

Nanostructures Toxicity and Computational Parameters

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ABSTRACT: Experimental determination of the toxicities of manufactured nanoparticles have so far revealed that acute or repeated exposure to certain manufactured nanoparticles may cause systemic, cellular or genomic toxicities. Understanding the underlying cause of these nanoparticles related toxicities is complex since the effects on health of a nanoparticle made from a specific chemical may be altered with changes in its size, shape, specific surface area, surface reactivity, and surface coatings. To reduce the need for costly, extensive experimental testing, alternative methods for determining the toxicities of nanoparticles are urgently required. Computational approaches are ideal for rapidly exploring the effects of a large number of variables in complex scenarios. One of the most promising approaches for predicting the biological properties of nanoparticles uses a method that has proven very useful in the pharmaceutical industry over several decades. Quantitative Nanostructure-Toxicity Relationships methods use statistical or computer learning methods such as neural networks, decision trees, and support vector software to model the relationships between microscopic properties of chemicals, and their biological properties.

KEYWORDS: Nanoparticles, Toxicity, Computational and Statistical.

I. INTRODUCTION

Nanotechnology produces nanoparticles having new or enhanced physico-chemical properties in comparison to their micron-sized counterparts. Some of these properties, like the high surface area to volume ratio, make them potentially dangerous to humans as shown by Nanotoxicity. To promote a new generation of nanoparticles that are safe by design, an understanding of the relationship between the nano particles/tubes structure and the biological activity is needed. In this context, Quantitative Nanostructure-Toxicity Relationships computational modeling technique is an effective alternative to experimental testing since it enables the prediction of toxicological effects based only on nanoparticles structure.

I A. TOXICITY BY METAL / NON METAL NANOPARTICLES

It is expected that the number and variety of engineered nanoparticles will increase rapidly over the next few years [1], and there is a need for new methods to quickly test the potential toxicity of these materials [2]. Metal oxides are an important group of engineered nanoparticles, because they are widely used in cosmetics and sunscreens, selfcleaning coatings and textiles. Other applications include their use as water-treatment agents and as materials for solar batteries and more recent automobile catalytic converters [2]. However, it has been shown recently that nanosized particles of these oxides (but not their macro or micro counterparts) are toxic to some organisms [3]. In parallel to experimental toxicity testing, a set of few parameters were quantitatively calculated that describe the variability in the structure of nanoparticles. The descriptors were obtained using the quantum-chemical PM6 method [4]. Because particle size does not influence toxicity in the relative size range, the selected descriptors predominantly reflect reactivity-related electronic properties. The four possible mechanisms for nanoparticle toxicity: (i) the release of chemical constituents from nanomaterials; (ii) the size and shape of the particle, which produces steric hindrances or interferences with the important binding sites of macromolecules; (iii) the surface properties of the material, such as photochemical and redox properties; and (iv) the capacity of nanomaterials to act as vectors for the transport of other toxic chemicals to sensitive tissues. It has been found that once a nanoparticle enters a cell, toxicity could occur through one or a combination of these mechanisms [5]. The most important parameter controlling the in vitro cytotoxicity of metallic nanoparticles [6] (that is, zero-valent metals, metal oxides) is their chemical stability, which is related to the dissolution of the particles (release of cations) and the catalytic properties and redox modifications of the surface.

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Green nanotechnology is particularly in demand to develop efficient and less-polluting energy sources. However, at least some manufactured nanoparticles intended for industrial applications are suspected to have potential toxicities in humans [7, 8] and the public concern about the safety of MNPs is on the rise. Biological effects could result from exposure and subsequent absorption of ultrafine MNPs via different routes [9]. MNPs getting entry into the systemic circulation can immediately interact with blood cells and then be either distributed throughout the body, or captured quickly by macrophages of the reticuloendothelial system. Acute or repeated exposure to MNPs present in commercial products may thus potentially cause systemic, cellular, and/or genomic toxicities. Experimental nanotoxicology is a very young field [10-14]. Our understanding of the toxicology of nano-based materials that are, (i) already contained in commercial products that are not intended for human exposure, (ii) could contaminate the environment while also not intended for human exposure, and (iii) intended for biomedical applications such as drug delivery, imaging, and sensing.

Regardless of the source or intended application of the nanomaterial, it is a need to develop a much more comprehensive and hopefully predictive knowledge of the effects of these nanomaterials on environment as well as animals and human beings. Although some data exist on the absorption properties and associated toxicities of certain types of NPs after exposure via the pulmonary, oral, and topical routes, little is known about the systemic distribution, metabolism, elimination, and health effects once the particles reach the systemic circulation. There were several reports on the deleterious effects of manufactured and environmental NPs on humans and wildlife. For instance, both multi-wall and single-wall carbon nanotubes caused platelet aggregation and accelerated vascular thrombosis [15]. Even at the 'high dose' of 1 ug/mL, the C60 fullerenes caused reactive-oxygen species-mediated necrotic cell damage [16] and thus proposed C60 fullerenes as an anti-cancer agent [17]. Silica NPs directly interacted with plasma and lysosomal membranes leading to Ca^{2+} influx, ATP depletion, and cell death [18]. It was observed that nano-TiO₂ caused ROS stress and DNA damage in lymphocytes [19]. PbCrO₄ particles resulted in ROS generation and upregulation of NF-kappa B and AP-1 in cells [20]. It was also reported that several carbon NPs increased ROS and decreased mitochondrial membrane potential in a dose- and time dependent manner in rat macrophages and human A549 lung cells [21]. A remarkable review on the subject of nanotoxicity was recently published [22] listing a few examples of known toxic effects of MNPs.

There are numerous difficulties in modeling nanoparticles. First, the availability of data concerning MNPs is sparse in the public domain, making difficult the development and the validation of computational models requiring relatively large amounts of data to obtain reasonable predictive abilities. Moreover, because of the high structural diversity of MNPs, it is a real challenge to develop quantitative parameters that are able to characterize the structural and chemical properties of MNPs. Systematic physico-chemical, geometrical, structural and biological studies of NPs are nearly absent due to practical and commercial issues. Therefore computational modeling of nanoparticles is only beginning to emerge and first attempts suggest that successful modeling studies will only be realized in close collaboration with experimental scientists. Most likely, the comprehensive computational nanotoxicology effort would require the integration of several computational techniques such as quantum mechanics, molecular dynamics simulations [22-24] and cheminformatics [25]. In another recent study in which [26-28] MNPs have been thoroughly tested in vitro against four cell lines in different assays to study the biological effects induced by these particles. Different common statistical techniques have been applied in order to find the correlations between the activity profiles of nanomaterials, and thus, to discover some hidden structure-property relationships. It is fully expected that, similar to other more traditional materials based on organic molecules, the experimental body of knowledge concerning the biological effects of MNPs will substantially increase in the near future.

Recently, it was advocated by the researcher that the utility of QSAR modeling as an important computational nanotoxicology approach. The authors illustrated the structural diversity of nanomaterials and concluded that no universal "nano-QSAR" model can be build to assess the toxicity of all possible nanoparticles. It was also emphasized the need of experimentally measured parameters such as the size of particles and suggested using these parameters as valuable variables for the modelling. The authors also reported a few QSAR models mainly developed for carbon nanotubes and fullerenes to assess either their solubility or lipophilicity. However these multi-linear models were developed using very small datasets (usually less than 20 particles) and were not validated according to rigorous statistical methods. Up to now, there have been no significant studies for large experimental nanoparticle datasets to model their induced biological effects and validate these models with external predictions.

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I B. TOXICITY BY CARBON NANOTUBES

Single-walled carbon nanotubes are hollow cylinders of carbon with diameters on the order of one nanometer, lengths ranging from tens of nanometres to centimetres, and walls that are one atomic-layer thick [10]. Like other nanomaterials, the properties of carbon nanotubes depend on their size and atomic structure. Carbon nanotubes have been widely studied for their potential application in biology and medicine. When injected into an animal, they enter various organs and cellular departments and bind to protein and DNA molecules. These properties offer functionalized nanotubes tremendous opportunities to function as intracellular probes, drug carriers, imaging agents, DNA modulators, and other medical devices on the condition that they are biocompatible. In general, the bioactivity of a nanomaterial is modulated by its surface chemistry, among other factors [29]. Single-walled carbon nanotubes modified by different types of organic molecules attached to their surfaces were shown to have noticeably different cellular location and behavior in biological systems [30]. However, the lack of knowledge on the adverse effect of carbon nanotubes on biological systems and human has impeded the application of these materials. Some researchers are fundamentally against using nanomaterials in medicine and in the environment while others are in favor. The important point here is that because there are many nanomaterials with multiple different uses, it is difficult to test all of them and estimate their effects on human health. Therefore, some scientists believe that MNT side effects are acceptable. Considering all factors, testing the effects of nanomaterials on mammals and the environment is necessary. Only with more research, and using scientific evidence, microscopy tools, and modern analysis methods, the advantages or disadvantages of their applications can be discovered. Currently, macrophage is one of the three in vitro systems that are widely used in the cytotoxicity evaluation of CNTs because of their relationship with respiratory, dermatological and immunological toxicity [31]. The toxicity results depend on the purity of CNT preparation and the assay method utilized.

II. COMPUTER SOFTWARE FOR QNSAR/QNAR/QNTR

A number of commercial and free software are available for facilitating the development of QSAR/QSPR models. A particularly useful source for such software is the public web-servers:

QSAR and Modelling Society (<http://www.qsar.org/>)

Cheminformatics (<http://www.cheminformatics.org/>)

Some of the software tools are based on a particular data analysis method while others include a number of data analysis methods. Moreover, some of the software tools do not include molecular descriptor computing module, in which case such software or web-servers as:

DRAGON (<http://www.vcclab.org/lab/edragon/>)

Molconn-Z (<http://www.edusoft-lc.com/molconn/>)

MODEL (<http://jing.cz3.nus.edu.sg/cgi-bin/model/model.cgi>)

PaDEL-descriptor (<http://padel.nus.edu.sg/software/padeldescriptor/>)

These web-servers can be used for deriving the needed molecular descriptors.

The Given table no. 1 lists the freely downloadable codes of regression methods useful for generating QSAR/QSPR models. These softwares can be used to correlate the physical and chemical properties of nanostructures to the induced toxicity.

Table I

Decision Tree		
1	Precision Tree	http://www.palisade.com.au/precisiontree/
2	Decision Pro	http://www.vanguardsw.com/decisionpro/jdtree.htm
3	C4.5	http://www2.cs.uregina.ca/~hamilton/courses/831/notes/ml/dtrees/c4.5/tutorial.html
4	C5.0	http://www.rulequest.com/download.html
Genetic Function Approximation (GFA)		
1	McQSAR	http://users.abo.fi/mivainio/mcqsar/
Neural Network (NN)		
1	Brain Maker	http://www.calsci.com/
2	Libneural	http://pcochat.online.fr/webus/tutorial/BPN_tutorial7.html
3	Fann	http://leenissen.dk/fann/

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4	Neural Works Predict	http://www.neuralware.com/products.jsp
5	NeuroShell Predictor	http://www.mbaware.com/neurpred.html
k-nearest neighbour (KNN)		
1	k Nearest Neighbor	http://www.cs.cmu.edu/~zhuxj/courseproject/knndemo/KNN.html
2	PERL Module for KNN	http://aspn.activestate.com/ASPN/CodeDoc/AI-Categorize/AI/Categorize/kNN.html
3	Java class for KNN	http://nlp.stanford.edu/nlp/javadoc/javanlp/edu/stanford/nlp/classify/old/KNN.html
Linear Discriminant Analysis (LDA)		
1	ALGLIB open-source LDA implementation	http://www.alglib.net/dataanalysis/lineardiscriminantanalysis.php
2	Psychometrica open source LDA implementation	http://www.psychometrica.de/lda.html
3	DTREG	http://www.dtreg.com/lda.htm
Linear Regression (LinR)		
1	Linear Regression in ALGLIB	http://www.alglib.net/dataanalysis/linearregression.php
2	GSL - GNU Scientific Library Ordinary Least Squares regression Algorithm	http://www.gnu.org/software/gsl/
3	Linear Regression at fyxm.net	http://linear-regression.fyxm.net/
4	SegReg : segmentedmlinear regression	http://www.waterlog.info/segreg.htm
logistic Regression (LogR)		
1	Paul Komarek's Logistic Regression Software	http://komarix.org/ac/lr/lrtrirls
2	Web-based logistic regression calculator	http://statpages.org/logistic.html
Partial Least Squares (PLS)		
1	Partial least squares add-in in Microsoft Excel On-line PLS regression at Virtual Computational Chemistry Laboratory	http://www.vcllab.org/lab/pls/
Support Vector Regression (SVR)		
1	SVM light	http://svmlight.joachims.org/
2	SVM light LIBSVM	http://www.csie.ntu.edu.tw/~cjlin/libsvm/
3	My SVM	http://www-ai.cs.uni-dortmund.de/SOFTWARE/MYSVM/index.html
4	BSVM	http://www.csie.ntu.edu.tw/~cjlin/bsvm/
5	SVM Torch	http://www.idiap.ch/learning/SVMTorch.html

III. RESULT & DISCUSSION

Challenges of computer-aided nanotoxicity are numerous because of the complex nature of nanoparticles and nanotubes. Although QSAR methodology is well known and has been massively applied in the areas of drug discovery [27] and chemical toxicity modeling [32], its application to model the biological effects of nanoparticles/nanotubes presents a real challenge for several reasons: (a) NPs are complex assemblage of inorganic and/or organic elements and sometimes, mixed or coated with diverse organic compounds (the exact stoichiometry varying from one particle to another); classical molecular descriptors are thus not appropriate any more. (b) The composition of a given Manufactured Nanoparticles (MNPs) is not exactly known or may not correspond to the information provided by the vendors. (c) Three-dimensional nanostructures including thousands of atoms are highly complex.

Many computational approaches (like quantum chemistry methods) where it is challenging even to handle small drug-like organic compounds cannot treat such large systems at all. This high structural diversity of MNPs as well as the sparse availability of data on structure and biological activity of nanoparticles in the public domain makes difficult the development and validation of computational QNAR models. Systematic physico-chemical, geometrical, structural and

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biological studies of NPs are nearly absent. Therefore computational modeling of nanoparticles/nanotubes is only beginning to emerge but some studies already pointed out the usefulness of molecular dynamics simulation and QSAR modeling to assess biological properties of MNPs. A public database comprising all available data concerning nanomaterials from their chemical characterization to their experimental testing results would definitely help to initiate and/or speed up the development of current and future researches in computational nanotoxicology. The overall goal of the research is to demonstrate the potential benefits of using cheminformatics approaches such as QSAR modeling to obtain predictive knowledge of the chemical, physical, and geometrical properties of MNPs that affect human cells and utilize this knowledge for improved MNP experimental design and prioritized toxicity testing. There are four fundamental hypotheses that drive this research study: (i) The effects of MNPs on different types of human cells depend on the/ physical/chemical/ geometrical properties of the MNPs: this implies that all such properties, i.e., composition, size, shape, aspect ratio, surface area, chemistry/morphology, zeta potential, chemical reactivity, structural descriptors should be explicitly experimentally characterized and/or computed in order to understand their individual or combined contributions that define the biological effects of MNPs. Materials at the nano-scale may have very different properties in comparison to the same material at the micron or macro scale. However, the field has been constrained by the lack of rationalization of possible relationships between these properties and the resulting biological endpoints including toxicity. (ii) Nano-bio interactions with human cells occur relatively rapidly, but the effects of these interactions (activation, production of free radicals, inflammation, etc.) are manifested over much longer time periods. However, the field of nanotechnology is creating new materials far too rapidly to make conventional toxicological testing feasible and/or practical. (iii) In addition, to understand the toxicological implications of MNPs in the body, one would have to have a quantitative bioassay for each tested MNP. (iv) Development of predictive Quantitative Nanostructure – Activity (QNAR) models using physical/chemical characterization and toxicological screens for an ensemble of MNPs. QNTR models correlating descriptors derived from the structure and physical/chemical/geometrical properties of nanomaterials with some toxicological endpoints will allow the field to both prioritize existing MNPs for toxicity testing and to rationally design benign MNPs for various applications. This approach addresses, both in the near- and long-term, a significant problem that exists in studying the biological activity, and especially, toxicity of nanoparticles. The problem relates to the complexity, time, and cost associated with performing sub-chronic and chronic toxicity studies of novel nanomaterials in animals [33]. Simply, these types of comprehensive studies are impossible. Thus, high-throughput cellular-based toxicity assays that provide critical and predictive data in just a few hours would be compelling. Moreover, using well-characterized key physical/chemical properties and structural parameters of nanomaterials, it would be possible to develop Quantitative Nanostructure-Toxicity Relationship (QNTRs) models to correlate these structural and physical/chemical descriptors of nanomaterials with a known toxicological endpoint. Similar to more traditional computational toxicology, these models can be used to predict toxicity of newly designed nanomaterials and bias the design and manufacturing towards safer products. An important component of data collection and preliminary evaluation is the search for potential “signal” indicating the presence of implicit structure-activity relationships. MNPs are complex chemical materials and before embarking on the huge task of predictive computational nanotoxicology, it is a need to prove that statistical and datamining techniques could indeed uncover the non-spurious nanostructure – activity correlations using measured properties of MNPs as structural descriptors. In summary, the trends in experimental nanotechnology and nanotoxicology require not only to explore and rationalize the experimental nanostructure-toxicity relationships but, most importantly, develop models that will help both designing the environmentally benign nanomaterials and prioritize existing and developing MNPs for toxicity testing.

IV. CONCLUSION

Challenges of computational nanotoxicology are numerous. To establish robust and predictive models to accurately predict biological responses associated with a given nanoparticle, it is the time to consider about the Quantitative Nanostructure-Activity Relationships (QNAR) approach. Using limited available published data which can be developed in statistically robust QNAR models that can successfully predict the biological effects of NPs solely from their descriptors either experimentally measured or theoretically calculated. To increase both accuracy and impact of models on the experiments, it is a need to have more systematic experimental data (structural and biological) that can be used both to build and to validate computational models. Using this data, QNAR approaches will allow rational design or prioritization of novel NPs with desired target (physical and biological) properties. To get more accurate results it is a need to make collaborations between specialists in nanotechnology and nanobiology, toxicology,

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cheminformatics and computer science. The unique blend of complimentary expertise needed to advance this new challenging field calls for the development of rigorous and extensible interdisciplinary framework that is bound to significantly create new forms of knowledge and advance the field of nanotoxicology. An intensified collaboration between industrials and academic institutions willing to share their data: computational tools can clearly help collecting, mining and sharing valuable MNPs' experimental data.

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