yet tested experimentally. This paper reviews the progress these methods, particularly those QSAR-based, have made in understanding and predicting potentially adverse biological effects of nanomaterials, and also the limitations and pitfalls of these methods.

1. Introduction

Nanomaterials provide an unprecedented opportunity to develop new materials with hitherto unattainable properties because of their unique and increasingly controllable molecular attributes. Consequently, nanomaterials research is accelerating, and products incorporating nanomaterials are being introduced to the marketplace very rapidly. It is estimated the approximately 50,000 products now contain some form of nanomaterial (the Wilson Centre has an inventory of ~2000 products, far from complete see http://www.nanotechproject.org/cpi/). The global market for nanotechnology products was valued at $26 billion in 2014 and is expected to reach about $65 billion by 2019, a compound annual growth rate 20% (bcc Research, 2014).

There is always a necessary tension between the need for new materials with useful properties to be made available quickly, and the need to protect workers, the public, and the environment from any deleterious effects of these materials (Forloni, 2012). The pace at which nanomaterials are being commercialized has left regulatory agencies struggling to provide legislative frameworks and guidelines on their safe use. The manufacturers cannot be relied on to know the extent of the nanomaterial content of their products or to state it (see Fig. 1). The 'precautionary principle' adopted by pharmaceutical and agricultural and veterinary chemical companies is not as rigorously applied to nanomaterials, opening the door for potentially serious consequences of premature translation to the market.

The assessment of the possible adverse biological effects of nanomaterials is more complex than with industrial chemicals and drugs. Small organic molecules are always identical (unless metabolized or chemically modified by their environment) and they have predictable properties can be readily encoded by mathematical objects called molecular descriptors. However, nanomaterials (and many other types of complex materials being actively developed) exist as populations of different but related materials that span a range of, most significantly, size, shape, and composition. The nature of the 'biologically relevant entity' that interacts with living systems is quite context dependent. The composition, size, shape, aqueous solubility, manufacturing and processing history, surface modifications, propensity to agglomerate, interactions with ions, salts, proteins, humic substances and other biological macromolecules can all have a major influence on the biological effects of nanomaterials, unlike small organic molecules which have unambiguous structures and potentially less complex, more specific biological interactions.

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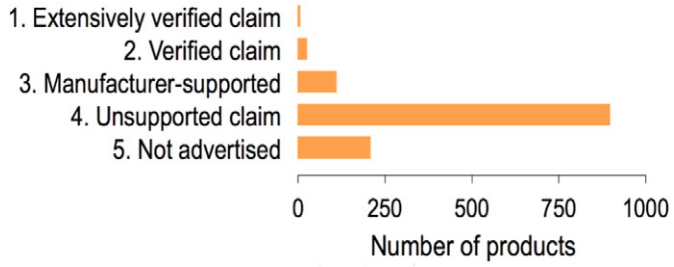

Fig. 1. Relative distribution of products according to how much is known about nanomaterials content (reproduced from Vance et al., 2015) under Creative Commons Licence).

Additional pressures have been brought to bear on regulatory agencies and research providers analysing the properties of nanomaterials due to the cost, time-consuming nature of biochemical assays, and the increasingly prominent ethical issues in using experimental animals. Consequently, the amount of data available on the effects of nanoparticles is insufficient for regulatory purposes (Arora et al., 2012).

The lack of data is being addressed by the development of high throughput synthesis, characterization, and biological testing methods at many sites around the world. This can greatly assist with the availability of data on possible adverse effects of nanomaterials. The development of surrogate assays, fast screens whose results correlate with those of slower more rigorous biological tests, can also accelerate data generation. In a similar vein, in vivo properties that are very difficult or impossible to conduct for cost or ethical reasons may sometimes be estimated by use of well-designed in vitro biological assays, with additional information from chemical or materials structure or physicochemical properties.

Modern molecular modelling methods, chiefly machine learning methods, that were developed for predicting the biological effects of drugs and industrial chemicals can play an important part in more widely leveraging this limited and expensive biological data. Data driven, statistical modelling methods have been valuable for analysing large biological data sets generated by the pharmaceutical and agrochemical industries using combinatorial chemistry and high throughput screening. If a model can be devised that can explain either the mechanism by which a nanomaterial exhibits its adverse biological effects, or predicts the probability and magnitude of such an effect (or both, ideally), then interpolation and some limited extrapolation can be used to infer the likely properties of other materials not tested. Such approaches have been widely used by major regulatory agencies to prioritize industrial chemicals for further mammalian or environmental toxicity testing, and agencies are comfortable with using a similar approach for nanomaterials.

These statistical methods, described generically as Quantitative Structure–Property (or Activity) Relationships (QSPR or QSAR) modelling, are data driven methods that work best with large, diverse data sets. Initial concerns that their use may not be translatable from the small organic molecule domain to the complex materials domain have largely dissipated. Most of these methods are 'platform technologies' than can make reliable, often quantitative models of complex relationships between objects (molecules, polymers, nanomaterials etc.) and properties (biological effects, physical and mechanical properties etc.) (Le et al., 2012). They are currently the only computational methods capable of making useful predictions of properties of nanomaterials in realistic (non-idealized) environments. The remainder of this paper summarizes successes and failures of computational modelling methods, largely QSPR methods, in providing mechanistic insight and/or predicting the effects of nanomaterials on biology from a nanosafety and regulatory perspective. There is a large amount of work on designing and modelling nanoparticles for diagnostic and therapeutic medicine, reviewed recently, and not discussed here (Teli et al., 2010; Zhang et al., 2012; Lehner et al., 2013; Chaudhury et al., 2014).

2. Ab initio modelling of the structure and properties of pristine nanoparticles

Although the nature of nanoparticles and their interactions with biological and other environments is very complex, much can be learned from high level ab initio quantum chemical calculations of pristine nanoparticles *in vacuo* or in solution. Barnard's group has lead much of this work (Barnard, 2009; Barnard, 2010; Feigl et al., 2010; Barnard and Snook, 2011b; Guo and Barnard, 2011a; Guo and Barnard, 2011b; Guo and Barnard, 2013; Barnard, 2014b; Barnard, 2014a). Molecular dynamics methods are increasingly being used to simulate the interactions of nanomaterials with proteins, cell membranes, DNA etc. (see specific examples below) (Makarucha et al., 2011). As computing hardware becomes faster and algorithms more efficient, these computational methods will start to impact increasingly on 'real world' nanoparticle properties (Barnard and Snook, 2011a). A synergistic merging or convergence of machine learning with first principles method (Barnard, 2014b) is also likely to accelerate progress into understanding the interactions of nanomaterials with their environments, and allow more accurate predictions of putative adverse effects.

3. Modelling the interaction of nanoparticles with their environments

The question of the nature of the 'biologically relevant' entity for nanoparticles is an important and largely unsolved one, as a recent Editorial in Nature Nanotechnology describes (Nature Nanotechnology Editorial, 2011). Nanoparticles and other nanomaterial rarely interact with biology in the pristine state. In blood or other biological fluids they attract a 'corona' of proteins (Bhunia et al., 2013; Docter et al., 2015a; Docter et al., 2015b) and, in the environment, of other macromolecules such as humic substances. This coating depends on both the nature of the nanoparticle surface chemistry and its size and shape, but also on the biological environment in which the nanoparticle resides. The corona is dynamic so changes over time, as more abundant proteins with lower affinity are exchanged for low abundance proteins with higher affinity. The corona composition can change as the nanoparticle passes from one biological compartment to another. This is the entity that interacts with cells in the first instance. This very complex area has been investigated experimentally by the Dawson group in Dublin, amongst others (Mahmoudi et al., 2011; Monopoli et al., 2012). Beddoes has very recently reviewed physicochemical and computational studies aimed at understanding how nanoparticle properties influence their interactions with lipid bilayers and how this affects cellular uptake (Beddoes et al., 2015).

Given the complexity of the nanoparticle-corona entity, computational approaches have mainly involved molecular dynamics (MD) with coarse-grained force fields, or machine learning models of nanoparticles with specific surface chemistries that are easier to model. The use of MD for simulating nanoparticle interactions has developed strongly in the past two years. De Leo et al. used molecular dynamics methods to study the interaction monoclonal antibodies with nanoparticles (De Leo et al., 2013). Gu and Lin, and more recently, Ding and Ma reviewed the use of Monte Carlo, molecular dynamics, and dissipative particle dynamics simulation to model the uptake of pristine nanoparticles with biomembranes (Ding and Ma, 2015) and earlier work on this topic was summarized by Qu et al. (Qu et al., 2013). Dobay et al. reported a novel stochastic pi calculus method to model nanoparticle cellular uptake (Dobay et al., 2012). Wang et al. studied the interaction dynamics of silver nanoparticles with proteins using discrete MD (Wang et al., 2015). Very recently, Tevanti et al. have begun using MD methods to understand competitive binding of proteins to nanoparticles (Tavanti et al., 2015a; Tavanti et al., 2015b) and Todorova et al. have used MD calculations to investigate the important issue of whether nanoparticles penetrating the brain (and elsewhere) can trigger the autocatalytic self-assembly of amyloidogenic peptides (Todorova et al., 2013). Zhang et al. have tackled the very complex area of nanoparticle aggregation using computational models (Zhang,