Perspectives in Science (2015) 3, 27–29

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/pisc

EXTENDED ABSTRACT

Development of computational models for the prediction of the toxicity of nanomaterials ☆

Andrea-Nicole Richarz[a,*], Judith C. Madden[a], Richard L. Marchese Robinson[a], Łukasz Lubiński[b], Elena Mokshina[c], Piotr Urbaszek[b], Victor E. Kuz'min[c], Tomasz Puzyn[b], Mark T.D. Cronin[a]

[a]*School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, England*
[b]*Laboratory of Environmental Chemometrics, Department of Chemistry, Sobieskiego 18, 80-952 Gdańsk, Poland*
[c]*Department of Molecular Structure and Chemoinformatics, A.V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine, 86 Lustdorfskaya Doroga, Odessa 65080, Ukraine*

Received 30 July 2014; accepted 31 August 2014
Available online 3 December 2014

Nanomaterials are defined as material consisting of particles, in an unbound state/as an aggregate/agglomerate, which for ≥50% of the particles in the number size distribution have a size between 1 and 100 nm, according to the European Commission Recommendation on the definition of nanomaterial (European Commission, 2011). They comprise different types of substances such as metal (e.g. Au, Ag, Fe) and metal oxide nanoparticles, as well as fullerenes, carbon nanotubes or quantum dots. Specific characteristics include the particle shape, surface area/charge/chemistry, state of dispersion, state of agglomeration, particle size distribution, solubility and porosity. These characteristics contribute to their properties, which has enabled the increasing use of nanomaterials in many fields of technology, a trend which is foreseen to considerably expand in the future.

The hazard and risk assessment of nanoparticles, however, is not yet developed adequately to ensure safety of their use. One reason is the lack of consistent, comparable and publicly accessible toxicity data. Efforts in nanotoxicity research are undertaken globally, however, they are disperse, as is the publication of data. Inconsistent data are due, for example, to poorly characterised nanomaterials or arbitrary experimental conditions. Moreover, the organisation and representation of the data is inconsistent.

Computational models for toxicity prediction are increasingly important to support risk assessment. They include the formation of categories of chemicals and subsequent read-across, i.e. prediction by interpolation of activities, as well as (quantitative) structure–activity relationships ((Q)SARs). The models are based on the understanding that chemical structure and thus the physico-chemical properties of a molecule are directly responsible for biological activity, and effects may be predicted from this relationship (see Figure 1). Their development relies on high quality experimental data and chemical structure information.

Therefore, in order to build a suitable foundation of toxicological data for the development of *in silico* models

☆This article is part of a special issue entitled "Tracing the elements – Diagnostic and medical importance of trace elements".

*Corresponding author.
E-mail address: a.richarz@ljmu.ac.uk (A.-N. Richarz).

http://dx.doi.org/10.1016/j.pisc.2014.11.015

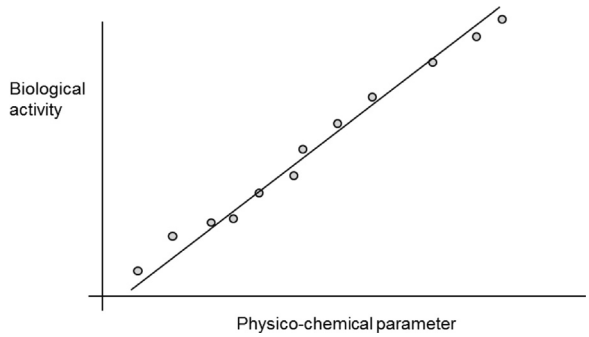

Figure 1 General scheme showing the correlation between a physico-chemical descriptor and biological activity/toxicity. The QSAR is built in the attempt to fit a line of best fit of the type $y=ax+c$, where a is the slope and c is the intercept. Usually, several descriptors are included.

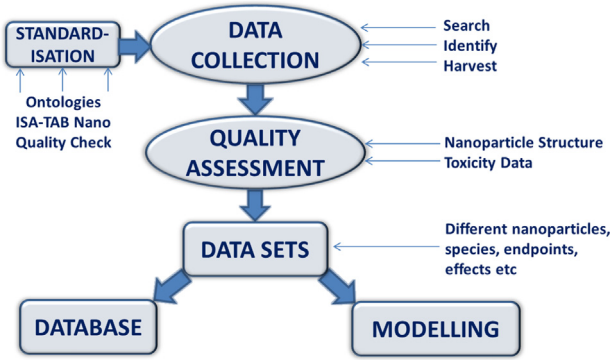

Figure 2 Workflow of data collection in view of the development of computational models for nanotoxicity prediction. Data collection taking into account standardisation efforts is followed by a step of quality assessment to obtain the final datasets, which can be integrated into overarching databases and feed into the development of *in silico* models predicting nanoparticle toxicity, both supporting the safety evaluation of nanomaterials.

for nanomaterial toxicity prediction, available data relating to the physical, chemical and toxicological properties of nanoparticles and their structures have been, and are being, collected from different sources and through a comprehensive literature review within the EU NanoPUZZLES and NanoBRIDGES projects.

Generally, a cross-institutional, cross-project, even global effort is needed to overcome the fragmentation of work to generate and evaluate toxicity data for nanoparticle risk assessment. Data collection needs to be coordinated in order to make valid conclusions on nanoparticle toxicity for risk assessment. Thus, this work is integrated in the ongoing research within the Nanosafety Modelling Cluster comprising five research projects developing *in silico* models for nanotoxicity, and generally within the NanoSafety Cluster for collaboration across EU projects (www.nanosafetycluster.eu) and the US-EU initiative for a dialogue between US and EU researchers (us-eu.org). A standardised data exchange format to share data and a unified ontology for data collection is needed to ensure a certain quality standard in terms of completeness, avoid duplication, allow a comparison between data from different sources and make it possible to integrate different datasets into one database. ISA-TAB-nano (Thomas et al., 2013) has been identified as a suitable standard format, defining a set of linked spreadsheet files (Investigation, Study, Assay and Material), with a pre-defined file structure and syntax for (meta)data.

Furthermore, the quality and suitability of the data for developing predictive toxicology models are being assessed. Evaluation criteria were developed to assess the relative quality of literature nanoparticle data sets and their usefulness for building computational models for nanoparticles based on Klimisch et al. (1997) criteria (Lubiński et al., 2013). The successful development of nano-QSAR models depends not only on the quality of experimental data, but also on the availability of sufficiently large data sets. The quality assessment approach is being extended in ongoing work.

The overall approach pursued in this project to collect data in view of the development of computational models for prediction of nanotoxicity is summarised in Figure 2.

The data compilation performed has allowed for the development of QSAR models for nanoparticle toxicity. As a first step, "nanodescriptors" have to be defined to reflect the specific intrinsic nanoparticle properties, e.g. stucture and electronic states resulting from quantum effects of the nanosize.

There are various types of methodologies to develop nano-QSAR models for the prediction of toxicity. One example of such a model for metal oxide nanoparticles is that developed by Puzyn et al. (2011). It describes the cytotoxicity of 17 metal oxide nanoparticles (ZnO, CuO, V_2O_3, Y_2O_3, Bi_2O_3, In_2O_3, Sb_2O_3, Al_2O_3, Fe_2O_3, SiO_2, ZrO_2, SnO_2, TiO_2, CoO, NiO, Cr_2O_3, La_2O_3) to the bacterium *E. coli*, based on experimental testing. The toxicity decreased in the order $Me^{2+} > Me^{3+} > Me^{4+}$. The model is based on the enthalpy of formation of a gaseous cation which has the same oxidation state as the metal ion in the oxide structure.

Another example is the model for genotoxicity of metal oxide nanoparticles developed by Golbamaki Bakhtyari et al. (2013). Chromosomal aberrations, oxidative DNA damage, DNA strand breaks, and mutations have been found in the literature to be caused by metal nanoparticles. The authors collected *in vivo* and *in vitro* data on nano metal oxide (Al_2O_3, NiO, Co_3O_4, CuO, Fe_2O_3, Fe_3O_4, TiO_2, ZnO, SiO_2, V_2O_3, V_2O_5, MnO_2) genotoxic effects and developed a nano-QSAR model for genotoxicity prediction, correlating genotoxicity to the electronegativity of oxygen, the core-core repulsion in eV – reflecting the binding energy between atoms in the cluster – and the enthalpy of detachment of metal cations from the cluster surface.

Regarding environmental effects, Mokshina et al. (2013) evaluated acute toxicity data for metal oxide nanoparticles towards the aquatic organisms *Daphnia magna* and *Paramecium multimicronucleatum*. They used descriptors based on the liquid-drop and surface-area-difference models applying statistical approaches such as random forest and neural network methods to develop models predicting the acute aquatic toxicity of metal oxide nanoparticles to these organisms.

Further *in silico* models for metal oxides in the literature include a model for predicting the oxidative stress potential of metal oxide nanoparticles (TiO_2, CuO, ZnO, FeO, Fe_2O_3, Fe_3O_4), using reactivity descriptors to characterise their energy structure (Burello and Worth, 2011). The oxidative stress potential is predicted through their ability to transfer electrons and perturb the overall intracellular redox state. Another nano-SAR model was based on high-throughput *in vitro* toxicity screening assay data for bronchial epithelial (BEAS-2B) cells and ranked the cytotoxicity of metal oxide nanoparticles (Al_2O_3, CeO_2, Co_3O_4, TiO_2, ZnO, CuO, SiO_2, Fe_3O_4, WO_3) based on the descriptors atomisation energy of the metal oxide, period of the nanoparticle metal, nanoparticle primary size, and nanoparticle volume fraction (Liu et al., 2011).

In conclusion, a global effort is needed to overcome the fragmentation of efforts to generate and evaluate toxicity data for the risk assessment of nanoparticles. The aim of the present work was to bridge the gaps between experimental and computational approaches and to compile data to create a dataset suitable for the development of *in silico* models for nanoparticle toxicity assessment. Nano-QSAR models can predict the toxicity for new nanoparticles and thus support the hazard and risk assessment of nanomaterials.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgements

Funding through the European Commission 7th Framework Programme NanoBRIDGES (FP7-PEOPLE-2011-IRSES, Grant agreement no. 295128) and NanoPUZZLES (FP7-NMP-2012-SMALL-6, Grant agreement no. 309837) projects is gratefully acknowledged.

References

Burello, E., Worth, A.P., 2011. A theoretical framework for predicting the oxidative stress potential of oxide nanoparticles. Nanotoxicology 5, 228–235.

European Commission, 2011. Commission Recommendation of 18 October 2011 on the definition of nanomaterial. Off. J. Eur. Union (L275/38–40).

Golbamaki Bakhtyari, N., Rasulev, B., Benfenati, E., Cronin, M., Leszczynski, J., 2013. Genotoxicity of metal oxide nanoparticles: a new predictive (Q)SAR model. Poster presentation at the Environmental Mutagenesis and Genomics Society (EMGS) 44th Annual Meeting, 22 September 2013. Monterey, California, USA.

Klimisch, H.J., Andreae, M., Tillmann, U., 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25, 1–5.

Liu, R., Rallo, R., George, S., Ji, Z., Nair, S., Nel, A.E., Cohen, Y., 2011. Classification NanoSAR development for cytotoxicity of metal oxide nanoparticles. Small 7, 1118–1126.

Lubiński, Ł., Urbaszek, P., Gajewicz, A., Cronin, M.T.D., Puzyn, T., Enoch, S.J., Madden, J.C., Leszczynska, D., Leszczynski, J., 2013. Evaluation criteria for the quality of published experimental data on nanomaterials and their usefulness for QSAR modelling. SAR QSAR Environ. Res. 24, 995–1008.

Mokshina, E., Richarz, A., Cronin, M., Kuz'min, V., 2013. NanoQSAR: metal oxides nanoparticles toxicity assessment. Poster Presentation at the MACC-5 – Methods and Applications of Computational Chemistry, Fifth Symposium, 4 July 2013. Kharkiv, Ukraine.

Puzyn, T., Rasulev, B., Gajewicz, A., Hu, X., Dasari, T.P., Michalkova, A., Hwang, H.M., Toropov, A., Leszczynska, D., Leszczynski, J., 2011. Using nano-QSAR to predict the cytotoxicity of metal oxide nanoparticles. Nat. Nanotechnol. 6, 175–178.

Thomas, D.G., Gaheen, S., Harper, S.L., Fritts, M., Klaessig, F., Hahn-Dantona, E., Paik, D., Pan, S., Stafford, G.A., Freund, E.T., Klemm, J.D., Baker, N.A., 2013. ISA-TAB-Nano: a specification for sharing nanomaterial research data in spreadsheet-based format. BMC Biotechnol. 132, 2.