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Invited review

(Q)SAR modelling of nanomaterial toxicity: A critical review

Ceyda Oksel[a], Cai Y. Ma[a], Jing J. Liu[a,b], Terry Wilkins[a], Xue Z. Wang[a,b,*]

[a] Institute of Particle Science and Engineering, School of Chemical and Process Engineering, University of Leeds, Leeds LS2 9JT, UK
[b] School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510641, China

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ABSTRACT

There is increasing recognition that some nanomaterials may pose a risk to human health and the environment. Moreover, the industrial use of the novel engineered nanomaterials (ENMs) increases at a higher rate than data generation for hazard assessment; consequently, many of them remain untested. The large number of nanomaterials and their variants (e.g., different sizes and coatings) requiring testing and the ethical pressure towards nonanimal testing means that in a first instance, expensive animal bioassays are precluded, and the use of (quantitative) structure–activity relationships ((Q)SARs) models as an alternative source of (screening) hazard information should be explored. (Q)SAR modelling can be applied to contribute towards filling important knowledge gaps by making best use of existing data, prioritizing the physicochemical parameters driving toxicity, and providing practical solutions for the risk assessment problems caused by the diversity of ENMs. This paper covers the core components required for successful application of (Q)SAR methods to ENM toxicity prediction, summarizes the published nano-(Q)SAR studies, and outlines the challenges ahead for nano-(Q)SAR modelling. It provides a critical review of (1) the present availability of ENM characterization/toxicity data, (2) the characterization of nanostructures that meet the requirements for (Q)SAR analysis, (3) published nano-(Q)SAR studies and their limitations, (4) in silico tools for (Q)SAR screening of nanotoxicity, and (5) prospective directions for the development of nano-(Q)SAR models.

Contents

Abbreviations: AES, Auger electron spectroscopy; AFM, atomic force microscopy; ANNs, artificial neural networks; APO or Apop., apoptosis; ATP, adenosine triphosphate (ATP); BET, Brunauer–Emmett–Teller; BSAI, biological surface adsorption index; CNTs, carbon nanotubes; DCF, dichlorofluorescein; DCS, dynamic centrifugal sedimentation; DLS, dynamic light scattering; DTs, decision trees; ELS, electrophoretic light scattering; ENMs, engineered nanomaterials; FCS, fluorescence correlation spectroscopy; FlFFF, flow field flow fractionation; GA, genetic algorithm; HR-TEM, high-resolution transmission electron microscopy; HTS, high-throughput screening; IR, infrared spectroscopy; kNN, k nearest neighbours; LDA, linear discriminant analysis; LDH, lactate dehydrogenase; LGR, logistic regression; LR, linear regression; Mito, mitochondrial potential; MLR, multivariate (or multiple) linear regression; MO, metal oxide; MWCNTs, multiwalled carbon nanotubes; NBC, naive Bayes classifier; Nec., necrosis; NHECD, Nano Health and Environmental Commented Database; NMs, nanomaterials; NMR, nuclear magnetic resonance spectroscopy; NPs, nanoparticles; NPTA, NP tracking analysis; NTA, nanoparticle tracking analysis; OECD, Organization for Economic Cooperation and Development; PBPK, physiologically based pharmaco-kinetic; PCA, principal component analysis; PCR, principal component regression; PCS, photon correlation spectroscopy; PLS, partial least squares; (Q)SAR, (quantitative) structure–activity relationship; REACH, registration, evaluation, authorization, and restriction of chemicals; RED or Red, reducing equivalents; ROS, reactive oxygen species; SAED, selected-area electron diffraction; SAR, structure–activity relationship; SAXS, small-angle X-ray scattering; SEM, scanning electron microscopy; SLR, simple linear regression; STM, scanning tunnelling microscopy; SVM, support vector machine; TEM, transmission electron microscopy; UV–Vis, ultraviolet–visible spectrophotometry; XPS, X-ray photoelectron spectroscopy; XRD, X-ray diffraction.

* Corresponding author at: Institute of Particle Science and Engineering, School of Chemical and Process Engineering, University of Leeds, Leeds LS2 9JT, UK. Tel.: +44 113 3432427/86 20 87114000; fax: +44 1133432405.
E-mail addresses: x.z.wang@leeds.ac.uk, xuezhongwang@scut.edu.cn (X.Z. Wang).

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Introduction

With the increasing use of engineered nanomaterials (ENMs) for commercial purposes, human and environmental exposure to ENMs has become more likely. Recent studies have shown that the distinctive nano-characteristics of ENMs not only make them superior to traditional bulk materials, but also may affect their potential toxicity (Arora, Rajwade, & Paknikar, 2012), and present a challenge for the existing regulatory systems (Falkner & Jaspers, 2012). There is a growing body of literature on the potential adverse effects caused by exposure to different types of ENMs (Horie & Fujita, 2011; Jeng & Swanson, 2006; Karlsson, Gustafsson, Cronholm, & Möller, 2009; Magrez et al., 2006); however, there are still numerous unanswered questions that complicate the appropriate evaluation of toxicity of ENMs.

Toxicological evaluation of ENMs involves many difficulties, such as the availability of a large number and variety of ENMs, the difficulties in categorizing nanomaterials (NMs) for toxicological considerations, and the fact that even a slight variation in the characteristics of ENMs may also be reflected in the biological response, that dramatically increase the effort required to evaluate the potential adverse effects of ENMs. It seems that the most reasonable approach to obtain toxicity information for the numerous ENMs without testing every single one is to relate the biological activities of ENMs to their structural and compositional features.

The value of using in silico methods, such as the (quantitative) structure–activity relationship ((Q)SAR) approach, for toxicity prediction of ENMs was reinforced with European Union's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation that promotes the use of alternative toxicity assessment methods. As the name suggests, (Q)SAR is a computational technique that attempts to predict the biological activity of a compound by relating this activity to a set of structural and compositional properties, such as particle size, size distribution, particle shape, surface area, zeta potential, and crystal structure. The basic idea behind this approach is that different types of toxic effects (e.g., cytotoxic, genotoxic, and inflammatory effects) can be related to measurable or calculable physicochemical descriptors. A schematic representation of the nano-(Q)SAR workflow is given in Fig. 1.

This computational approach has many advantages in terms of cost, time-effectiveness, and ethical considerations. Although it has been satisfactorily used to predict the physicochemical properties of NMs, such as solubility (Gajewicz et al., 2012; Sivaraman, Srinivasan, Vasudeva Rao, & Natarajan, 2001; Toropov, Leszczynska, & Leszczynski, 2007; Toropov, Toropova, Benfenati, Leszczynska, & Leszczynski, 2009) and elasticity (Mohammadpour, Awang, & Abdullah, 2011; Toropov & Leszczynski, 2006), development of reliable (Q)SAR models becomes more complicated when the actual processes and the endpoints of interest are biologically complex.

Despite all the challenges and open questions, there have been some pioneering studies investigating the use of (Q)SAR models to predict the toxicity of ENMs (Epa et al., 2012; Fourches et al., 2010; Liu, Rallo, et al., 2013; Puzyn et al., 2011; Sayes & Ivanov, 2010; Wang et al., 2014; Zhang et al., 2012). We are now at the stage of obtaining the results of initial nano-(Q)SAR modelling attempts. Although the initial findings are encouraging, there is also a strong need to ensure the reliability of these models to gain the acceptance and confidence of potential end-users including regulatory bodies. We believe that once the main challenges related to extension of the conventional (Q)SAR approach to nanotoxicology have been overcome, nano-(Q)SAR models will be able to reach their full performance potential and their outcomes will be more valuable for predicting the toxicity of ENMs.

This review will focus on (Q)SAR analysis of ENMs for the purpose of toxicity modelling. The main aim of this paper is to give the reader a detailed understanding and present a critical analysis

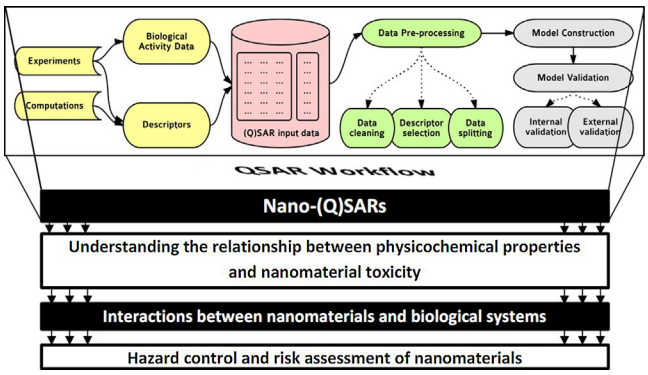

Fig. 1. (Q)SAR modelling of nanomaterial toxicity.