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Assessing Hazard Potential of Select Chemicals using Computational Toxicology Models

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Abstract*: Release of potentially persistent, bioaccumulative and inherently toxic chemicals into the environment may cause adverse effects to plants and animals. Hundreds of thousands of chemicals are manufactured each year and experimentally assessing them for these parameters is costly, time consuming and requires animal testing. To address these concerns there has been a paradigm shift in adoption of computational chemistry and toxicology methods for assessing environmental risks posed by such chemicals. These computer-based methods harness the power of fast processors, high speed internet, statistical methods, and curated toxicological databases to fulfil this need. In this work a summary of selected publicly available computational models and databases is presented. Global regulatory agencies apply these predictive models to support their decisions. Indian regulatory bodies too could benefit from this exercise in identifying chemicals of ecotoxicological concern and in taking an appropriate regulatory decision thereby protecting the environment.

***Keywords*: Chemicals, Computational, Environmental, Toxicity**

I. INTRODUCTION

Exposure of flora and fauna to potentially persistent, bioaccumulative and inherently toxic (PBiT) chemicals leads to adverse impact on the food chain. Hence, it is necessary to understand the chemistry and toxicity of chemicals present in our products so that they can be regulated thereby minimizing their release into the environment. Due to animal rights issues and high costs associated with experimental testing these days non-animal rapid screening methods to assess ecotoxicity of organic chemicals are being increasingly adopted by global regulatory agencies. Computational models, based on the concept of Quantitative Structure-Activity Relationship (QSAR) have been reported to be reliable, user-friendly, and useful as decision-support tools. QSAR methods gained importance in regulatory risk assessments since the publication of the Organisation for Economic Co-operation and Development (OECD) QSAR Validation Principles [1] that laid out the five guiding principles. 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).

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II. COMPUTATIONAL MODELS

Several computational chemistry and toxicology methods are used to assess PBiT properties of chemicals. These are generally based on traditional statistical approaches or read across. These models 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 even human health relevant toxicity such as mutagenicity, skin sensitization and potential for endocrine disruption [2]. Computational models used in ecotoxicological research and environmental risk assessments are mainly based on the concepts of structure-activity relationships and read-across. Tools based on the concept of QSAR generally use mathematical algorithms to predict the physicochemical properties and ecotoxicity of chemicals based on their molecular structures. Some of the freely available tools include the USEPA's Epi Suite [3], [4] and VEGA [5], [6]. On the other hand, those that are based on concept of read-across allow the ecotoxicity 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 [7]. The US EPA ECOTOX knowledgebase is a publicly available online resource that contains information on the environmental toxicity of many chemicals [8].

Epi Suite: 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 based on machine learning algorithms, 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 is a is a chem(bio)informatics tool developed by the OECD and European Chemicals Agency (ECHA) to support the prediction of the toxicological properties of chemicals using concepts of QSARs. It allows users to store, search, and retrieve chemical structures, as well as predict a variety of chemical properties.

The software integrates multiple databases and computational tools 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 also 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

This study highlights how the different computational chemistry and toxicology models described above are applied to predict PBiT properties of couple of chemicals. Such data in turn are helpful to assess their potential to adversely impact the environment. Example of two chemicals, polychlorinated biphenyl congener 118 (PCB-118) and perfluorooctanoic acid (PFOA) (Fig. 1) has been used to illustrate the process. PCB-118 is a specific congener of the polychlorinated biphenyl family. It is a chlorinated organic compound that was used in a variety of industrial applications, including electrical equipment and hydraulic fluids. It is persistent, meaning it does not break down easily in the environment, and it is also bioaccumulative, meaning it can build up in the tissues of living organisms. It is also known to be toxic and has been associated with a range of health effects, including immune system dysfunction, developmental delays, and cancer. The second example that is discussed here is PFOA which is a synthetic organic chemical that belongs to the class of compounds known as per- and polyfluoroalkyl substances (PFAS). It is mainly used in the manufacture of non-stick coatings, stain-resistant fabrics, and other products. Like PCBs, PFOA is persistent, bioaccumulative, and inherently toxic. It has been linked to a range of health effects, including liver damage, reproductive problems, and developmental delays.

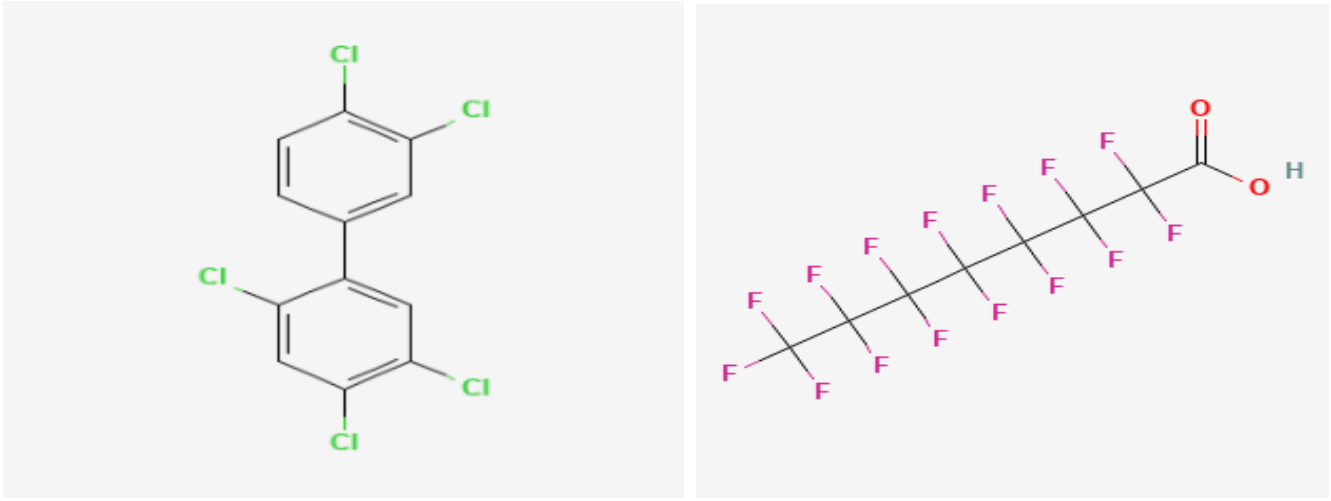

Fig. 1. Molecular structures of PCB-118 and PFOA

It can be observed from Table I that PCB-118 is sparingly water soluble and hydrophobic. When it is released into the environment it undergoes very slow biodegradation. It exhibits high bioconcentration factor which is reflected in its propensity to bioaccumulate in aquatic organisms. If we look at its ecotoxicity, its low LC_{50} value indicates it is toxic to fish. VEGA model classifies it as 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.

Table-I Modelled properties.

Model/ Database	Endpoint	PCB-118	PFOA
EpiSuite BCFBAF	Bioconcentration factor (log(L/kg))	4.65	0.5

EpiSuite BCFBAF	Bioaccumulation factor (log (L/kg))	6.68	3.89
EpiSuite KOWWIN	log Kow	6.98	4.81
EpiSuite WSKOWWIN	Water solubility (mg/L)	0.0071	0.48
EpiSuite BIOWIN	Biodegradation probability	Biodegrades slow	Biodegrades slow
VEGA	Fathead minnow LC_{50} 96h (mg/L)	0.049	4.34
QSAR Toolbox	Oasis DNA binding profiler	No alert	No alert
QSAR Toolbox	Cramer Toxic hazard classification	High (class III)	High (class III)
QSAR Toolbox	Estrogen receptor binding	Non binder	Non binder
VEGA	Androgen receptor binding	Inactive	Inactive
VEGA	Algal toxicity classification	Toxic	Toxic
VEGA	Adipose:Blood partition	2.35	0.78
VEGA	MoA fish toxicity	Narcosis	Narcosis

BCF-bioconcentration factor; Kow-octanol-water partition coefficient

Similarly, PCB-118 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 the presence of many chlorine atoms in the molecular structure of PCB-118 makes it particularly persistent in the environment and difficult to break down. Consequently, PCB-118 is not intentionally added to consumer products today due to their harmful effects. Trace amounts of PCBs may be present as contaminants in some consumer products, such as certain types of fish and seafood, but overall, regulatory bodies have strict standards to ensure that consumer products are free from harmful levels of PCBs in general.

PFOA on the other hand, has been found to be persistent in the environment, and it can bioaccumulate in aquatic organisms. Table I highlights the high log Kow, high BCF and low water solubility of PFOA. Consequently, PFOA tends to remain in water for a longer duration and because of its lipophobic 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. VEGA models clearly show 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 PFOA does not have endocrine disruption tendency. This is exhibited by negative predictions for both ER and AR binding. In general, PFOAs belongs to the class of compounds known as per- and polyfluoroalkyl substances that are a large group of man-made persistent organic pollutants that are classified as PBiT chemicals because they are persistent in the environment, can accumulate in the fatty tissues of organisms, and have been shown to be toxic to both humans and wildlife. PFOA is known to accumulate in the liver and has been linked to a range of health effects, including developmental delays, immune system dysfunction, and cancer. Due to these concerns, both PCBs and PFOA are subject to regulatory restrictions in many countries due to their PBiT properties and potential health and environmental risks. For PCBs, many countries have implemented regulations to ban or severely restrict their use and release. For example, in the United States, the manufacture, import, processing, and distribution of PCBs were banned in 1979 under the Toxic Substances Control Act. Other countries, such as Canada, have also banned or restricted the use of PCBs. In addition, the Stockholm Convention on Persistent Organic Pollutants (POPs), a global treaty, has listed PCBs as one of the 12 most hazardous POPs, calling for their reduction and eventual elimination. For PFOA, regulatory restrictions vary by country, but many have implemented regulations to limit their use and release. For example, in the United States, the EPA has worked with industry to phase out the use of PFOA and related chemicals by 2015 under the PFOA Stewardship Program. The European Union has also restricted the use of PFOA and related chemicals under the REACH regulation. In addition, PFOA has been added to the Candidate List of Substances of Very High Concern (SVHCs) under the REACH regulation, which may lead to further restrictions.

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 [9]. Every chemical plays a role in a product. For example, oil and water resistant properties of PFOA make it useful for non-stick coating 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 so-called regrettable substitutions. The reliability of predictions obtained from computational models is important to assess. A prediction is generally considered reliable when the chemical being assessed falls within the model's applicability domain and is supported by similar predictions on close structural analogues.

In India, the use of PCBs has been banned since 1989 under the Manufacture, Storage, and Import of Hazardous Chemicals (MSIHC) Rules, which were later replaced by the Hazardous Waste (Management, Handling and Transboundary Movement) Rules in 2008. The rules prohibit the manufacture, trade, import, export, transport, storage, and use of PCBs and PCB-contaminated materials, and provide guidelines for their safe disposal. As for PFOA and related chemicals, the Indian government has not yet implemented specific regulations to restrict their use or release. However, the use of PFOA and related chemicals in some products may be subject to regulation under India's Chemicals (Management and Safety) Rules, 2021, which were enacted to regulate the manufacture, import, export, and storage of chemicals in India.

Under the new rules, certain chemicals may be subject to import or export restrictions, and companies may be required to provide information on the hazards and risks of the chemicals they produce or use. Even though the use of PCBs has been banned in India, it is still important to conduct risk assessments to identify and evaluate the potential risks posed by PCBs that may still be present in the environment or in products that were manufactured before the ban. PCBs are highly persistent and can remain in the environment for a long time, which means they can still be present in soil, water, air, and food even decades after their use were banned. Furthermore, improper disposal of PCBs and PCB-containing materials can result in their release into the environment, which can pose risks to human health and the environment. Therefore, it is important to identify and manage PCB-containing materials that may still be present in the environment or in products to prevent their release and minimize the potential risks. Risk assessments can also help in the development of strategies to manage and dispose of PCBs and PCB-containing materials safely and effectively, and to minimize the potential risks to human health and the environment.

IV. CONCLUSION

Computational toxicology models serve as a useful tool for informing regulatory decisions related to persistent, bioaccumulative, and inherently toxic chemicals like PCBs and PFOA. These models can provide a more comprehensive understanding of the potential risks associated with these chemicals, including their potential for endocrine disruption, which can help regulatory agencies to develop appropriate risk management strategies. Integrating data from various sources and applying advanced computational models can help to identify and prioritize chemicals that may pose the greatest risks to human health and the environment. They can also provide insights into the mechanisms of toxicity and help to identify potential biomarkers or early indicators of adverse effects that can be used for risk assessment and monitoring.

In summary, computational toxicology models can provide a cost-effective and efficient alternative to traditional animal testing methods, which can help to reduce the need for expensive animal testing in chemical risk assessment. This is important from an ethical standpoint, as well as from a practical standpoint, as it can help to accelerate the regulatory decision-making process by reducing the overall costs associated with chemical risk assessment especially when the number of chemicals in commerce are in very large numbers.

DECLARATION

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Renu Nayar is Professor and former Head of the Department of Chemistry, D.P. Vipra College, Bilaspur, Chhattisgarh, India. She holds a Ph.D. degree in Chemistry and has around 25 years of teaching experience. She has published more than 30 peer-reviewed journal articles in the areas of environmental pollution and material science. She has authored, contributed chapters, and have served as co-Editor on different books. She is currently pursuing research in the emerging areas of computational toxicology and chemistry.