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Computational nanotoxicology: a case study with silver and zinc nanomaterials

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Nanomaterials (NMs) have been the focus of basic and applied research for more than two decades. According to the updated consumer materials inventory, over 1800 commercial NMs have taken their place in the market, 42% of which are in health and wellness category[1]. The widespread use of NMs in health-related products made not only the human exposure to the (residues of) NMs inevitable but also the long-recognized concerns over their safety a priority. Despite this pressing need, more than 70% of commercially available nano-containing products do not include sufficient information about their physicochemical and/or toxicological characteristics. From the scientific perspective, the issue of under-reported (and in some cases, improperly-measured) raw data undermines the validity of the findings, obstructs the replication of analyses, complicates data integrity and subsequently, hinders the overall advancement of the nano-related fields[2]. As an attempt to collect and organize data records of NMs and their safety, a large number of databases have emerged in recent years. However, direct access to these databases is usually restricted to specific people or projects. All of these difficulties resulted in substantial knowledge gaps in fate, exposure and toxicity of NMs and led to a growing interest among regulatory authorities in the use of computational approaches to fill gaps in nano-safety knowledge.

The aim of this study is to use the computational power to complement and extend existing knowledge on NM safety and to maximize the use of accumulated nanotoxicity data. Our overarching goal is to support safe(r)-by-design concept which requires an early integration of the safety component into the design plan of NMs by means of structural manipulation strategies. In particular, we present an exploratory meta-analysis of 43 studies containing 78 individual nanomaterials and 1579 toxicity estimates. After a set of data pre-processing steps, various data visualization tools (e.g., circular bar plots, heatmaps and parallel co-ordinate plots) were employed to gain insights into the vast amount of nanotoxicity data collected. As a next step, a set of supervised (e.g., decision tree analysis and regression-based methods) and non-supervised (e.g., principal component analysis, k-means clustering, hierarchical clustering) learning algorithms were employed to relate experimentally-measured (e.g., particle size, shape, coating, surface charge etc.) and theoretically-calculated (e.g., quantum-mechanical calculations) descriptors to both toxicological endpoints (e.g., cytotoxicity) and test parameters (e.g., cell line, cell morphology, tissue-source, NM concentration, exposure duration etc.). Our findings suggest that the typical approach of toxicity evaluation which is solely based on the core of materials should be expanded for metal-core NMs as different dimensions of physicochemical features and experimental procedures directly affect their *in vitro* toxicity.

References

[1] Vance M.E. *et al*., *Nanotechnology in the real world: Redeveloping the nanomaterial consumer products inventory. Beilstein journal of nanotechnology*, 2015. 6(1): p. 1769–1780.
[2] Oksel Karakus C., Bilgi E., and Winkler D.A., *Biomedical nanomaterials: applications, toxicological concerns, and regulatory needs*. *Nanotoxicology*, 2020: p. 1–21.

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Fipronil and tebuconazole and their respective metabolites fipronil sulfone and hydroxytebuconazole are potential ecotox pesticides to fish and crustaceans: prediction using in silico models

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In silico tools and models developed for toxicity assessments can be implemented in tiered testing approaches, such as integrated testing strategies (ITS), integrated approaches to testing and assessment (IATA), and adverse outcome pathways (AOP) frameworks, balancing transparency, mechanistic interpretability, and predictivity. In this regard, here we used Pred-Ecotox tool in the iS-Tox® Platform (Altox Ltda, funded by FAPESP process number 2016/08322-5) to evaluate and predict the toxicity of 2 pesticides and their main metabolites, fipronil and its active metabolite fipronil sulfone, and tebuconazole and its metabolite hydroxytebuconazole). The Pred-Ecotox is a computational tool for the prediction of aquatic acute toxicity of chemicals for fish (96- hours lethal concentration, LC_{50}) and Daphnia magna (48-hours lethal concentration, LC_{50}) by mode of action (MOA) classification, statistical and machine learning-models, validated following the Organization for Economic Co-operation and Development (OECD) Principles for the Validation for Regulatory Purposes of (Q)SAR Models. The pesticides studied here are used in grain crops such as rice, beans, corn, soybeans and wheat, among others in order to inhibit pests growth and, therefore, increase agricultural production. These pesticides are between the most commonly used pesticides in Brazil and the assessment of its toxicity to non-target organisms is extremely important. In this way, the in silico prediction showed that both pesticides and their respectively metabolite are toxic to fish with an LC_{50} of 0.1 mg/L (0.3 μM), 0.1 mg/L (0.2 μM), 6.1 mg/L (19.9 μM) and 11 mg/L (33.9 μM), for fipronil, fipronil sulfone, tebuconazole and hidroxitebuconazole, respectively. Regarding their Mode of Action (MoA) while fipronil most likely act as a neurotoxicant, the others will probably induce narcosis. While for Daphnia magna the LC_{50} found were 0.2 mg/L (0.4 μM), 0.07 mg/L (0.2 μM), 8.1 mg/L (26.2 μM) and 12 mg/L (37 μM), for fipronil, fipronil sulfone, tebuconazole and hidroxitebuconazole, respectively. Thus the results indicate that further tests are needed to be done in order to better evaluate and understand their toxic potential to non-target organisms.

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