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PUBLICLY AVAILABLE COMPUTATIONAL TOXICOLOGY TOOLS FOR EVALUATION OF (ECO)TOXICITY OF CHEMICALS– A CONCISE SUMMARY

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Abstract: To address the concerns of high costs, long test durations, and animal rights issues there has been a paradigm shift in the adoption of non-animal methods for assessing environmental and human health risks due to chemical exposures. Computational methods harness the power of fast processors, high-speed internet, cloud environment, statistical/ machine learning algorithms, and curated toxicological databases to fulfill this need. This short paper presents a concise summary of publicly available computational toxicology methods and databases. Global regulatory agencies are using these methods and databases to support their decision-making and we are confident that these methods would help India's regulatory bodies in assessing risks and in making appropriate regulatory decisions on chemicals in consumer products.

Keywords - chemical, computational, environmental, toxicity, regulatory

I. INTRODUCTION

Globally, there is a paradigm shift towards promoting humane, cost-effective, and rapid screening methods to assess (eco)toxicology typically of organic chemicals used in consumer products. Computational toxicology tools based on the concept of Quantitative Structure-Activity Relationship (QSAR) represent such a method. These methods have been reported to be reliable, user-friendly, and useful as decision-support systems for regulatory bodies. QSAR methods gained importance in regulatory risk assessments since the publication of the Organization for Economic Co-operation and Development QSAR Validation Principles that laid out the five guiding principles (OECD, 2014). According to these a predictive model would be considered valid if it meets the five criteria, a defined endpoint, unambiguous algorithm, defined domain of applicability, appropriate measures of goodness-of–fit, robustness and predictivity, and a mechanistic interpretation if possible.

II. COMPUTATIONAL TOXICOLOGY METHODS

Several computational toxicology methods are used in (eco)toxicology. Whereas some are built on traditional statistical approaches and machine learning algorithms others use the concept of read across. These methods can be applied to assess environmental properties such as octanol-water partition coefficient, vapour pressure, water solubility, biodegradability, ecotoxicity such as acute toxicity to aquatic flora and fauna, and human health relevant toxicity for example, genotoxicity, skin sensitization and potential to cause endocrine disruption. Computational methods in (eco)toxicology research and chemical risk assessments are principally based on the concepts of structure-activity relationships and read-across. Models based on the concept of (Q)SAR generally use mathematical algorithms to predict the toxicity of chemicals based on their molecular structures. Some of the publicly available tools include the EPA's EpiSuite (US EPA, 2019) and VEGA (Benfenati et al., 2013). On the other hand, those that are based on concept of read-across allow the toxicity of a new chemical to be estimated from the known toxicity of a similar chemical. One of the commonly used tools to perform read-across assessments is the OECD QSAR Toolbox (Dimitrov et al., 2016). The US EPA ECOTOX knowledgebase (Olker et al., 2022) is a publicly available online database that contains information on the environmental toxicity of chemical substances.

EpiSuite: It is a suite of physical/chemical property and environmental fate estimation programs developed by EPA's and Syracuse Research Corp. It uses a single input to estimate parameters including octanol water partition coefficient, Henry's law constant, biodegradability, water solubility and bioconcentration factor.

VEGA hub: It is a web-based platform for quantitative structure-activity relationship (QSAR) modeling developed by the VEGA (Virtual models for the Evaluation of Global Actions) project. It provides access to a range of QSAR models, which have been developed and validated using a large database of experimental data. These models can be used to predict a range of toxicological endpoints, such as acute toxicity, skin sensitization, genotoxicity, endocrine disruption among others. It is widely used in industry, academia, and regulatory agencies for chemical safety assessment.

QSAR Toolbox: This a software platform developed by the Organization for Economic Co-operation and Development (OECD) for the prediction of the properties and hazards of chemicals using quantitative structure-activity relationship (QSAR) models. It features variety of (Q)SAR models that can predict a wide range of toxicological and physicochemical properties of chemicals, including environmental fate and effects, human health effects, and physicochemical properties. Using molecular structure, the tools contained in the Toolbox can compute potential mechanisms of action and potential adverse effects. It also integrates mammalian metabolism simulators to predict likely metabolites. QSAR Toolbox is a very sophisticated read-across tool for filling (eco)toxicological data gaps on chemicals. Read-across is a method where a property (e.g. toxicity, physicochemical) of a chemical predicted using similar property of a structurally similar chemical (analogue) or a group of similar chemicals (chemical category). Read-across is therefore, a valuable tool in chemical risk assessment that can help to reduce the need for animal testing and promote more efficient and cost-effective chemical testing. However, it should be used with caution, and in conjunction with other methods and data sources, to ensure the accuracy and reliability of the predictions.

US EPA ECOTOX: It is the world's largest compilation of curated ecotoxicity data that provides support for chemical safety assessments and ecological research through systematic and transparent literature review procedures. The latest version of ECOTOX (Ver 5, www.epa.gov/ecotox) provides single-chemical ecotoxicity data for over 12,000 chemicals and ecological species with over one million test results from over 50,000 references. It is maintained by the US EPA. The database includes information on the effects of thousands of chemicals on a wide range of ecological receptors, such as aquatic and terrestrial organisms, and includes data on both acute and chronic toxicity. Some of the key features of the ECOTOX knowledgebase include the ability to search for toxicity data by chemical name, CAS number, or taxonomic group, inclusion of multiple toxicity endpoints, such as mortality, growth, and reproductive effects, availability of both experimental and predicted toxicity data and the ability to download and export data in various formats.

III. RESULTS AND DISCUSSION

Here we highlight how the models described above are helpful in predicting physicochemical and toxicological properties of chemicals that in turn are helpful to assess their potential to negatively impact the environment and human health. To illustrate this, we took example of two chemicals lactic acid and triclosan (Figure 1). Lactic acid is a common ingredient in many cosmetic and personal care products. It is a naturally occurring organic acid that is found in many foods. The second example that is discussed here is triclosan.

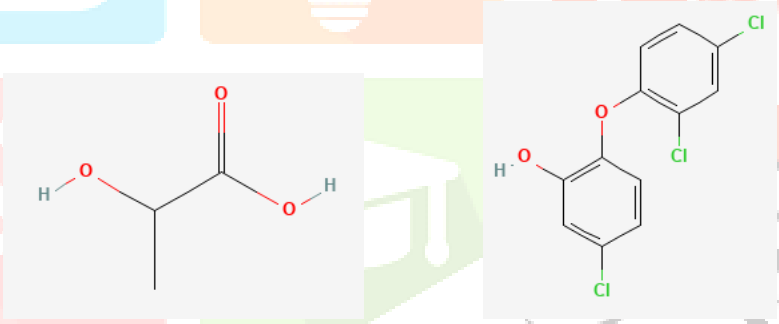

Figure 1. Molecular structures of Lactic acid and Triclosan.

It is an antimicrobial agent that has been widely used in a range of consumer products, including soaps, toothpaste, and cosmetics. It can be observed from Table 1 that lactic acid is highly water soluble (1x106 mg/L) and hydrophilic (logKow -0.65). When it is released into the environment it undergoes rapid biodegradation. It exhibits small bioconcentration factor meaning it does not bioaccumulate in aquatic organisms. If we look at its ecotoxicity, its high LC50 value obtained from ECOTOX Knowledgebase indicates it is not toxic to fish. VEGA model classifies it as non-toxic to algae. In terms of its effects on human health the different models categorize it as a non-binder to DNA suggesting that it is non-mutagenic. Similarly lactic acid is predicted to be a non-endocrine disruptor by both VEGA and QSAR Toolbox since these models predict negative for ER and AR binding. Literature indicates that lactic acid is generally considered safe and non-toxic at low concentrations, and it has been extensively studied for its use in cosmetic and personal care products. Triclosan on the other hand, has been found to be persistent in the environment, and it can bioaccumulate in aquatic organisms. It has also been shown to have endocrine-disrupting effects in some species. This is corroborated by the modelled data. Table 1 highlights the high log Kow, high BCF and low water solubility of Triclosan. Consequently, triclosan tends to remain in water for a longer duration and because of its lipophilic character tends to bioaccumulate and biomagnify in the aquatic organisms. If these aquatic organisms are consumed by humans, then they also get exposed to it indirectly. BIOWIN predicts that this chemical biodegrades very slowly upon its release into the environment. Such persistent and bioaccumulative chemicals pose a threat to the environment. ECOTOX Knowledgebase provides experimental fish toxicity data. It clearly shows a low LC_{50} value indicative of potential toxicity to fish. The Cramer classification also categorises it into High hazard class. On the human health side, the models predict that triclosan has endocrine disruption tendency. This is exhibited by positive predictions for both ER and AR binding.

Table 1: Modelled Properties

Model/Database name	Endpoint	Lactic acid	Triclosan
EpiSuite BCFBAF	Fish bioconcentration factor (BCF) (log(L/kg)	0.5	2.81
EpiSuite KOWWIN	Octanol-water partition coefficient (log Kow)	-0.65	4.6
EpiSuite WSKOWWIN	Water solubility (mg/L)	1E+06	4.62
EpiSuite BIOWIN	Biodegradation probability	Biodegrades fast	Biodegrades slow
ECOTOX Knowledgebase	Rainbow trout LC_{50} 96h (mg/L)	180	0.49
QSAR Toolbox	Oasis DNA binding profiler	No alert	No alert
QSAR Toolbox	Cramer Toxic hazard classification	Low (class I)	High (class III)
QSAR Toolbox	Estrogen receptor binding	Non binder	Strong binder
VEGA	Androgen receptor binding	Inactive	Active
VEGA	Algal toxicity classification	Non-toxic	Toxic

Due to these concerns, triclosan has been banned or restricted in several countries, including the European Union, Canada, and the United States. In the United States, the Food and Drug Administration (FDA) has banned the use of triclosan in over-the-counter antiseptic wash products, and the Environmental Protection Agency (EPA) has listed triclosan as a chemical of concern due to its potential environmental and human health effects.

In this way one can assess the hazard potential of any organic chemicals using such public domain tools. Other examples of chemicals that have been regulated and/or restricted in consumer products due to their harmful properties include bisphenol A (BPA), brominated flame retardants and phthalates (Erickson, 2014). Every chemical plays a role in a product. For example, triclosan is an antibacterial whereas phthalate and bisphenol A are used as plasticizer. When a specific chemical ingredient in a consumer product is found to be a potential risk to humans and/or environment it is subjected to regulatory restrictions. As a result, that chemical gets replaced by alternative chemicals that can perform the same role in the consumer product. Sometimes the potential replacements are safe and sometimes these are found to be unsafe after studies. The reliability of predictions obtained from computational models is important to assess. A prediction is generally considered reliable when the chemical being assessed falls under the model's applicability domain and is supported by similar predictions on close structural analogues.

IV. CONLUDING REMARKS

Computational methods in (eco)toxicology provide future directions for research in this area. This can include potential improvements in predictive models, the use of big data and other advanced analytical tools, and the integration of computational methods with other ecological research approaches. It is worth noting that some of these tools may have limitations, and it is important to carefully consider the reliability and accuracy of the data and models produced by these tools. Additionally, many of these tools require some level of technical expertise to use them effectively. However, these freely available tools serve as a valuable resource for researchers looking to apply computational methods in ecotoxicology research. Computational method is one of the green technologies that promote sustainability, have smaller footprint, and aligns with the 3R principles of Replace (animal testing), Reduce (suffering of animals) and Refine (provide reliable toxicological assessments). In this paper we presented some of the most important publicly available computational toxicology resources (tools, databases) that are commonly used by global regulatory agencies in their decision-making process. The examples discussed here illustrate the value of the computational toxicology tools and the methodology described could be easily applied to study other chemicals. In future there is a plan to integrate such tools in a decision-making framework.

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