Chapter 5

In Silico Approaches for Predictive Toxicology

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INTRODUCTION

Chemical utilization is on ever-increasing trend in everyday life. For instance, more than 80,000 commercial products with myriad applications are intensely linking one into the world of chemicals [1]. Industrialization and by various means of technological advancements and intervenes, chemicals are posing the major source of threat toward several health and the environmental issues. Understanding and characterization of chemical properties and its interactions with biological systems are essential for the safe use of any existing and emerging chemicals/drugs/materials [2]. Due to the complexity of various toxicological endpoints to ensure the safety of chemicals, a variety of techniques are being performed [3]. Currently available methods to determine the safety of chemicals are mainly concentrating on battery of toxicological testing and assessment using animals [3–5]. However, great efforts have been instigated for developing alternatives to the traditional toxicity testing regime [6]. Hence, paradigm shift in regular practice is needed in terms of proper validation and acceptance of alternatives toxicology evaluation as replacements. In silico toxicology is one of the alternatives to animal testing that complement in vitro and in vivo toxicity assessments to potentially minimize animal testing, reduce the cost and time, and improve toxicity prediction and safety assessment [3,4,7]. In addition, in silico toxicity models have a unique advantage of being able to predict toxicity of chemicals prior to synthesis and to innovate the process of developing new chemical entities with desired properties [2,6].

IN SILICO TOXICOLOGY FRAMEWORK FOR TOXICITY/SAFETY PREDICTION

Toxicity is a measure of potential adverse effects caused by chemicals on humans, animals, plants, or the environment through acute-exposure (single dose)

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or multiple-exposure (multiple doses). The goal of toxicity testing is to develop quantifiable information for enabling adequate precaution and protection for the societal health against adverse effects of various chemicals, and drugs. [8–10]. Adverse effects of chemicals are determined by toxicity endpoints, such as carcinogenicity or genotoxicity (quantitative: lethal dose to 50% (LD_{50}), effective concentration (EC_{50}), lethal concentration (LC_{50}), concentration to inhibit growth (IGC_{50}); qualitative: toxic or nontoxic, low, moderate, and high toxicity) [11]. List of factors such as route of exposure (oral, dermal, inhalation, etc.), dose (concentration), frequency/duration of exposure, ADME properties (absorption, distribution, metabolism, and excretion/elimination), physiology and biological properties (weight, age, gender), and chemical properties influence the toxicity of chemicals [1,12]. In vivo animal toxicity testing (typically rodents, dogs, and/or nonhuman primates) has been considered as the standard for identifying potential adverse effects of chemicals [13]. However, information on the mode and the mechanism of toxicity and differences in toxicological responses of animal data to humans are few concerns on in vivo approaches. In vitro toxicity tests have become more attractive and feasible due to the advances in high-throughput screening, require minimal quantities of testing compounds and reduce animal testing (Reduce, Replace, and Refine animal testing [the 3R principles]) [14,15]. In vitro toxicity assays are conducted primarily with cells or cell lines, ideally from humans or transfected prokaryotic cells for mechanistic investigations. In vitro toxicity methods are well suited for initial screening of toxicity and is to combine predictions with in silico models for overcoming the impact on interpretation of selective endpoints, discovery, and decision space [16–18].

In silico toxicology is a broad term multidisciplinary area; in general computational toxicity assessment, virtual screening, and predictive platform that uses computational resources (methods, algorithms, software, data, etc.) to organize, analyze, model, simulate, visualize, or predict toxicity of chemicals/drugs (Fig. 5.1) [17,19]. It is intertwined with physics, chemistry, biology, mathematics, computer science, and informatics with toxicology, which uses information from computational tools to analyze beneficial or adverse effects envisaging toxicity endpoints of compounds [11]. It is important to highlight here that a variety of computational technique, which relate the structure of a chemical to its toxicity or end effects. In silico toxicology is a predictive technique that helps in retrieving relevant data and/or make predictions regarding the effects of chemicals. There are, obviously, many advantages of computational techniques: in silico predictive toxicology is used in combination with in vitro and in vivo experimental data obtained at the molecular, cellular, organ, organism, and population levels, provide the possibility of improved safety at molecular and functional changes occurring across multiple levels of biotic organization to characterize and evaluate interactions between potential hazards with the components of biological system [20–23]. Predictive toxicology, therefore,

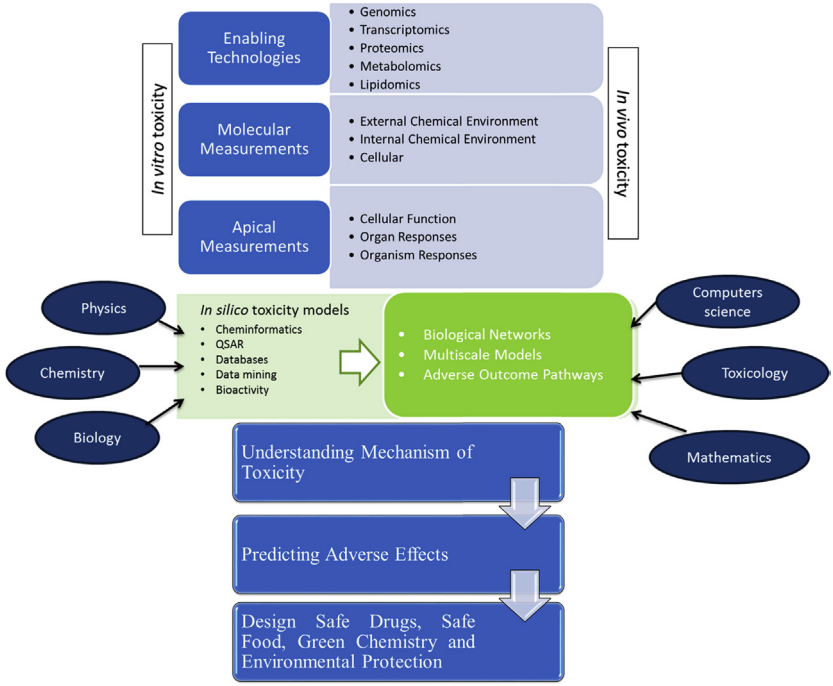

FIGURE 5.1 In silico toxicology framework for toxicity/safety prediction of chemicals/drugs and integrated in vivo and in vitro methodology for a priori risk assessment.

has an ultimate potential for extrapolating quantifiable chemical toxicity endpoints (Table 5.1), and its application could be part of a new paradigm for risk assessment.

In Silico Toxicology

Several in silico approaches have been developed for predictive toxicology. In silico tools vary in complexity and performance and can be broadly classified into four major categories (Fig. 5.2). (1) Structure activity modeling: quantitative structure activity relationships (QSAR), expert systems, grouping and read-across techniques; (2) chemoinformatics: generating molecular descriptors using computational tools including quantum chemical methods and molecular dynamics simulations for toxicity prediction; (3) databases and gathering biological data that contain relations between chemicals and toxicity endpoints, databases for storing data about chemicals, toxicity and chemical properties; (4) data mining and analysis: calculating molecular descriptors, generating a prediction model, evaluating the accuracy and interpreting the model, statistical methods and prebuilt models in web servers or standalone applications for

TABLE 5.1 In Silico Tools Used for Predicting Toxicity Endpoints of Chemicals/Drugs

In Silico Methods	Description	Software/ Databases
Quantitative structure activity relationship models	Use molecular descriptors to predict chemical toxicity	OECD QSAR
		TopKat
		Derek Nexus
		VEGA
		METEOR
		vLife-QSARpro
Structural alerts and rule-based models	Chemical structures that indicate or associate to toxicity	OECD QSAR
		Toxtree
		OCES
		Derek Nexus
		HazardExpert
		Meteor
		CASE
		PASS
		cat-SAR
Read-across	Predicting unknown toxicity of a chemical using similar chemicals with known toxicity from the same chemical category	OECD QSAR
		Toxmatch
		ToxTree
		AMBIT
		AmbitDiscovery
		AIM
		DSSTox
		ChemIDplus
Dose–response and time–response models	Relation between doses (or time) and the incidence of a defined biological effect.	CEBS
		PubChem
		ToxRefDB
Pharmacokinetic (PK) and Pharmacodynamics (PD) models	PK models calculate concentration at a given time. PD models calculate effect at a given concentration	WinNonlin
		Kinetica
		ADAPT

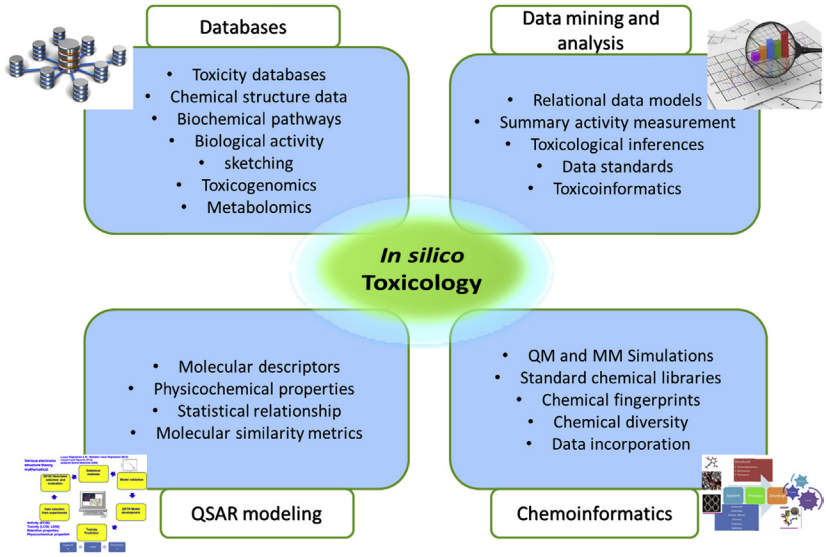

FIGURE 5.2 Multidimensional and broadly integrated in silico categories of predictive toxicology.

predicting toxicity. There are various procedures to unravel general or specific compound toxicity/safety and each method has respective strengths, limitations, the scope of application and interpretation [9]. The underlying principle is to find the suitable and the most effective method to address the particular issue. However, all the four categories mentioned in this section for in silico predictive tools are highly interrelated. The scope of this chapter covers the QSAR, the state-of-the-art method for generating toxicity prediction models in association with descriptors used to form correlation with in vivo/in vitro toxicity endpoints and also providing a highlight on diverse and/or large data sets of toxicology databases and online/standalone computational tools utilized for predictive toxicology.

QSAR FOR PREDICTIVE TOXICOLOGY

The QSAR, quantitative structure property relationship, and quantitative structure toxicity relationship are the important tools of the bio-chemo-informatics, which can be constructed primarily based on the data generated from the molecular modeling and computational chemistry. In general, QSAR framework attempts to find a mathematical relationship between chemical structure and biological activity or chemical property including toxicity for a series of compounds [24]. These series of compounds are called the training set. The generated mathematical equation can be used to predict the activity or property of any new compound, which has been built from the chosen training set. It is noteworthy to mention that the seminal contribution made by Hansch and coworkers for the development of QSAR area of predictive activity [25].

Eq. (5.1) portraits the definition of QSAR, as that a given biological activity can be correlated with the physicochemical properties (size/shape parameters, lipophilicity, electronic properties, structural information) of a compound using a quantitative mathematical relationship [26,27].

$$\log\frac{1}{C} = 4.1\pi - 2.1\pi^2 + 2.8\sigma + 3.4 \tag{5.1}$$

where C is the concentration to produce herbicidal effect, π is an indicator of hydrophobicity, and σ is a measure of electronic effects within the molecule. Many detailed descriptions of QSAR methods and development have been published in the literature [27,28]. Here, the emphasis is on the current state-of-the-art, with comment on the future of QSAR and its potential utility in predictive toxicology.

The fundamental approach for developing, validating, and using QSARs is moderately consistent. QSAR is a technique that tries to predict the activity, reactivity, and properties of an unknown set of molecules based on analysis of an equation connecting the structures of molecules to their respective measured activity and property. Generally, at first the variation in activity and/or property and/or toxicity of a known set of structurally analog samples is studied with the changes in their molecular frameworks. The trends obtained from the study are then transformed into the form of model equations, and, further they are applied to determine the activity, property, and/or toxicity of compounds that are not tested experimentally or new structurally similar set of systems. Because mathematical models are utilized to develop equations, the quantification of different properties of a set of molecules is also readily carried out. Thus, the QSAR based models become useful toward predicting chemical activity and toxicity of molecules. They act as a novel technique to build models correlating structure, activity, and toxicity. QSAR-based studies have shown their applications in many fields like ecotoxicology, drug discovery, antitumor, molecular modeling, biotoxicity, chemico-biological interactions, toxicity predictions, gastrointestinal absorption, activity of peptides, pharmacokinetics/toxicokinetics, data mining, drug metabolism, determination of anti-HIV enzyme inhibitors, antitumor enzyme inhibitors, anticancer drugs, coinage metals, pesticide toxicity, fragrance, nanotoxicity, and in many other fields [9,18,29–37].

Apart from traditional QSAR methods, other QSAR techniques have also been developed. Three-dimensional correlation models (3D-QSAR) is another widely used method for analyzing the structure–property relationships. Using statistical correlation methods, their algorithm analyzes the relationship between the biological activity of a set of compounds and their 3D properties. Based on the applied energy functions involving force field calculations, it inspects both the steric fields (shape of the molecule) and the electrostatic fields. The other type of QSAR involves in silico tools like 3D Markovian Electron Delocalization Negentropies for toxicity predictions and 3D-QSAR comparative molecular field analysis (CoMFA) have also been applied extensively in the discovery

and design of different molecules having desired properties [38]. CoMFA tries to predict the properties of a molecule by developing correlations between the structure and the pharmacological activity of compounds [39]. The potency of it in the design of effective enzyme inhibitors has also been explored. CoMFA has been applied for studying the toxicity of different organic polychlorinated derivatives with aryl-hydrocarbon receptors [40]. QSAR prediction strength lies in the information extracted from different databases. Some articles highlight various computational approaches for better correlative predictions, the role of QSAR in chemical toxicology, and prediction of biotoxicity [41]. Different topological descriptors [42] based QSAR models have been developed to correlate the hazardous effect of chemical compounds on the ecosystem [43].

DESCRIPTORS FOR PREDICTIVE TOXICOLOGY

A molecular descriptor is a structural or physicochemical property of a molecule or part of a molecule. A QSAR model for predictive toxicology is a mathematical relationship between a chemical's quantitative molecular descriptors and its toxicological endpoint [9,44]. Molecular descriptors derived from atomic or molecular properties that translate physicochemical, topological, and surface properties of compounds to establish the foundation for in silico predictive toxicology. Table 5.2 provides various molecular descriptors within the purview of structure–toxicity relationships have been proposed to predict toxicity properties of molecules. Chemoinformatics approaches including quantum chemical methods and molecular modeling techniques enable the definition of a large number of structural, molecular, and local quantities characterizing the reactivity, shape, and binding properties like atomic charges, molecular orbital energies, frontier orbital densities, superdelocalizabilities, atom–atom polarizabilities, molecular polarizability, charge transfer, dipole moment, and polarity indices and energy of a complete molecule as well as of molecular fragments and substituents [24,45,46]. These descriptors have been used to provide insights into the molecular effects that play an important role in a given chemical's toxicity, especially those aiding in constructing correlation models based on the observed manifestations [47]. Popular qualitative chemical concepts such as density functional theory (DFT) based electronegativity and hardness have been widely used in understanding various aspects of chemical reactivity [48]. The nature of basic chemical concepts, electronegativity, hardness, and softness, called global reactivity descriptors (GRD), has been theoretically justified within the framework of DFT. Along with these global descriptors, other important local reactivity descriptors (LRD), such as Fukui function and local softness, were also proposed to rationalize the reactivity of a particular atomic site or group in a molecule [24]. A series of new reactivity descriptors such as electrophilicity [49], local electrophilicity index [50], and group philicity [51] have been defined to understand the chemical reactivity and site selectivity. Generally GRD are used to probe the global reactivity of the molecules whereas the LRD provide information about the particular site in the molecule.

TABLE 5.2 Examples of Commonly Used Descriptors in In Silico Toxicology to Construct Predictive Models

Descriptor Type/Group	Definition
Electronic descriptors	These represent diverse properties which are associated with many effects
E_{LUMO}	Energy of the lowest unoccupied molecular orbital
E_{HOMO}	Energy of the highest occupied molecular orbital
μ	Chemical potential (negative of electronegativity) $\mu = (E_{LUMO} + E_{HOMO})/2$
η	Chemical hardness $\eta = (E_{LUMO} - E_{HOMO})/2$
σ	Chemical softness $\sigma = 1 - \eta$
ω	Electrophilicity $\omega = \mu^2/2\eta$
A_{max}	Maximum atomic acceptor superdelocalizability within a molecule
D_{max}	Maximum atomic donor superdelocalizability within a molecule
A_N	Atomic acceptor superdelocalizability for atom N
D_N	Atomic donor superdelocalizability for atom N
$A_{orbital}$	One-orbital delocalizability associated with a given orbital (e.g., LUMO or LUMO+1)
HD/HA	Hydrogen bond donating/accepting ability.
Electronegativity (χ)	Ability of an atom (or group) to attract electrons associated with reactivity.
Atomic charge (q_n)	Charge associated with atom "n"
Dipole moment (δ)	Distribution of charge within a molecule
Steric descriptors	Associated with ability to reach target site (e.g., be absorbed across relevant biological membranes) and fit within specific receptors
Molecular weight	Relative molecular mass indicating general size of the molecule.
Molecular volume	This may be calculated using the sum of van der Waals atomic volumes; indicates general size.
Molecular surface area/solvent accessible surface area	Computationally, a probe molecule can be "rolled" over the surface of a molecule to determine the area that is accessible (to solvents or interacting molecules such as receptors)

K	The kappa index is a shape parameter based on the degree of branching of the molecular graph.
Sterimol (L_1, B_1–B_5)	Shape descriptors that indicate the length (L) of a substituent and its widths in different directions (B_1–B_5)
Es	The Taft steric constant indicates the size contribution of substituents on a parent molecule
Topological descriptors	These are based on graph theory and relate to overall topology, dictated by the way in which atoms are connected to each other
${}^{n}\chi$	Nth order connectivity index
${}^{n}\chi^{v}$	Valence corrected connectivity indices are used to distinguish between heteroatoms
3D descriptors	Three-dimensional representation of molecules provides a more accurate description of molecular dimensionality
Composite parameters	These represent combination effects and can provide additional information reflective of more than one feature
Polar surface area; hydrophobic surface area	Dividing the surface area of a molecule into regions of polarity or hydrophobicity can provide useful information for example in terms of specific receptor binding interactions
Electro topological state indices	A combination of electronic features and topological environment for given atoms
Functional groups/structural alerts	Certain toxicities may be associated with specific structural features
Similarity indices or similarity scores	Similarity of size, shape, spatial distribution of key atoms/functional groups, reactive potential
Indicator variables	These indicate the presence or absence (usually denoted by 1 or 0, respectively) of specific structural features (e.g., hydrogen bond donating/accepting groups, presence of particular functional group)
Hydrophobic/hydrophilic descriptors	Indicate solubility in aqueous and/or organic medium and relative partitioning between phases
Log P	Logarithm of the partition coefficient
Log D	Logarithm of the distribution coefficient
Log k′	Logarithm of the high performance liquid chromatography capacity factor
Log S_{aq}	Logarithm of the aqueous solubility
Lipole	Distribution of lipophilicity within a substituent or whole molecule
Molecular lipophilicity potential	Geometric distribution of lipophilicity within a molecule
π	Substituent constant indicating the influence of individual substituents on overall partitioning behavior: $\pi = \log P_{(\text{substituted derivative})} - \log P_{(\text{parent})}$

The applications of these descriptors toward the prediction of chemical reactivity, especially in the prediction of toxicity of polychlorinated biphenyls [52,53], polychlorinated dibenzofurans [54], and benzidines [55], biological activity of testosterone and estrogen derivatives [46] and other chemical reactive site and group identification studies have been of demonstrated to establish predictive toxicity models of potentially toxic molecules [56]. Considering an appropriate rationale to develop suitable predictive model depends on identifying key molecular descriptors of compounds for predicting activity. These descriptors are then correlated with a toxicological endpoints through appropriate statistical approach, such as linear multiple regression, discriminant analysis, recursive partitioning, or artificial neural networks [57,58].

DATABASES AND WEB TOOLS FOR PREDICTIVE TOXICOLOGY

To support the development and use of in silico methods, it is highly necessary to organize the chemical and toxicity data in a consistent way. Currently, there is a large number of toxicity data available, which are collected across several domains, and numerous research works have been published in the literature or online databases [43]. In silico toxicology models improve several applications in the alternative testing era to estimate potential toxic effects of a large number of chemicals using data on individual chemicals and their relationship to other series of chemicals/drugs [59]. Developed predictive approaches cannot completely replace standard bioassays or protocols, however, they can provide an earlier decision-making process until required data become available. Table 5.3 provides various in silico predictive toxicology data sources, online and standalone methods that are commonly employed for QSAR prediction and modeling. Some of the predictive toxicity models are publicly available as open web-based services for SAR modeling, molecular docking, QSAR predictive model for acute toxicity, antitarget activity, ecotoxicity, databases, and validated predictive models on the ADMET (absorption, distribution, metabolism, and excretion—toxicity) endpoints, blood–brain barrier permeability, human intestinal absorption, etc. [60,61] Computational tools for the visualization and analysis of the results are also available. In addition, researchers can use online/standalone computational tools for uploading their own data to develop models or to screen the compounds (toxicophores) using a variety of molecular descriptors and machine learning techniques [62]. Many commercial and open source software predictive toxicology tools (TOPKAT, CASE, and MultiCASE, Derek (Lhasa), and ToxTree) allow us to predict toxicity from the structure of chemical/drug compounds. Some in silico tools for toxicity prediction are simpler and other in silico tools are highly complex, involving multivariate modeling of large toxicological databases. This is an enormously promising area for the development of more sophisticated algorithms/methods/models to improve the predictive accuracy for improving risk assessment of chemicals. However, it should be recognized that the toxicity data/models are generated with very specific purposes and there is no unified

TABLE 5.3 Predictive Toxicology Relevant Data Sources: Databases, Online and Standalone Toxicity Predictive Tools[a]

Data Source	Description	Type
Pathguide	Contains information about 325 biological pathway related resources and molecular interaction related resources including Protein-Protein interactions and toxicity	A pathway resource list [http://www.pathguide.org/]
EYESOPEN	ADME (absorption, distribution, metabolism, and excretion/elimination)/tox eyes open, commercial	ADME/tox, online [https://www.eyesopen.com/]
PharmGKB	A knowledge base that captures the relationships between drugs, diseases/phenotypes and genes involved in pharmacokinetics and pharmacodynamics	ADME/tox; PK/PD, online [https://www.pharmgkb.org/]
Myc	MycPermCheck: Online tool for permeability prediction of small molecules against *Mycobacterium tuberculosis*. Basis of the prediction program is a logistic regression model of the physico-chemical properties of permeable substances	Chemistry tools, online [http://www.mycpermcheck.aksotriffer.pharmazie.uni-wuerzburg.de/]
Edetox	Find compound properties	Chemistry, online [https://apps.ncl.ac.uk/edetox/]
LIVERTOX	Search for hepatoxicity of drugs and herbs	Database [https://livertox.nih.gov/]
Danish	Danish quantitative structure activity relationship (QSAR) database. A repository of estimates from over 70 (Q)SAR models for 166,072 chemicals	Database [https://eurl-ecvam.jrc.ec.europa.eu/]
eTOX	The eTOX Library of Public Resources for in silico toxicity prediction	Database [http://www.etoxproject.eu/]
ToxCast	Screening chemicals to predict toxicity faster and better	Database [https://www.epa.gov/chemical-research/toxicity-forecasting]
CEBS	Chemical effects in biological systems knowledge base (application of systems biology to ADME/Tox)	Database [https://cebs.niehs.nih.gov/]
PASS	PASS Inet predicts over 4000 kinds of biological activity, including pharmacological effects, mechanisms of action, toxic and adverse effects, interaction with metabolic enzymes and transporters, influence on gene expression, etc.	Online [www.pharmaexpert.ru/passonline/]
AERS spider	An online interactive tool to mine statistical associations in adverse event reporting system pharmacoepidemiology and drug safety	Online [http://www.chemoprofiling.org/AERS/]
SwissADME	Compute physicochemical descriptors as well as predict pharmacokinetics properties and drug like nature of one or multiple small molecules (BBB, Cyp, Pgp)	Online [www.swissadme.ch/]

Continued

TABLE 5.3 Predictive Toxicology Relevant Data Sources: Databases, Online and Standalone Toxicity Predictive Tools[a]—cont'd

Data Source	Description	Type
DILI	DILIserver: Deep Learning for Drug-Induced Liver Injury, this has been the single most frequent cause of safety-related drug marketing withdrawals for the past 50 years	Online [http://www.pkumdl.cn/DILIserver/DILIhome.php]
Open	OpenVirtualToxLab: ADMET prediction, 16 proteins, known or suspected to trigger adverse effects are implemented at present: 10 nuclear receptors (androgen, estrogen a, estrogen b, glucocorticoid, liver X, mineralocorticoid, peroxisome proliferator-activated receptor g, progesterone, thyroid a, thyroid b), four members of the cytochrome P450 enzyme family (1A2, 2C9, 2D6, 3A4), a cytosolic transcription factor (aryl hydrocarbon receptor) and a potassium ion channel (hERG).	Online [http://www.biograf.ch/index.php?id=home]
iPrior	Using online tool for modeling ToxCast-TM assays towards prioritization of animal toxicity testing	Online [(http://iprior.ochem.eu)]
Chemo tools	Fraggle, the fragment store (search for fragments by drug names or PDB header). It provides property information (charge, hydrophobicity, and binding site preferences) and performs statistical analysis and can view the IDS of drugs and toxic compounds, which contain the fragments	Online [http://bioinf-applied.charite.de/fragment_store/]
SCYPPred	A web-based predictor of SNPs for human cytochrome P450	Online [https://omictools.com/scyppred-tool]
AOP	Define adverse outcome pathways (AOPs)	Online [http://aopkb.org/]
AOP-XPlorer	Explore AOPs	Online [aopxplorer.org]
Effectopedia	It is an open-knowledge aggregation and collaboration tool designed to facilitate the interdisciplinary efforts for delineating AOPs	Online [https://www.effectopedia.org/]
IntSide	A web server for the chemical and biological examination of drug side effects	Online [https://omictools.com/intside-tool]
ToxPredict	ToxPredict (associated to OpenTox)	Online [https://apps.ideaconsult.net/ToxPredict]
admetSAR	Models and databases: provides the manually curated data for diverse chemicals associated with known absorption, distribution, metabolism, excretion, and toxicity profiles. many endpoints, hERG, CYP, PgP, oral, toxicity, Ames test	Online [http://lmmd.ecust.edu.cn:8000/]
hERG	The hERG 1.0 server predicts cardiotoxicity of drug molecules	Online [http://www.cbs.dtu.dk/CBS/services/hERG/]

ADME SARfari	Predict likely ADME targets for an input molecule, Find ADME targets similar to an input FASTA sequence, Find ADME targets related to text terms, Find pharmacokinetic data relating to an input target, sequence or text term, Find activity pharmacokinetic data for an input molecule or related compounds (via a similarity substructure search), match expression levels in human tissues for found targets	Online [https://www.ebi.ac.uk/chembl/admesarfari]
ProTox	A web server for the in silico prediction of rodent oral toxicity	Online [http://tox.charite.de/]
Alkemio	Association of chemicals with biomedical topics by text and data mining	Online [http://cbdm.mdc-berlin.de/~medlineranker/cms/alkemio]
ACD/I-Lab	ADME-Tox prediction	Online [https://ilab.acdlabs.com/]
ToxCreate	Creates computational models to predict toxicity	Online [http://www.toxcreate.net/]
HExpoChem	The server contains information on diverse sources of chemicals with the aim to explore human health risk from diverse chemicals exposure. Five sources of information are considered i.e., drugs, foods, cosmetics, industrial chemicals and human metabolites corresponding of 10,183 unique chemicals with bioactivities for 19,483 human proteins. HExpoChem can help in the decision of potential proteins and proteins complexes associated to life style diseases. It can assist also to the possible cumulative risk of chemicals that interact to a same set of proteins	Online [http://www.cbs.dtu.dk/services/HExpoChem-1.0/]
QED	A webserver for quantitative estimating the drug likeness of a molecule	Online [http://crdd.osdd.net/oscadd/qed/]
DrugMint	Predict the druggabilty of a compound. This server has been developed on the basis of difference in descriptors of approved and experimental small molecules. This server will help in knowing the druggable properties of a chemical structure	Online [http://crdd.osdd.net/oscadd/drugmint/]
Mcule	Toxicity checker, searching for substructures commonly found in toxic and promiscuous ligands, based on more than 100 SMARTS toxic matching rules	Online [https://mcule.com/]
Gusar	Gusar ecotoxicity	Online [http://www.way2drug.com/gusar/environmental.html]
Gusar	Gusar antitargets, rat toxicity	Online [http://www.way2drug.com/gusar/antitargets.html]
CoFFer	A QSAR web service that predicts chemical compounds and provides fragments to aid interpreting predictions. QSAR models (ADMET, off targets, repositioning)	Online [http://coffer.informatik.uni-mainz.de/]
Gusar	Gusar acute rat toxicity prediction	Online [http://www.way2drug.com/gusar/acutoxpredict.html]

Continued

TABLE 5.3 Predictive Toxicology Relevant Data Sources: Databases, Online and Standalone Toxicity Predictive Tools[a]—cont'd

Data Source	Description	Type
ToxiPred	Prediction of aqueous toxicity of small chemical molecules in *T. pyriformis*	Online [crdd.osdd.net/raghava/toxipred]
Lazar	Lazy structure–activity relationships is a tool for the prediction of toxic activities	Online [http://lazar.in-silico.de/]
VirtualToxLab	The VirtualToxLab, 3D ADME/tox	Online [https://omictools.com/virtualtoxlab-tool]
Toxpredict	Web service to estimate toxicological hazard of a chemical structure. Molecules can be drawn, or input by any identifier (CAS, Name, EINECS) or SMILES or InChI or URL of OpenTox compound or dataset	Online [https://apps.ideaconsult.net/ToxPredict]
AlogP	Tools to predict logP (with several methods)	Online [www.vcclab.org/web/alogps/]
ZINC	Some ADME/tox filtering	Online [http://zinc.docking.org/]
ICM	ADME/tox molsoft, commercial and demo	Online [http://www.molsoft.com/mprop]
Chemaxon	ADME/tox chemical	Online [https://chemicalize.com/welcome]
MOLNetwork	ADME/tox online molecular networks	Online [https://github.com/pyeguy/MolNetwork]
ToxAlerts	Web server of structural alerts for toxic chemicals and compounds with potential adverse reactions. The database already contains almost 600 structural alerts for such endpoints as mutagenicity, carcinogenicity, skin sensitization, compounds that undergo metabolic activation, and compounds that form reactive metabolites and, thus, can cause adverse reactions, QSAR models can be built	Online [https://omictools.com/toxalerts-tool]
EPA USA	TEST estimates the toxicity values and physical properties of organic chemicals based on the molecular structure of the organic chemical entered by the user	Standalone [https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test]
Tox-Comp.net	Prediction for hERG	Standalone [http://www.tox-comp.net/]
Vega-QSAR	Vega-QSAR.eu: Tools for QSAR prediction of ADMET (ORCHESTRA is an EU project, funded to disseminate recent research on in silico (computer-based) methods for evaluating the toxicity of chemicals, REACH, courses); ANTARES, alternative to animal testing, CAESAR, EC funded project which was specifically dedicated to develop QSAR models for the REACH legislation	Standalone [http://www.vega-qsar.eu/]

Natural Product Likeness	The Natural-Product-Likeness scoring system is also implemented as workflows, and is available under Creative Commons Attribution-Share Alike 3.0. The present link goes to the executable standalone java package (under Academic Free License)	Standalone [http://sourceforge.net/projects/np-likeness/]
PaDEL	PaDEL-DDPredictor: Calculate pharmacodynamics, pharmacokinetics and toxicological properties of compounds	Standalone [http://www.yapcwsoft.com/dd/padelddpredictor/]
QSAR TOOLBOX	Software for grouping chemicals into categories and filling gaps in (eco)toxicity data needed for assessing the hazard of chemicals	Standalone [http://oasis-lmc.org/products/software/toolbox.aspx]
Toxtree	Application for grouping chemicals and for predicting various types of toxicity based on decision tree approaches.	Standalone [http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/laboratories-research/predictive_toxicology]
Checkmol	Checkmol is a command-line utility program which reads molecular structure files in different formats	Standalone [http://merian.pch.univie.ac.at/~nhaider/cheminf/cmmm.html]
Lilly Open Innovation ADMET	Rejection rules from Lilly Open Innovation Drug Discovery initiative (reactivity and promiscuity filters, drug similarity). Over 275 rules addressing a variety of possible reasons to reject a molecules and the BMS rules. Lilly-Med Chem-Rules stand-alone distribution. Thanks to Greg Durst for pointing to the Lilly-Med Chem-Rules stand-alone command line utility titled "tsubstructure", which lets you search very large SMILES files for specific SMARTS queries	Standalone [https://github.com/IanAWatson/Lilly-Medchem-Rules]
MetaSite	Predict the site of metabolism for substrates of 2C9, 2D6, 3A4, 1A2, and 2C19 cytochromes	Standalone, commercial [http://www.moldiscovery.com/soft_metasite.php]
MedChem Designer	MedChem Designer 2.0, chemical drawing and ADMET prediction	Standalone [https://simplus-downloads.com/index2.htm]
TissueTool	Tissue distribution databases: A repository of tissue distribution profiles for identifying and ranking the genes in the spectrum of tissue specificity based on expressed sequence tags. This repository is currently available for several model organisms across animal and plant kingdoms and is fundamentally based on the UniGene database	Tissue distribution of several targets, online [http://genome.dkfz-heidelberg.de/menu/tissue_db/examples.html]

[a]*As on April 2017.*
BBB, blood–brain barrier; *BMS*, Bristol-Myers Squibb; *hERG*, human Ether-à-go-go Related Gene; *IDS*, identifications; *PDB*, Protein Data Bank; *SNPs*, single-nucleotide polymorphisms; *TEST*, Toxicity Estimation Software Tool.

in silico platform for toxicity prediction. It is essential to ensure the validity of any predictive toxicity model, nature/use of chemical for predictive applications, choice of descriptors, rationalization of the process and approach, and relationship with available toxicity endpoints should be critically considered in a context-dependent pragmatic way.

SUMMARY

Determining the toxicological effects of chemicals as early as possible is essential for human health and the environmental safety. Toxicity of a chemical/drug refers to the adverse effect on the whole organism (animal), particular organ (liver), or substructure of the organism (cell). However, in vivo and in vitro high-throughput assays are expensive and time consuming. In silico toxicity predictive models offer robust and economical alternative to in vivo and in vitro bioassays and reduce animal experiments as well as experimental resources. The main objective of this chapter is to summarize various aspects of in silico models used to solve many problems in predictive toxicology and furthering knowledge on toxicity mechanisms to design safe chemicals/drugs/materials. This chapter provides a framework for the development and use of in silico models. There are a large number of in silico models are developed to categorize the toxicity of chemical compounds, the toxicological endpoints or the effect of different concentrations of the chemicals. *Structure–activity–toxicity* models for predicting activity of compounds can be developed based on knowledge of chemical structure and particular properties or relevant combination of descriptor series. The properties such as physicochemical, structural, and electronic properties can be computed using a range of software suites and correlated with the information determined experimentally. A variety of QSAR approaches are applied in diverse areas covering a range of endpoints (LD_{50}, LC_{50}, EC_{50}, etc.) to predict the biological activities, pharmacokinetic properties, and toxicities, as well as physicochemical properties of drugs and drug-like compounds. This chapter also covered toxicity databases and online service tools used for predicting toxicity of different types of substances both quantitatively and qualitatively. An increasing number of open toxicity in silico prediction sources are available and some of them are commercial. Implementing and integrating in silico methods into regulatory risk assessment is rapidly evolving. In silico predictive toxicology enables toxicity regulation/safety formulation to impact the discovery of chemicals/drugs with a superior safety profile. Continuous development of more physiologically relevant predictive toxicity model systems, advanced algorithms, and analysis methods can replace battery of in vitro and in vivo toxicity tests in the near future.

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