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Toxicity of contaminants of emerging concern to *Dugesia japonica*: QSTR modeling and toxicity relationship with *Daphnia magna*

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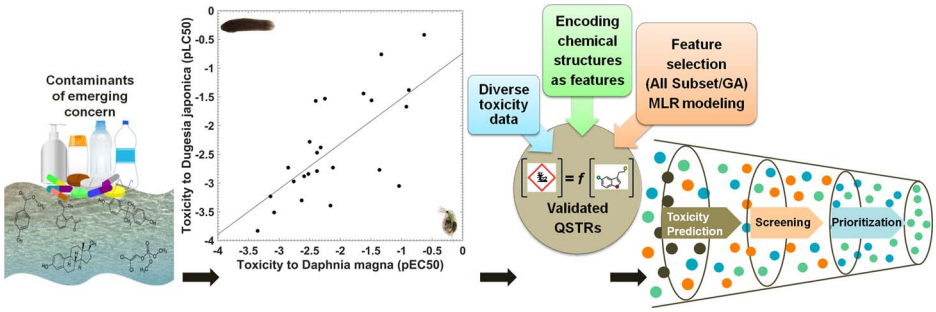
GRAPHICAL ABSTRACT



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ABSTRACT

Freshwater planarian *Dugesia japonica* has a critical ecological importance owing to its unique properties. This study presents for the first time an *in silico* approach to determine *a priori* the acute toxicity of contaminants of emerging concern towards *D. japonica*. Quantitative structure-toxicity/toxicity-toxicity relationship (QSTR/QTTR) models provided here allow producing reliable information using the existing data, thus, reducing the demand of *in vivo* and *in vitro* experiments, and contributing to the need for a more holistic approach to environmental safety assessment. Both models are promising for being notably simple and robust, meeting rigorous validation metrics and the OECD criteria. The QTTR model based on the available *Daphnia magna* data might also contribute to the US EPA Interspecies Correlation Estimation web application. Moreover, the proposed models were applied on hundreds of environmentally significant chemicals lacking experimental *D. japonica* toxicity data and predicted toxicity values were reported for the first time. The models presented here can be used as potential tools in toxicity assessment, screening and prioritization of chemicals and development of risk management measures in a scientific and regulatory frame.

1. Introduction

Chemicals are indispensable part of life with substantial benefits. However, some of them can pose environmental risk towards water and aquatic biota. Consequently, environmental monitoring and risk assessment are crucial for ensuring their safe use. Indeed, existing

Abbreviations: AD, applicability domain; CEC, contaminants of emerging concern; CEFIC, European Chemical Industry Council; EDCs, endocrine disrupting chemicals; GA, genetic algorithm; HPV, high production volume according to OECD; ICE, interspecies correlation estimation; log K_{ow}, *n*-octanol/water partition coefficient; MLR, multiple linear regression; MOA, mode of action; OECD, Organization for Economic Co-Operation and Development; OLS, ordinary least squares; PPCPs, pharmaceuticals and personal care products; REACH, Regulation for the Registration, Evaluation, Authorization and Restriction of Chemicals; QSAR, quantitative structure-activity relationship; QSTR, quantitative structure-toxicity relationship; QTTR, quantitative toxicity-toxicity relationship; TSR, training set range; US EPA, the United States Environmental Protection Agency

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chemicals are extensively regulated regarding exposure and hazard profiles [1]. Contrarily, identification, safety assessment, and prioritization of the contaminants of emerging concern (CEC) remain vague [2]. CEC, such as pharmaceuticals and personal care products (PPCPs), pesticides, and endocrine disrupting chemicals (EDCs), are environmentally challenging for their ubiquitous, yet, low detectable levels, potential toxicity, and persistent, bioaccumulative and biomagnifying properties. Importantly, the environmental impacts of the CEC have not been adequately explored and information on spatial and toxicological assessment is required, particularly for key geographical regions and representative species [2].

Asia is the main contributor to the global chemical burden with production volumes outpacing other regions. According to a recent report by the CEFIC (European Chemical Industry Council), chemical production in Asia equals that of the Europe and America [3].

Dugesia japonica is an aquatic invertebrate widely distributed in freshwater environments in East Asia acting as omnivore and detritivore, thus, has a critical ecological importance [4]. *D. japonica* is best known for its sensitivity to low concentrations of chemicals, including certain CEC [5–10], and a remarkable regeneration capacity [11]. Despite being a simple organism, it has biochemical and physiological properties comparable to higher vertebrates: a basal evolutionary position with well-organized central nervous system and a brain homologous to mammalian [12]. Recently, it becomes prominent as an ideal model for environmental toxicology as well as developmental neurotoxicology and regeneration studies due to its unique properties [5–10,13].

Nevertheless, before being accepted as a surrogate model, information on acute toxicity towards as many chemicals as possible is required, particularly for the high production volume (HPV) chemicals [14]. Moreover, acute toxicity data is a prerequisite for determining other toxicity endpoints. Furthermore, given the need for a more holistic approach to regulatory environmental safety assessment, results of more diverse species (besides *Daphnia magna*, *i.e.* the most studied aquatic invertebrate) are appreciated [1].

In consideration to ethical issues; animal welfare and sustainability, *in silico* models, such as quantitative structure-activity/toxicity relationship (QSAR/QSTR), are of great importance for predicting environmental toxicities. QSTRs developed and validated in accordance with the Organization for Economic Co-Operation and Development (OECD) principles [15] are well recognized under the Regulation for the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) to provide reliable toxicity data without the need for *in vivo* and *in vitro* experiments [16]. Correspondingly, they can be applied in screening and prioritization of chemicals regarding potential hazard. In a recent perspective, Cronin assessed the current status and future needs of QSTRs in environmental toxicity predictions as well as their regulatory uses [17].

Likewise, quantitative toxicity-toxicity relationship (QTTR) models generated with interspecies toxicity data are promising “green” alternatives to the evaluation of chemicals missing experimental data. Based on extrapolation, from the results of “tested” to “untested”, such models can allow producing information using the existing data on surrogate species, such as *Daphnia magna*, while reducing *in vivo* and *in vitro* experiments [18]. A comprehensive review of earlier efforts towards *Daphnia*-fish QTTR modeling [19–21], as well as the web-based Interspecies Correlation Estimation (ICE) application [22,23] of the United States Environmental Protection Agency (US EPA) was provided by Kar et al. [24]. Although there are studies published on different aquatic species, interestingly, no report on the relationship between toxicity and hydrophobicity (*n*-octanol/water partition coefficient (log K_{ow})), QSTR and QTTR modeling of *D. japonica* has been published yet.

In this study, we aimed at presenting an *in silico* approach to determine *a priori* the acute toxicity of CEC to *D. japonica* to fill the current data gap. Another objective was to evaluate the use of *D. japonica* as a model species; therefore, we examined the interspecies toxicity relationship with *D. magna*. To this end, we developed QSTR and QTTR models in line with the OECD principles [15] using toxicity and log K_{ow} data of CEC from different chemical classes. We, then, used the generated models to predict the toxicity of a large diverse group of environmentally important chemicals with no experimental *D. japonica* toxicity data. To the best of our knowledge, the present study is the first report on QSTR and QTTR modeling of CEC to freshwater planarian *D. japonica*.

2. Materials and methods

2.1. Experimental data

This study is based on the acute toxicity of CEC towards the freshwater planarian *D. japonica*. The experimental data for 55 CEC from different chemical classes, such as PPCPs, EDCs including synthetic and natural hormones, insecticides, pesticides, and nonionic surfactants, were compiled from the literature [5–10]. The reported 48-h concentration causing 50% mortality (LC_{50}) were converted into micromolar (μM) unit for environmental relevance [2] and transformed to the negative logarithm scale (pLC_{50}) for modeling purpose. The compiled toxicity data appear to follow a normal distribution (Kurtosis = 0.16, Skewness = −0.56, Fig. S1) and range from −5.14 to −0.42. Of the 55 chemicals in the data set, 24% were designated as HPV chemicals (Table S1).

2.2. Chemical structures and molecular descriptors

Chemical structures were drawn manually and the conformer with the lowest energy was geometry optimized using the semi-empirical Parameterized Model 6 (PM6) [25] method implemented in the software SPARTAN 10 [26]. PM6 was rationally preferred based on a recent approach to the selection of geometry optimization method for QSAR model development [27]. Further vibrational analysis on each of the optimized geometry allowed verifying the absence of imaginary frequency and evidenced that the structure is an accurate saddle point rather than a transition state.

For QSTR modeling, quantum chemical descriptors, such as dipole moment, the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), and gas-phase energy (E), were calculated. The logarithms of the *n*-octanol/water partition coefficient (log K_{ow}) were retrieved from Danish (Q)SAR Database [28]. Preferably experimental, otherwise estimated values of log K_{ow} were used (Table S1). The software DRAGON 6 [29] was used to generate a great variety of theoretical molecular descriptors.

Daphnia magna toxicity data comprising the concentration causing 50% immobilization (48-h EC_{50}) were collected from the literature [30,31], converted into μM unit for relevance, transformed to the negative logarithm scale (pEC_{50}), and used as the independent variable for QTTR modeling. Of the 55 chemicals in the original data set, 26 chemicals have a reported experimental pEC_{50} (Table S1).

2.3. Modeling and validation

Data set preparation, training/test set division, descriptor selection for QSTR and model development were carried out using the software QSARINS 2.2.1 [32,33]. Prior to QSTR modeling, constant (> 80%) and highly intercorrelated descriptors (pair-wise correlations among all pairs of descriptors > 95%) were filtered due to statistical insignificance. For QTTR modeling, experimental *D. magna* data (Table S1) was used as the only descriptor.

For QSTR modeling, two different methods at varying ratios were employed for training set (~75–85%, to develop models) and test set (~15–25%, to validate the developed models) division to avoid a possible bias that might have arisen if a single approach was applied: 1) by ordered response and 2) by ordering the molecules based on the