Can Toxicity for Different Species be Correlated?
The Concept and Emerging Applications of Interspecies Quantitative Structure-Toxicity Relationship (i-QSTR) Modeling

Supratik Kar, Jackson State University, Jackson, MS, USA
Rudra Narayan Das, Jadavpur University, Kolkata, India
Kunal Roy, Jadavpur University, Kolkata, India
Jerzy Leszczynski, Jackson State University, MS, USA

ABSTRACT

Experimental evaluation of the toxicity of a compound is an expensive practice, and it requires sacrifice of a large number of animals. As a consequence, in silico techniques for predictive toxicology are taking the central stage of attention of the scientific community. Interspecies quantitative structure-toxicity relationship (i-QSTR) modeling provides a tool for estimation of contaminant’s sensitivity with known levels of uncertainty for a diverse pool of species. It is capable of extrapolating data for one toxicity endpoint to another toxicity endpoint when the data for the second species are unavailable. The emerging i-QSTR approach can overcome the cost of multiple toxicity tests, improve the understanding of the mechanism of toxic action (MOA) of chemicals for different organisms and endpoints and is very useful in order to fill the data gaps where toxicity value for a particular compound is absent for a specific endpoint.

KEYWORDS
Extrapolation, i-QSTR, Interspecies Correlation, Mode of Action, QSAR, REACH, Toxicity, US EPA

1. CHEMICAL TOXICITY

Chemical toxicity refers to the adverse effects of chemicals on the ecosystem, humans or other living systems in the environment with many dimensions (Colton, 2002). Chemicals are prospective poisons as they can cause injury or death due to their excessive exposure at various concentrations. A chemical may cause irreversible change in homeostasis or increased susceptibility to other chemical or biological stress, functional or anatomical damage, including infectious diseases. Even prolonged and continuous exposure of any so called ‘safe’ chemical may show serious toxicity after years. The continuous increase of the world’s population, combined with industrial progress, has made a significant impact of chemicals (including pharmaceuticals) on the world’s ecosystems and living bodies. As human society depends on so many diverse types and classes of chemicals, it is very imperative to understand the way in which the chemicals interact with the living system and the ecosystem. The magnitude of eco-toxicity of hazardous chemicals, pesticides, agrochemicals, synthetic and semi-synthetic chemicals, dyes, pollutants, pharmaceuticals and food products, is a matter of...
great concern considering that though huge numbers of compounds are in commercial use, while relatively few of these have been subjected to sufficient evaluation for their hazardous properties to the environment (Cronin et al., 2004; Kar and Roy, 2010a).

Chemicals are commonly characterized into broad classes based on modes of action such as inert chemicals (non-polar narcosis), less-inert chemicals (polar narcosis), reactive chemicals (free-radical formation, weak acid respiratory uncoupling, as well as electrophilic reactions) and specifically acting chemicals (Schultz et al., 2006). The narcosis mode of action is related with reversibly altered structure and function of the cell membranes from non-specific non-covalent interactions with cell membranes. The polar narcotic chemicals are generally more toxic than chemicals which act through non-polar (baseline) toxicity. Reactive chemicals exhibit toxicity in excess of that predicted by either non-polar or polar narcosis (Verhaar et al., 1992). The term “reactive” encompasses a wide spectrum of competing electrophilic and nucleophilic, redox, and free-radical processes (Enoch et al. 2008). The categorization of chemicals according to mechanism of action is a very tedious and complex task (Netzeva et al., 2008). For example, anilines are considered to be narcotics to fish but are more toxic to *Daphnia magna* (Netzeva et al., 2008). Therefore, the underlying mode of action may completely depend on the exposed species (Jager et al., 2007). The mechanism of (toxic) action (MOA) of the chemicals under investigations should be taken into account during analysis of chemical toxicity for a better understanding. It may be noted here that there may be significant differences between the mode of action and the mechanism of action of a chemical with respect to a specific response. The former is defined in terms of various incompletely characterized biochemical, physiological, or behavioral responses leading to the behavioral changes upon exposure to chemicals, while mechanism of action refers to explicit and detailed understanding of all steps reflecting the necessary sequence of events involved in the manifestation of toxicity of chemicals (Borgert et al., 2004; ECETOC, 2007). However, in this review, we have used the abbreviation MOA for both the terms.

The modern growth of chemical industry has been a concerning issue as it has led to an increasing overall toxicity to the living ecosystem in a multidimensional way. The occurrence of an enormous number of various chemicals in the environment necessitates the assessment of their detrimental effects. The large-scale production of chemicals has increased from merely 1 million tons to 400 million tons in the last six decades. Around 100000 different chemicals are registered in the European market of which 10% are marketed in volumes of more than 10 tons, and a further 20% are marketed at 1-10 tons every year (European Union, 2001). Testing and assessment of their risks to human health and the environment are required before marketing in volumes above 10 kg/year according to the European Commission Directive 67/548. In case of larger volumes, more in depth testing and focusing on long-term and chronic effects are essential. In contrast, more than 99% of the total volumes of all substances in the market are not subjected to the same testing requirements. Most of them have never been tested at all (European Commission, Directive 2006/121/EC).

In December 2006, the European Community (EC) issued a new regulation REACH concerning the Registration, Evaluation, Authorization and restriction of Chemicals which brought about a rebellion in the chemical regulatory world (European Commission, Directive 2006/121/EC). The main aim of REACH is: ‘to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation’ (European Commission, Directive 2006/121/EC). REACH recommends important regulatory guidelines for accountable, sustainable, and green use of chemicals following the principle ‘No data – no market’ and is tracked through the authorization and restriction processes in place for the most hazardous substances. Any chemical which is produced or imported in Europe in a quantity above 1 ton per year has to be registered to the European Chemicals Agency (ECHA) by submitting a record describing physicochemical, biological, and toxicological properties. The registration requirements are stricter for carcinogens, mutagens, and reproductive toxicants (CMRs) which are highly toxic to the aquatic organisms, and as well as for large production volume chemicals. In the other part of the
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