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Aquatic ecotoxicological models and their applicability in Arctic regions

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ABSTRACT

Dose-response modeling is one of the most important steps of ecological risk assessment. It requires concentration-effects relationships for the species under consideration. There are very limited studies and experimental data available for the Arctic aquatic species. Lack of toxicity data hinders obtaining dose-response relationships for lethal (LC50 values), sub-lethal and carcinogenic effects. Gaps in toxicity data could be filled using a variety of in-silico ecotoxicological methods. This paper reviews the suitability of such methods for the Arctic scenario. Mechanistic approaches like toxicokinetic and toxicodynamic analysis are found to be better suited for interspecies extrapolation than statistical methods, such as Quantitative Structure-Activity Relationships/Quantitative Structure Activity-Activity Relationship, ICE, and other empirical models, such as Haber's law and Ostwald's equation. A novel approach is proposed where the effects of the toxicant exposure are quantified based on the probability of cellular damage and metabolites interactions. This approach recommends modeling cellular damage using a toxicodynamic model and physiology or metabolites interactions using a toxicokinetic model. Together, these models provide more reliable estimates of toxicity in the Arctic aquatic species, which will assist in conducting ecological risk assessment of Arctic environment.

Arctic regions are of great interest to the petroleum industry due to depleting energy resources in other regions (Camus et al., 2003; Hoop et al., 2011). Receding seasonal sea ice has increased access to remote areas in the Arctic region, along with associated human activity, such as hydrocarbon exploration, shipping, and tourism (Chapman and Riddle, 2003; Gardiner et al., 2013; Hoop et al., 2011). The Arctic ecosystem is a fragile ecosystem (Hansen et al., 2013; Chapman and Riddle, 2005), vulnerable to impacts from anthropogenic activities and climate change (Hansen et al., 2014). Therefore, the need to understand the impacts to the aquatic animals in case of oil spills, and the capability to conduct environmental risk assessment (ERA) of the aquatic animals are imperative. Two of the steps in the ERA framework involve i) determining the concentration exposed and ii) obtaining the toxicity data (dose-response curves) for the species of concern and, subsequently, for measurement endpoints, such as No Observed Effects Level (NOEL), to determine the species' sensitivity to the exposure (Fahd et al., 2014). The results from these steps in ERA are used to determine the survivability in populations of organisms and their recolonization potential. Such exposure concentrations and toxicity data are obtained by developing the ecotoxicological modeling or conducting toxicity experiments with 'toxicant of concern' and target organisms. To experimentally define toxicity value for new chemicals and the large number of Arctic aquatic animals is costly and involves techniques that raise ethical issues. Instead, the European Chemicals Legislation, Registration, Evaluation and Authorization of Chemicals (REACH) recommends in-silico ecotoxicological methods to be utilized to generate missing toxicity data (Brinkmann et al., 2014; Patlewicz and Fitzpatrick, 2016). Apart from the EU commission, the National Academy of Science and US EPA have proposed a shift from whole organism toxicology to a pathway perturbation based paradigm for toxicity testing and subsequent environmental risk assessment studies (Euling, 2013).

Ecotoxicological modeling refers to the study of the chemical interactions in the target tissues of an individual organism and the effects of the toxicant on life expectancy and other reversible and/or irreversible effects in an organism and, subsequently, the ecosystem (Escher, 2001). Ecotoxicology modeling faces two main challenges: i) the large number of species that can come in contact with the target chemical; and ii) the large number and variety of chemicals that can affect a target organism (Verhaar et al., 1997). The latter is further complicated by the presence of multiple chemicals acting at one time. Owing to the descriptive nature (testing and experimenting) of earlier toxicology studies, large data sets of the dose-response for specific chemicals are available. Databases for ecotoxicity information include

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ECETOC Aquatic Toxicity (EAT) database and ECOTOXicology (ECOTOX) by US EPA, and TOXicology data NETwork (TOXNET) by the US National Library of Medicine. In spite of the availability of large aquatic animal toxicity literature, there is a paucity of toxicity data for Arctic marine species (Jensen, 2011; Chapman and Riddle, 2003). Limited experimental work on ecotoxicological effects (Chapman, 1993; Chapman and McPherson, 1993; Lenihan and Oliver, 1995; Ling et al., 1998; King and Riddle, 2001; Liess et al., 2001; Olsen et al., 2011; Jensen, 2011) have been conducted on the Arctic aquatic animals.

The current practice of using temperate marine species toxicity data as a representation of the Arctic marine species toxicity data is much debated (Olsen et al., 2011; Olsen et al., 2007). Studies have shown that isomorphic animals in temperate and Arctic regions differ significantly in physiology at some or all stages of the life cycle (Sobek et al., 2010; Hallanger et al., 2011; Olsen et al., 2007; Olsen et al., 2011; Veltman et al., 2014). The physiological factors, such as lipid content and rate of metabolism, in aquatic animals alter the toxicity effects in the organism (Gewurtz et al., 2006; Ashauer et al., 2011a, 2011b; Gergs et al., 2015). Factors such as Voltinism and fecundity also impact the toxic effects in individual organisms (Galic et al., 2014) and Arctic aquatic species have shorter breeding periods than their temperate counterparts. Environmental and geophysical factors, such as presence of sea ice, sediments, and prolonged exposure to UV light, also affects aquatic species toxicity. The sea ice is intertwined with behavioral and feeding habits of many aquatic species, thus playing a major factor in bioaccumulation of contaminants. Bioaccumulation of xenobiotics leads to bio-distribution, biotransformation and eventually a possible toxic scenario.

Sparsely available toxicity data for Arctic aquatic organisms' risk assessment and the unsuitability of most temperate species data to their Arctic counterparts mandates the development of a novel mechanistic model that circumvents the need for animal testing. The proposed mechanistic model should predict the effects in the animals exposed to toxic pollutants considering their ambient environment, behavior and physiology along with using available temperate and Arctic aquatic animal toxicity data and data of known toxicity mechanisms in surrogate organisms.

A review of the current in-silico ecotoxicological methods is presented in this paper and their applicability to the Arctic aquatic environment is also discussed. The study details different approaches described in the literature for the estimation of aquatic toxicity from chemicals of concern. An approach that best suits the effect assessment in the Arctic aquatic animals is identified as using physiology based toxicokinetic (TK) models and molecular damage based toxicodynamic (TD) models. The proposed mechanistic molecular damage based TD model is based on metabolomics and metabolic pathway network. Metabolomics, a branch in ecotoxicogenomics, is the study of the molecule metabolic intermediates and products from the processes of metabolism and excretion. Metabolic pathway network is the illustrations of the interactions of the exposed toxicant to induced enzymatic activity and possible intermediate metabolites and final soluble metabolites before final excretion. Ecotoxicogenomics is defined as the study of the set of the genes or protein expression in an ecological organism to provide insight into its toxicity (Kim et al., 2015). Molecular mechanism in effects is to be quantified in terms of the enzymatic activity (Haber et al., 2001). To accomplish such a task, a great deal of study is required for each of the target species. However, if such a study is available, a molecular mechanism based effect assessment modeling will circumvent the need for further experimental work and produce data resulting from a mechanistic understanding, as opposed to a statistical (regression) modeling, thus answering the Arctic challenge posed above.

Toxicology studies were initially restricted to the field of drug effectiveness studies and pharmacology, to cope with the changing/new drugs and their use in humans. The focus of researchers in toxicology then shifted from pharmacology to physiology based pesticide studies (Raies and Bajic, 2016). The assessment endpoints in pharmacology emphasized on sublethal effects, while the endpoints in ecotoxicology focused on lethal (survival) and, to some extent, sublethal endpoints (larval growth and development, reproduction and recolonization) (Ashauer et al., 2011b). Ecotoxicology in pesticide studies dealt with biocidal actions in target organisms and residual toxic effects in non-target organisms. Ecotoxicological models fall under two categories, namely, experimental models and in-silico (computational) models. Most of the early advances in the science of ecotoxicology have been descriptive in nature (i.e., based on experimental works). This led to accumulation of empirical effects data sets of specific pollutants on selected species. Using in-silico methods, rather than only experimental tests, enables computer-based tools to estimate toxicity end-points and dose response curves. The in-silico methods can further be classified into two groups: statistical and physiology based methods. The rhetoric of the ecotoxicological models has shifted from experimental methods to in-silico methods, such as the Quantitative Structure-Activity Relationships (QSAR) that could determine the relevant concentration endpoints of various chemicals. Quantitative Structure Activity-Activity Relationship (QSAAR) models were developed to assess chemical toxicity endpoints and also to extrapolate species to species toxicity endpoints. Subsequently, mechanism based methods were developed to determine the toxicity endpoints. The mechanism based ecotoxicological methods are developed in two tiers. The first tier (toxicokinetic step) estimates the internal concentration of the contaminant. The second tier (toxicodynamic step) determines the effects from the exposure. Fig. 1 presents an overview of various in-silico methods and statistical methods used in the field of aquatic toxicology to determine toxicity endpoints. The arrows in the Fig. 1 do not show dependency, but rather the general progression of the research in the ecotoxicological field.

One of the first non-testing models to determine the acute aquatic toxicity adopted the QSAR and read across (RA) models. The QSARs are computational models used to fill data gaps for chemical endpoints using regression analysis of the known toxicity endpoints of chemicals with similar chemical structure as that of the toxicant (OECD, 2004; Netzeva et al., 2007). Hoff et al. (2010) and Patlewicz and Fitzpatrick (2016) presented a detailed description of the QSAR methodology. The first step in QSAR methodology is grouping of the chemicals based on molecular structure; the understanding is that molecules with similar structure have similar toxicity endpoints. Gathered data is processed to achieve normality and the processed data is divided into a training set and a testing set to evaluate internal and external predictive performance, respectively. Grouping of chemicals is an important step in all the statistical approaches, as will be discussed in latter methods. Studies have also grouped chemicals based on their modes of action (MOA), along with grouping based on common chemical functional group (Nendza et al., 2014; Netzeva et al., 2007). Netzeva et al. (2007) argued that combining the data based on modes of action along with chemical class would give a better understanding of the interaction between the chemical and the target organism. The four MOAs associated with different chemicals are described by Verhaar et al. (1992) and are based on selective reaction of the chemical when exposed to a target organism. The QSARs can be a linear relationship between the toxicity and descriptor, or a quadratic relationship. For detailed understanding and illustration of the QSAR model refer Dimitriv et al. (2000), Austin et al. (2015), Barron et al. (1990) and Furuhuma et al. (2015). A couple of the descriptors used in the QSARs are membrane-water partition coefficient (K_{mw}), and octonal-water partition coefficient (K_{ow}).

The QSAR method is used to predict the toxicity end point of a chemical to any target organism when the chemical adheres to the assumed toxicity MOA. However, QSARs methodology is modified to predict interspecies toxicity data by introducing additional descriptors and thus the methodology is termed quantitative structure activity-activity relationship (QSAAR). Variables, such as molecular weight, certain indicator descriptors, log K_{ow}, and pH, can be taken into account