A review of recent advances towards the development of QSAR models for toxicity assessment of ionic liquids

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Abstract

Ionic liquids (ILs) are considered as an alternative to traditional organic solvents due to their unique physical and chemical properties. On the one hand, they have promising solvating characteristics, on the other hand, they are considered as environmentally friendly "green" solvents. Recent studies of ILs toxicity however questioned the safety of ILs.

Assessment of the toxicity of ILs based on laboratory testing is time-consuming and requires significant resources. Complementing this task by applying computational methods is an option for filling data gaps and allows predicting the toxicity of ILs that lack experimental data. Development and application of quantitative structure–activity relationships (QSARs) for innovative design of safe-by-design ILs became recently a research priority. In this review, we summarize the current knowledge on development of *in silico* models in predicting and classifying the hazards of ILs. In addition, we discuss biodegradability of ILs and assessment of mechanisms of toxicity of ILs based on the reported models.

Keywords: Ionic Liquids; Computational Toxicology; Hazard Assessment; Green Solvents; QSAR.

1. Introduction

Ionic liquids (ILs) are suggested as a promising alternative to volatile organic liquids [1] that are a major source of environmental pollution [2,3]. Nevertheless, ILs, sometimes called "green solvents", are not intrinsically safe as some of them are actually rather toxic, but they can be designed to be environmentally friendly [4].

ILs consist mainly of a bulky non-symmetric organic cation incorporated into the structure of a salt together with a weakly coordinating anion. Imidazolium, ammonium, pyridinium, pyrrolidinium, phosphonium are the most widely used cations for the preparation of ILs, anions could be inorganic like Cl^-, $[BF_4]^-$, $[PF_6]^-$, Br^-, or organic such as trifluoromethylsulfonate, bis(trifluoromethyl)sulfonylimide, and others. Combinations of various anions and cations give a tremendous number of ILs with unique properties. At least a million binary ILs can potentially be obtained [5].

ILs represent an attractive medium for various types of chemical processes due to their significant thermal stability, negligible vapor pressure, high conductivity, low volatility. ILs can be applied for electrode modification due to their hydrophobicity, ionic structure, and appropriate viscosity [6]. ILs can find application in separation processes and electrochemistry. ILs received attention as solvents or electrolytes for utilization in energy storage and conversion, catalysis, organic synthesis, drug delivery [7–9].

Nevertheless, owing to the good solubility of many ILs in aqueous media, they can be released into environment with wastewater [10]. There is therefore a significant concern that these chemicals may get in contact with living organisms, cause harm to biota and, eventually, human beings. Several studies showed that ILs can induce toxic effects in ecosystem [11,12]. Also, the risk of accumulation of high concentrations of ILs in environment due to their high stability to heat and other factors is a significant concern. Therefore, it is of relevance to monitor the behavior and biodegradation of ILs in environment and to get knowledge of the fate and effects of ILs for the environment.

Considering the time needed to perform experimental studies [13], computational modeling (*in-silico*) methods may be a robust and less expensive alternative in the risk assessment of ILs. Methods of QSAR (quantitative structure–activity relationships) interlink the structural characteristics and properties of a substance, for instance, biological effects of chemicals in nature [14]. The QSAR approach provides a rapid possibility to fulfilling data gaps for limited or absent experimental information [15]. This computational method was applied successfully in different areas such as drug development, toxicity and pharmacy. Several attempts have been

made to apply the QSAR approach to correlate the structure of ILs with their biological effects, cytotoxicity and degradation (Table 1). In this article, the present knowledge on the application of computational approaches in hazard assessment of ILs is reviewed. The main parts of this review are the following:

- Section 2 illustrates the progress in understanding the degradation of ILs according to the published works and experiments/
- Section 3 is dedicated to overviewed of published computational models with information about the used datasets and database, sources, tested animals and cell lines.
- Section 4 summarizes the current knowledge of the relationship between the structure of ILs and their biological activity
- Section 5 resumed QSAR/QSPR models based on different modeling approaches such as non-linear and linear regressions (PLS, SVR, MLR, KNN, WEKA, ANN). Finally we discuss possible mechanisms of toxicity of ILs based on published models and provide an outlook for future research in prediction of ILs toxicity and biodegradation.

2. Ionic liquids degradation

Understanding and quantification of degradation and biodegradation parameters of ILs [16] is very important to enable decreases of their potential exposure. Research results on biodegradation and chemical degradation studies of ILs [17–20] demonstrated that the percentage of degradation is strongly dependent on the length of the alkyl side chain, core ring structure, and the presence of functional groups [21,22], while the role of the anion is less important[23]. It was observed that cations with short side chains are not biodegradable [18,22–27]. Several authors demonstrated that phosphonium ILs are better degradable than imidazolium and pyridinium ILs [21–23,28–31]. Furthermore, it was indicated [32] that protic ILs have poor biodegradability. Figure 1 depicts the pattern of parameters affecting the biodegradation of ILs.

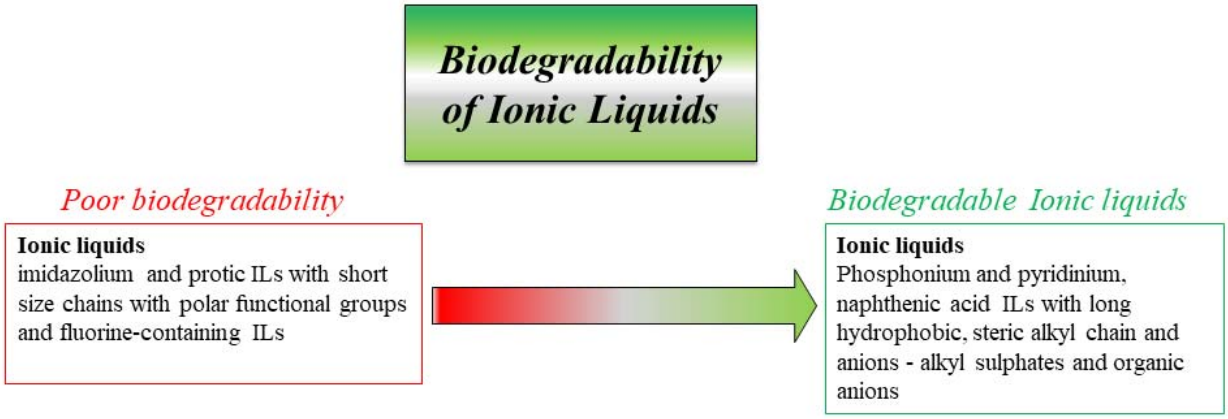

Figure 1. Interpretation of biodegradability of ILs with respect to their structural features.

Commonly used ILs are not easily biodegradable and might accumulate in environment in case of an accidental release [22]. However, some naphthenic acid-derived ILs can be rapidly and completely biodegraded in aquatic environments under aerobic conditions [33].These authors investigated the structure and properties of these ILs and made an attempt to build a predictive model of biodegradation. For this purpose, four descriptors were chosen: the logarithm of the n-octanol/water partition coefficient (logP), van der Waals volume (VvdW), energy of the highest occupied molecular orbital (E_{HOMO}), and energy of the lowest unoccupied molecular orbital (E_{LUMO}). According to the developed Quantitative Structure–Biodegradation Relationship model, E_{HOMO} was suggested as an important parameter in the discovery of other biodegradable ILs:

$$Extent\ of\ biodegradability = 119.294 + 37.821 * E_{HOMO} \quad \text{(Eq. 1)}$$
$$n=10,\ R=0.875$$

In summary, it was proposed that hydrophobic, steric, and electronic parameters are responsible for biodegradability of ILs. These properties determined the possibility of ILs to penetrate through membrane barriers, their ability to interact with active sites of oxygenase, and the potential of being oxidized and degraded. ILs may insert into the lipid bilayer of the membrane and may disturb structural and dynamical systems of bio-membranes [34]. For instance, ILs may act as end-capping agents for the hydrophobic edge of the lipid bilayer [35] and may cause swelling of the lipid bilayer. The interaction of ILs is strongly correlated with the hydrophobicity of the IL cationic alkyl chain and anions, and these parameters determine the dependences observed in studying IL cytotoxicity [35].

3. State of the art of *in Silico* models applied for hazard assessment of ionic liquids

A literature search was performed until February 2019 using the ScienceDirect, PubMed databases and the Web of Science™ using the search terms “ionic liquid modeling”, “ionic liquid toxicity QSAR”, “ionic liquid QSTR modeling” and “ionic liquids QSAR” in the title, abstract or keywords. In this part, the obtained data are presented and the state of the art of development of QSAR models for toxicity of ILs is analyzed. Table 1 summarizes endpoints and number of ILs in the datasets, tested organisms, and data resources that are described in the articles devoted to modeling the toxicity of ILs.

1 Table 1. Summary of the experimental data used for the reported QSAR models and the state of
2 the art of developed (Q)SARs for ILs.

Model[1]	Reference	End points	Number of ILs (anion and cation)	Data sources
Tested species - Vibrio fischeri (V. fischeri)				
M1	[36]	EC_{50}	43 ILs	Experimental [36] and literature data [28,37]
M2	[38]	EC_{50}	75 ILs with 17 anions and 9 cations	Experimental [38] and literature data [25,28,36,37,39–42]
M5	[43]	EC_{50}	51 ILs	Experimental [43] and literature [36,39–41] data
M6	[44]	EC_{50}	97 ILs	UFT/Merck database [45]
M14	[46]	IC_{50}, LC_{50}	24 bromide based ILs	Experimental data [46]
M17	[47]	EC_{50}	69 ILs	UFT/Merck database [45]
M18	[48]	EC_{50}	157 ILs composed of 74 cations and 22 anions	[11,13,52–55,18,36,37,39,40,49–51]
M19	[56]	EC_{50}; LC_{50}	40 and 33 ILs	[11,13,61,62,24,41,46,50,57–60]
M26	[63]	EC_{50}	56 ILs	[64]
M30	[65]	EC_{50}	110 ILs with 29 anions and 49 cations	[18,25,68,69,28,37,42,49,52,53,66,67]
Tested species - Staphylococcus aureus (S. aureus)				
M21	[70]	EC_{50}	25 imidazolium based ILs	Experimental data [70]
M24	[71]	MIC, MBC	NA	[72–77]
M33	[78]	MIC, MBC	169 and 101 ILs with MICs and MBCs, respectively	[72,73,85–87,75,77,79–84]
M35	[88]	MIC	131 ILs	[76,79,95,96,80,85,89–94]
M42	[97]	MIC	242 ILs	OCHEM database [98]
Tested species - Leukemia Rat Cell Line (IPC-81)				
M3	[99]	EC_{50}	227 ILs with 25 anions and 227 cations	UFT/Merck database [45]
M6	[44]	EC_{50}	97 ILs	UFT/Merck database [45]
M10	[100]	EC_{50}	281 ILs with 15 cation head group and 31 anions	UFT/Merck database [45]
M12	[101]	EC_{50}	100 ILs	UFT/Merck database [45]
M13	[102]	EC_{50}	100 ILs	UFT/Merck database [45]
M16	[103]	EC_{50}	253 ILs	[104]
M22	[105]	EC_{50}	289 ILs	[99,104,106]
M28	[107]	EC_{50}	17 ILs	[99]
M31	[108]	EC_{50}	10 groups of 304 ILs	304 experimental data points from the literature [10,18,40,81,104,106,109,110]
M36	[111]	EC_{50}	119 ILs with 57 cations and 21 anions	UFT/Merck database and literature data [45,112]
M37	[113]	EC_{50}	269 ILs with 9 cationic cores and 44 types of anions	UFT/Merck database and literature data [45,81,109]
Tested species - Scenedesmus vacuolatus (S. vacuolatus)				
M8	[114]	EC_{50}	40 ILs	UFT/Merck database [45]
M11	[62]	EC_{50}	60 ILs	UFT/Merck database [45]
M19	[56]	EC_{50}; LC_{50}	40 and 33 ILs	[11,13,61,62,24,41,46,50,57–60]
M20	[61]	EC_{50}	41 ILs	Collected toxicity data (NA)
Tested species - Daphnia magna (D. magna)				
M4	[115]	EC_{50}	64 ILs	[11,24,28,41,57–59,116]

[1] Numbers of the models represent in chronological order

Model[1]	Reference	End points	Number of ILs (anion and cation)	Data sources
M7	[117]	LC_{50}	62 ILs	[11,13,24,41,50,57–60]
M9	[118]	LC_{50}	62 ILs	[119]
M14	[46]	$IC_{50,}$ LC_{50}	24 bromide based ILs	Experimental data [46]
M19	[56]	EC_{50}; LC_{50}	40 and 33 ILs	[11,13,61,62,24,41,46,50,57–60]
Other species				
M15	[120]	EC_{50}	14 imidazolium based ILs	Experimental data [120]
M21	[70]	EC_{50}	25 imidazolium based ILs	*Listeria monocytogenes; Staphylococcus aureus; Escherichia coli; Aeromonas hydrophila*
M23	[121]	MIC	83 ILs - *B. subtilis* and 47 ILs - *Ps. aeruginosa*	*B. subtilis and Ps. aeruginosa*
M24	[71]	MIC, MBC	NA	[72–77]
M25	[122]	MIC	83 ILs	*B. subtilis; Ps. aeruginosa*
M27	[123]	aquatic toxicity scores, ADME properties	ILs with 48 anions and 128 cations	*fungi and bacteria, IPC-81 rat cell lines*
M29	[124]	EC_{50}, LC_{50}, IC_{50}, MIC and MBC	ILs with 60 anions and 250 types of cations	58 biological systems: water fleas; algae; animal cells; bacteria; enzyme activity
M32	[125]	Vermicidal activity and cell viability in %	30 ILs	*Pheretima posthuma and 3T3-40 L1 cells*
M34	[126]	EC_{50}	52 ILs with 11 organic and inorganic anions and 4 different cations	Experimental data [126] and literature data [70,127]
M38	[128]	Vermicidal activity and cell viability in %	1-Butylimidazole-derived ILs – (15 ILs)	Experimental data [128]
M39	[129]	IC_{50}	28 ILs	Experimental data [129]
M40	[130]	Vermicidal activity and cell viability in %	1-methyl-3-alkylbenzimidazolium and 1-methyl-3-alkylimidazolium derived ILs (15)	Experimental data [130]
M41	[131]	EC_{50}	40 ILs	[132,133]
M42	[97]	MIC	242 ILs	OCHEM database [98]

Development of QSAR Models for Ionic Liquids

According to the literature, there is a wide variety of organisms with different sensitivity to ILs, whereas the sensitivity depends on the test duration. Main endpoints studied are related to three common effect levels, i.e. the concentration at which 50 % of biota are affected (EC_{50}), minimal inhibitory concentration (MIC), and minimal biocidal concentration (MBC). MIC defines the lowest concentration, which prevents the growth of bacteria, MBC is the lowest concentration that leads to death of bacteria.

In the case of modeling the toxicity of ILs, *V. fischeri* and *Scenedesmus vacuolatus* were the most studied organisms. The *cell line IPC-81* was chosen as one of the most often studied cell

lines. Several studies reported results of modeling the critical micellar concentration [134,135] and enzyme activity of ILs [10,16,136–140].

Most of models were developed on the basis of an average dataset size (about 100 ± 50 datapoints), several models were built using a dataset of 200-300 endpoints, whereas two models (M29 and M12) contained 1633 and 4000 datapoints, respectively.

Databases of Ionic Liquids toxicity and data availability

Specific databases of ILs toxicity are available, supplemented with physical, chemical, and biological properties of ILs [45,98,112,141]. The work with databases is a well-established essential component for the development of ILs hazard identification. To be useful for modeling purposes, databases must cover the chemical space of the known ILs. For QSAR modeling, databases must provide bioactivity data (cell-based assays or tested species) and data about chemical compounds tested in cell lines with their molecular structures in chemical file formats. Some of presented databases are collections of chemical structures and measured bioactivities and properties of ILs collected from literature such as the Online Chemical Modeling Environment (OCHEM) database [98]. In this database, the structure of ILs can be introduced as a mixture of separate ions presented by SMILES formula. The database contains antimicrobial datapoints (MIC values) for approximately 618 ILs.

The UFT/Merck database [45] (http://www.il-eco.uft.uni-bremen.de/)[2] includes catalogues of commercially available data from screening toxicity assays. It contains information about the toxicity of over 300 different ILs and their precursors.

4. Profiling Green Solvents such as Ionic Liquids based on *In Silico* Models

One of main tasks of structure-activity models is identification of factors (signified by different descriptors) affecting the ILs toxicity and properties. The role of different factors should be discussed by analyzing the represented descriptors in the published models to draw a conclusion about the toxicity mechanism of ILs with respect to living organisms.

According to the models, phosphonium-based ILs are more toxic than their imidazolium analogs [51]. The contribution of the cation to the toxicity of ILs with respect of *V. fischeri* increases in the following order:

Pyrrolidinium < imidazolium < pyridinium [36].

The central role of the cation alkyl chain length was found for different types of organisms (*E. coli*, *S. aureus, A. hydrophila and L. monocytogenes*) used for toxicity assessment of ILs [70].

[2] The database is disabled since 19 January 2019

ILs with a longer chain length show less eco-friendly behavior than ILs with cations containing hydroxyethyl or butyl chains. At the same time, toxicity decreases with introduction of amino acid anions compared with other anions ([$N(CN)_2$], [BF_4], [Br], [Cl]) [70].

The contribution of the anion to the toxicity of ILs is still under investigation. Without considering the effect of anions, it can be assumed that pyridinium, (dimethylamino)pyridinium, tetramethylguanidinium and cholinium cations contribute in a similar manner to the toxicity with respect to *V. fischeri* [38]. With respect to the structure of the anion, it was found that chloride-based ILs are the least toxic for *Scenedesmus vacuolatus* [99,114]. Ghanem [70] observed reduction of antimicrobial activity of ILs composed of 1-octyl-3-methylimidazolium and 1-(2-hydroxyethyl)-3-methylimidazolium cations with different anions towards *A. hydrophila* and *L. monocytogenes* in order:

[$N(CN)_2$] > [Br] > [BF_4] > [Cl] > [Asparagine] > [Glycine] > [Alanine] > [Proline] > [Serine].

Additionally it was shown that [bis((trifluoromethyl)sulfonyl)imide] anion strongly increases toxicity of ILs towards *Aeromonas hydrophila* in contrast to other hydrophilic and amino acid derived anions [126]. The developed MLR models [65] based on the σ-profile descriptors highlighted the difference between the minor and major effect of hydrophilic and hydrophobic anions. Furthermore, negatively charged atoms in the anion provide reduced cytotoxicity towards *cell line IPC81* as compared to anions with positively charged atoms [99].

Lipophilicity [70,142] is another important parameter that influences toxicity of ILs. Due to their strong lipophilic properties, phosphonium ILs are interfaced with the membrane of *Escherichia coli* cells [143]. Increasing branching and the presence of N-atoms in the cationic structure were proven to significantly increase toxicity towards *D. magna* and *V. fischeri* [118]. Additionally, the molecular volume of the cation is the most significant factor determining ILs toxicity towards *E. coli* [71]. The second most important factor affecting the toxicity of ILs is related to hydrogen-bonding acidity and ionic interactions of the cation. The excess molar refraction (the function of interaction of *n*- or π-electron lone pairs) and hydrogen bonding basicity of the cation are less significant for toxicity of ILs with respect to *E. coli.* It was suggested that the MIC and MBC values of ILs tested with *E. coli* were determined by lipophilic interaction and H-bonding interactions of the cation. Figure 2 depicts the role of different structural characteristics according to the analyzed models.

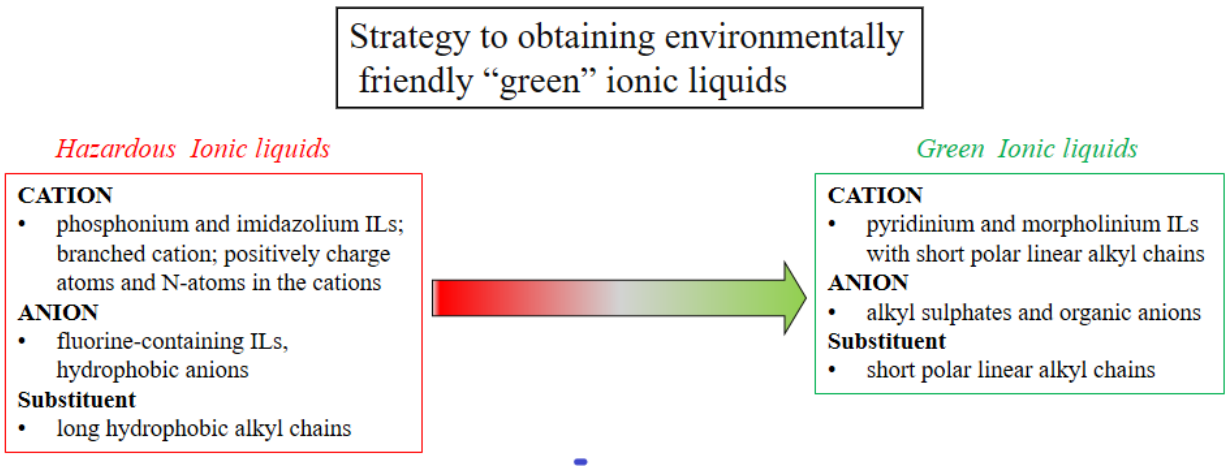

Figure 2. Overview of the role of different factors affecting the toxicity of ILs according to the state of the art of the published models.

5. Critical analysis of QSPR/QSTR models

Several predictive QSPR (Quantitative Structure-Property Relationships) and QSTR (Quantitative Structure-Toxicity Relationships) models were developed for risk assessment of ILs towards different biological species. Table 2 represents the summary of the used methods, descriptors and parameters of the developed models. The role of different structure characteristics (according to descriptors applied in the models) is analyzed.

Two types of models are presented in literature. One of them includes models developed to offer quantitative assessments for hazardous effects caused by ILs; the other models contribute to the categorization and labeling of substances according to their toxicity. Data of models as reported in Table 2 show that both types of models were developed for toxicity of ILs in respect to biota.

Table 2. Summary of the state-of-the-art of predictive toxicity models for ILs involving descriptors and statistical coefficients.

Model	Descriptors	Stat. coefficients		
		R^2	Q^2	Ac (%)
M1	GCM	0.925	-	-
M2	GCM	0.924	-	-
M3	RARS, Kier symmetry index, heavy atom count, topological charge index of order 8	0.92	-	-
M4	GCM	0.974	-	-
M5	minimum net atomic charge for a C atom; WPSA-1; PPSA1; TMSA; maximum atomic orbital electronic population; LUMO+1 energy	0.903 – 0.912	-	-
M6	excess molar refraction; dipolarity/polarizability, hydrogen-bonding acidity, hydrogen-bonding basicity and McGowan volume	0.778 for IPC-81; 0.762 for *V. fischeri;* 0.776 for *S. vacuolatus*	-	-

Model	Descriptors	Stat. coefficients		
M7	ETA index, topological non-ETA and thermodynamic parameters	0.948	0.875	72.22 - 100%
M8	piPC10; RDF095m; $R3_+$; RARS; HAC descriptors	R^2=0.964 R^2pred = 0.948 for MLR; R^2= 0.976 R^2pred= 0.967 for MLP	-	-
M9	Lipophilicity, atom-type fragment, QTMS and ETA descriptors	R^2 = 0.912 - 0.955 R^2pred = 0.771 - 0.815	0.874 - 0.917	-
M10	Molecular ACCess System (MACCS) structural keys	-	-	80%
M11	ETA indices; topological non-ETA parameters; atom-type fragment descriptors	0.883	0.829	-
M12	Min partial charge for a N atom; relative number of O atoms; TMSA; number of C atoms	Training set: 0.918 - 0.959 Test set: 0.892 for MLR and 0.958 for SVM	-	-
M13	Ferreira–Kiralj hydrophobicity parameter; CrippenlogP and Mannhold log P descriptors	0.762 – 0.813	0.731 – 0.792	-
M14	E_{LUMO}; dipole moment; total energy, volume of ILs cation; molecular volume; the electron affinities	0.895 for *D. magna* 0.954 for *V. fischeri*	0.876 for *D. magna* 0.942 for *V. fischeri*	
M15	QTMS; Petitjean Number - defines the shape of the cations; lipoaffinity index; E-state	0.987; 0.961	0.926	
M16	XLogP, NAtoms, TPSA, Polariz, Dipole, InertiaZ, and Span	>0.9	-	>86%
M17	DisPm, Mor16u, HATSv, C08AL, MW	0.903 for GFA; 0.933 for LSSVM	0.847 for GFA; 0.897 for LSSVM	-
M18	topological index, character vector CV of atoms, distance matrix for atom position	0.908	-	-
M19	ETA indices, QTMS descriptors and computed lipophilicity	0.843 - 0.910	0.832 - 0.952	-
M20	E-state and ETA indices, QTMS separately for cations and anions	0.904 - 0.914	0.851 - 0.864	-
M21	σ - Profile as molecular descriptors	R^2 = 0.963 - 0.972;	cross validation, R^2 average = 0.97 - 0.98	95%
M22	Two-dimensional structural and QTMS indices Molar refraction, solute dipolarity, polarizability, hydrogen-bond acidity and basicity, McGowan volume; Lipophilicity, Randic's parameter, molecular connectivity, ETA indices, etc.	0.869	0.856	-
M23	E-State indices, ALogPS, ADRIANA.Code, Dragon V6.0, Chemaxon, Inductive descriptors	0.79 – 0.92	0.770-0.92	83-88%
M24	LFER descriptors: excess molar refraction, dipolarity/ polarizability, H-bonding acidity, H-bonding basicity, McGowan volume, cationic interaction, and anionic interaction;	Predictability 0.803 - 0.947 R^2 = 0.921.	-	-
M24	E-State indices, ALogPS, ADRIANA.Code, Dragon V6.0, Chemaxon, Inductive descriptors	0.75 - 0.87	0.73 - 0.87	80% ± 5
M26	LOC, nOC for cations and GMTI index for anions	0.78	Q^2_{CV} = 0.72 Q^2_{ext} = 0.75	-

Model	Descriptors	Stat. coefficients		
M27	VolSurf+ *in silico* physicochemical descriptors for both cations and anions counterparts	-	0.57 - 0.62[3]	-
M28	Electrophilic indices (ω), the energy of highest occupied (E_{HOMO}) and lowest unoccupied molecular orbital, (E_{LUMO}) and energy gap (Δ E)	0.999	-	-
M29	Excess molar refraction due to interaction of n- or pi- electron lone pairs Dipolarity/polarizability by dipole-dipole and dipole-induced dipole interactions Hydrogen bonding acidity and hydrogen bonding basicity McGowan volume Ionic interactions of the anion and the cation	R^2 = 0.593-0.978 for local models R^2 = 0.901 for the global model	-	-
M30	σ-Profile descriptors	0.906 - 0.910 for MLR; 0.961 - 0.979 for MLP	0.907 – 0.912 for MLR;	-
M31	Weighted Holistic Invariant Molecular Descriptors (WHIM), ring descriptors, functional group counts, topological and constitutional indices	R^2 = 0.77~0.95 for local models R^2 = 0.772 for the global model	Q^2_{CV} = 0.73 – 0.92; Q^2_{ext} = 0.75 - 0.94 for local models Q^2_{CV} = 0.758, Q^2_{ext} = 0.839 for global model	-
M32	DFT based descriptors of cationic head and anionic counterparts. A: LUMO, B: FPSA, and C: HOMO descriptors	0.8174	-	-
M33	Matrix norm index, atomic radius, atom weight, electronegativity, number of atoms, atom charge, molecular weight, branching degree	0.919 for pMIC; 0.913 for pMBC	-	-
M34	Molecular descriptors based on the functional group contribution method	0.904-0.927	0.907-0.933	-
M35	E-State indices, ALogPS, ADRIANA.Code, Dragon 7.0, Chemaxon, Inductive descriptors, Fragmentor descriptors, GSFrag	0.83-0.88	0.82-.087	80.0-82.1%
M36	S_{EP} and $S_{\sigma\text{-profile}}$, electrostatic potential V(r)	MLR – 0.92; SVM - 0.941; ELM – 0.969	MLR - 0.849; SVM - 0.874; ELM - 0.940	-
M37	free GRid-INdependent Descriptors (GRINDs)	0.67 – 0.86	0.66-0.84	
M38	LUMO of anion, fractional polar surface area of cation	0.85	-	-
M39	Rotatable bond number (RBN), mean atomic van der Waals volume and the interaction of second power carbon numbers with the molar ratio of hydrogen-bond acceptor to hydrogen-bond donor	0.698 – 0.764	-	-
M40	DFT based descriptors, LUMO of anion, fractional polar surface area of cation, chemical potential of anion	0.942		88.33%
M41	average coefficient of the last eigenvector from Burden matrix weighted by ionization potential; topological charge index of order 1randic molecular shape profile, etc.	0.82 – 0.96	0.77 – 0.94	
M42	E-State indices, ALogPS, Chemaxon, GSFrag, ToxAlerts (Structural Alerts)	0.85	0.82	

[3] Q^2 value - the fraction of the total variation of the interested properties which can be predicted by the four extracted components

Hazard assessment and information on safe-by-design ILs can be retrieved from the frequency of applying a certain descriptor in the designed models of ILs toxicity. This information allowed one to discuss the role of different parameters in determining the hazardous properties of ILs for environment. With respect towards the type of descriptors, the published models can be labeled as models based on (i) quantum-chemical descriptors; (ii) other theoretical molecular descriptors, and (iii) quantitative structure–toxicity–toxicity relationship (QSTTR) models. The descriptors and structure fragments affecting the ILs toxicity are discussed below.

Quantum-chemical descriptors-based models[4]

The combined study based on experiments and QSAR modeling was performed for 24 bromide ILs towards *V. fischeri* and *D. magna* [46]. According to the QSAR model for *V. fischeri*, toxicity was negatively correlated with E_{LUMO}; for *D. magna*, toxicity increased with increasing dipole moment and decreasing total energy. Models of cytotoxicity (*cell line IPC81*) of 17 ILs with imidazolium, pyrrolidinium, and pyridinium cations were obtained by Salam [107]. The models were developed with electrophilic indices (ω), E_{homo} and E_{lumo}, the energy gap as quantum chemical reactivity descriptors and based on the density functional theory (DFT). PCA analysis was carried out to access the distribution and inter-relation of descriptors of the model.

A predictive QSAR model of ecotoxicity of ILs with respect to *V. fischeri* was designed by Ghanem [65] by using COSMO-RS descriptors. To obtain linear and non-linear QSAR models, the authors used a set of toxicity data (EC_{50}) for 110 ILs: a combination of 49 cations and 29 anions. A high prediction accuracy of 0.906 was obtained for the linear model. Five descriptors were selected from the linear model and used to develop the non-linear model by applying the multi-layer perceptron (MLP) technique. The accuracy of the constructed model was evidenced by the high correlation coefficient 0.961 and mean square error 0.157. Another predictive model of the vermicidal activity and cell viability for 30 ILs with various alkyl chains was constructed [125]. It was stated that an increase in the alkyl chain length leads to an increase in the vermicidal activity.

The applicability of the extreme learning machine (ELM) model was compared with SVM and MLR methods for prediction of toxicity of ILs towards *cell line ICP-81* [111]. The electrostatic potential surface area (S_{EP}) and charge distribution area ($S_{\sigma\text{-profile}}$) were used to predict toxicity of 119 ILs. The model obtained by ELM shows the highest value of R^2 0.969 in comparison with R^2 0.92 for MLR and 0.941 for SVM models. Experimental generation and subsequent modeling of

4 Quantum-chemical descriptors represent only descriptors that are calculated from the molecular structure by using ab initio and semi-empirical quantum chemical methods

toxicity of 15 1-butylimidazolium ILs was performed using LUMO of the anion and the fractional polar surface area of the cation as descriptors [128]. Based on the results [130] showing strong relationship between cytotoxicity and vermicidal activity of 1-methyl-3-alkylbenzimidazolium derivatives towards *Pheretima posthuma and A549 cell lines* and certain descriptors (*LUMO* of anions and *c_FPSA* of cations), the authors supposed that the presence of OH (as a counter anion) increases the polar surface area of the cationic head, which leads to higher toxicity [130].

Other theoretical molecular descriptors

Theoretical molecular descriptors are most frequently applied. Multiple linear regression (MLR) and non-linear models were obtained for 227 ILs [99] by applying the multilayer perceptron neural network (MLP NN), MLR methods, genetic algorithm approach (GA). Four of the five descriptors applied in the linear model (R matrix average row sum, R maximal autocorrelation of lag 1/unweighted heavy atom count, topological charge index of order 8, Kier symmetry index) are associated with the cationic part of ILs. In case of anions, the authors used the HAC descriptor, which correlated with the number of heavy atoms (for instance fluorine atoms) in the anion. The order of significance of applied molecular descriptors is as follows: RARS > GGI8 > S0K > $R1u^+$ > HAC. The first four descriptors belong to the topological descriptor and GETAWAY classes and demonstrate the importance of cationic substituents on cytotoxicity of ILs. According to models, authors concluded that an increase of the number of heavy atoms in the anion leads to an increase of toxicity of ILs.

In another study several predictive models [44] were built for cytotoxicity of ILs towards different species using the excess molar refraction; dipolarity/polarizability, hydrogen-bonding acidity, hydrogen-bonding basicity and McGowan volume as descriptors. Using the excess molar refraction; dipolarity/polarizability, hydrogen-bonding acidity, hydrogen-bonding basicity and McGowan volume as descriptors, several predictive models were built for cytotoxicity of ILs towards the cell line *IPC-81* (R^2 of 0.778, SE of 0.450 log units), the bacterium *V. fischeri* (R^2 of 0.762) and the algae *Scenedesmus vacuolatus* (R^2 of 0.776). According to analysis of descriptor sensitivity, the McGowan volume was determined as the most important predictor of cytotoxicity in terms of the cation nature.

Predictive classification and regression models were developed by Roy et al. [117] for the toxicity assessment (LC_{50}) of 62 ILs towards *D. magna* using an extended topochemical atom (ETA) and other two-dimensional topological and constitutional descriptors. The authors proposed that in order to reduce toxicity of ILs, one must design ILs with lower electronegativity and lipophilicity. Electronegativity can be decreased by minimizing the presence of heteroatoms

and unsaturated carbon-heteroatom and heteroatom-heteroatom bonds. Reducing the chain length of the cationic head groups can decrease lipophilicity of ILs. The same authors [43] carried out another study on the same data set. A previously reported MLR model was outperformed by the best PLS model. Authors demonstrated that by avoiding the aromaticity, nitrogen atoms and increasing branching in the cationic structure might be the key factor in obtaining more lipophilic ILs with reduced toxicity. According to models developed by Izadiyan [114], ecotoxicity of ILs is highly related to their chemical structure and especially to the special fragments on the cation skeleton. Moreover, the authors elaborated a practical toxicity classification model of ILs toxicity by applying cluster and principal component analysis (PCA). The toxicity data of 40 ILs towards *S. vacuolatus* were obtained from the UFT/Merck database [45]. Most of 40 ILs were split in three separate clusters according to their structural similarities and level of toxicity based on the covariance matrix.

The network-like similarity graph (NSG) approach was combined with the classification and regression tree (CART) classifier [100] to find the relevant structure-toxicity relationship trends in case of activity of 281 ILs with respect to *cell line IPC-81*. The obtained results assembled from both quantitative (CART) and qualitative (NSG) approaches helped to design a combinatorial library of about 700,000 ILs with 80% accuracy to exhibit an acceptable hazard profile of ILs. This library can play important role for development of ILs for desirable technical applications as a decision-making element.

ETA indices, atom-type fragment descriptors and other categories of chemical descriptors were applied to develop prognostic classification and regression models of toxicity of 60 ILs toward *S. vacuolatus* [62]. Research activities were carried out with reference to OECD guidelines for QSAR modeling. The authors proposed that reducing the chain length of cationic substituents and increasing hydrogen bond donor features in cations can lead to a decrease of ecotoxicity of ILs. Furthermore, unsaturated anions in ILs are more toxic than bulky anions with a simple saturated moiety with less lipophilic heteroatoms.

Within a study of Zhao [101], a comprehensive database on toxicity of ILs with over 4,000 EC_{50} values was collected. QSAR models (M12, Table 2) were derived by incorporating support vector machine (SVM) and MLR methods. The authors [101] showed that toxicity of ILs can be decreased by increasing the relative number of O atoms in the molecules. In this work, a nonlinear SVM model performed better in the prediction of toxicity of ILs compared to MLR (R^2 for MLR and SVM models was 0.892 and 0.958, respectively).

Hydrophobicity is known to significantly affect toxicity of ILs, thus the Ferreira–Kiralj hydrophobicity parameter was suggested [102] as a constitutional descriptor for modeling toxicity endpoints of ILs. The model with the Ferreira–Kiralj parameter gives a correlation

coefficient 0.809 and proves correctness of suggestion. In research devoted to investigation of cytotoxicity of 14 imidazolium-based ILs towards *Channel Catfish Ovary cell line*, the role of the shape of cationic head groups, length of alkyl substituents, and hydrophobicity was pointed out [120]. The developed LDA (linear discriminant analysis) and MLR models were characterized by a high R^2 value of 0.961. A nonlinear QSAR model of toxicity of 198 ILs towards *cell line IPC-81* was constructed with the cascade correlation network (CCN), probabilistic neural network (PNN), and generalized regression neural networks approaches [103]. The generated model allows one to predict discrimination of ILs into four categories of cytotoxicity with an accuracy higher than 86% and performed correlation with regression models with R^2 over 0.9.

Ecotoxicity of ILs towards *V. fischeri* was predicted by applying the genetic function approximation and least squares support vector machine methods (LSSVM) with R^2 0.903 and 0.933, respectively [47]. With respect to the used five descriptors for the cation and one for the anion, the authors suggested that ecotoxicity of ILs mainly depends on the size, lipophilicity, and 3D structure of cations and concluded that the anionic parameters have little influence on ecotoxicity.

Another QSAR study on toxicity of 157 ILs towards *V. fischeri* was performed using a topological method [48]. MLR models were developed by combining the topological index, a character vector of atoms, and a distance matrix for atom positions as descriptors ($R^2 = 0.908$).

In the work [105], classification and regression-based models were developed with two-dimensional topological descriptors for a dataset of 289 ILs. Linear discriminant analysis (LDA) and PLS (partial least squares regression) models of cytotoxicity (EC_{50}) values towards rat *cell line IPC-81* were designed. The obtained models were in agreement with previously reported models [43].

Classification and regression QSAR models with good predictive power with accuracy over 88% and a coefficient Q^2 0.77-0.92 were designed [121]. The obtained model of antibacterial activity of imidazolium-based ILs was stored in the OCHEM database (www.ochem.eu) and assisted in searching for new potential antimicrobial agents against *B. subtilis* and *Ps. aeruginosa*.

Linear free energy relationship (LFER) descriptors were applied to obtain six prediction models of toxicity of ILs to two bacteria and a fungus [71]. The authors considered the following parameters of ILs as factors modifying their toxicity: molar refraction, dipolarity/polarizability, H-bonding acidity, H-bonding basicity, McGowan volume, cationic interaction, and anionic interaction. The chosen species had different sensitivity to the considered characteristics. For instance, the molecular volume of the cation was a more critical parameter for *E. coli* and *S. aureus*, whereas dipole interactions and H-bonding basicity of a cation was more influential for *C. albicans.*

QSAR modeling was done with the purpose to access the possibility of application of imidazolium ILs as potential anti-candida inhibitors [122]. Modeling was performed on the toxicity dataset (MIC) of 88 1,3-dialkylimidazolium ILs towards *C. albicans* strains with a wide range of toxicity endpoints (from 0.01 to 8,600 μg/mL). The authors used the following machine-learning methods: the WEKA-RF method for creating classification models; Associative Neural Network (ASNN) and k-Nearest Neighbor Method (k-NN) for generation of the regression models. The 5-fold cross-validation method was applied for internal validation.

In another study [63], a QSAR model was developed by using MLR. According to the published model of the toxicity of ILs towards *V. fischeri*, the toxic effect of ILs can be reduced by introducing a polar group in the cation. The authors showed that toxicity of ILs mainly depends on the cation properties, namely, the size and length of the substituent group.

In another study, the authors [124] applied unified descriptors to predict toxicological effects of ILs towards 58 different biological systems. A model with LFER descriptors was proposed for 250 cations and 60 anions. The sensitivity of each biological system was estimated based on the obtained models.

The predictive ability of local vs. global QSAR models was compared by Sosnowska [108] for predicting ILs toxicity (EC_{50}) against *IPC-81 cell line.* 304 experimental data points were accumulated from literature for 10 groups of ILs according to the IL cation type. Both internal and external validation was performed. The authors recommended using the global model in practice instead of local models.

MLR models with matrix norm indexes were built to predict toxicity of 169 and 101 ILs with minimal inhibitory concentration (*MICs)* and minimal bactericidal concentration (*MBCs)*, respectively, against *S. aureus*. Two QSAR models were developed with a correlation coefficient (R^2) 0.919 and standard error of estimate (*SE*) 0.341 for MIC, and R^2 0.913 and *SE* 0.282 for MBC. Both external and internal validation indicated a good predictability of the model.

Combined work [126] was done by generating effect data **[**50% effective concentration - EC_{50}] and modeling toxicity of 52 ILs towards *Aeromonas hydrophila* featuring 4 different cations and 11 anions. The obtained QSAR models indicated that toxicity of ILs depends strongly on the presence of a hydrophobic anion such as bis((trifluoromethyl)sulfonyl)imide and the length of the cation substituents. The k-fold cross-validation was carried out for reliability evaluation. The obtained QSAR model was found to have a high value of the correlation coefficient R^2 0.904 and a small mean square error 0.095.

Combination of QSAR methods and molecular docking was used to obtain several classification and regression models for 131 imidazolium ILs [88]. Comparative analysis of the models showed the advantage of regression models for analysis of ILs activity. Several models were

constructed with various descriptors such as E-State indices, ALogPS, Chemaxon descriptors, inductive descriptors. The developed models are available in the OCHEM database [98].

Predictive QSAR modeling studies were carried out by Luis [38]. MLR models with group contribution descriptors were developed based on *V. fischeri* toxicity data (EC_{50}) for 75 ILs: 9 cations and 17 anions. The lowest aquatic toxicity was found for the imidazolium cation and p-toluenesulfonate and $N(CF_3)_2$ anions. Free GRid-INdependent descriptors (GRINDs) were applied to design citotoxicity models of 296 ILs towards *cell line IPC-81* [113]. Descriptors were derived from GRid molecular interaction fields. Data of citotoxicity for data sets were obtained from UFT/Merck database [45].

Modeling on experimental data was performed for 28 ILs based on the following descriptors: rotatable bond number (RBN), mean atomic van der Waals volume (Mv) and interaction of second power carbon numbers with the molar ratio of hydrogen-bond acceptor to hydrogen-bond donor [129] (HBA and HBD). Authors demonstrated that RBN and Mv of HBD compounds showed positive effects on cytotoxicity of tested ILs, then the molar ratio of HBA to HBD and the number of HBD carbons exhibited the negative impact on activity of ILs. Models of minimal inhibitory concentration [97] were developed based on data for 242 ILs from the OCHEM database [98]. According to the predictions obtained, the authors [97] supposed that 1,3-oxazol-4-yl(triphenyl)phosphonium derivatives have antibacterial activities. Substances of interest were synthesized and screened for their antibacterial activity towards *Staphylococcus aureus* ATCC 25923 *and Staphylococcus.* According to performed antibacterial tests all compounds demonstrated the expected activity towards bacteria [97].

Influence of physicochemical properties

The relationship between structural physicochemical properties of ILs and their aquatic toxicity was investigated by Paternò et al. [123]. The authors applied the *in-silico* approach VolSurf+ to design a PLS model for a dataset of 128 cations and 48 anions. In this method, the information is presented as 3D GRID molecular interaction fields (MIFs). Most of the authors suggest to design descriptors separately for anions and cations. There are only several publications [118,142] which consider cation-anion interactions in their models. However, in their final discussion and conclusion, interactions between the ions has not received significant attention. Most of the researches point to the leading role of the cation and its substituents in ILs toxicity. Besides the structure of ILs, other factors can influence their toxicity. It was shown [144] that the toxicity of ILs towards algae is reduced in saline water. The choice of the type of organisms is also essential for determining and modeling the ILs toxicity.

Quantitative structure–toxicity–toxicity relationship models

Quantitative structure–toxicity–toxicity relationship (QSTTR) models perform interspecies correlation between simple and more complicated species. Different groups of organisms can differently respond to the ILs, but species of the same family may identically respond to the chemicals, whereas species from close families responded the same way with a different degree. Such research is aimed to find out the interconnection for different species. QSTTR model was successfully used to interconnect toxicity of substances for two or more closely related species. For QTTR models, it is typical when available experimental toxicity data for one species are use as independent variables for prediction of toxicity of the ILs for another species. For example, QTTR was employed by Das [56] for extrapolating toxicity of ILs towards *V. fischeri* and *D. magna*. An external data set of toxicity of 302 ILs towards bacterium (*V. fischeri*) was used to develop the model of toxicity of these ILs towards a cladoceran (*D. magna)* and green algae (*S. vacuolatus)*. It was found that the contribution of the cation into toxicity of ILs was more prominent than that of the anions.

Another predictive interspecies QTTR model was obtained to interlink algae toxicity of ILs with toxicity [61]. Primarily the authors developed a PLS model of toxicity of 41 ILs towards *S. vacuolatus* using E-state indices and extended topochemical atom (ETA) indices calculated separately for cations and anions. Computational QTTR models [131] were obtained for the entire set of 64 ILs based on two different experiments [132,133] with different cell lines (with only two ILs being the same in different data series). By applying theoretical molecular descriptors and two approaches for feature selection (classical GA and its modified version – Multi-Objective Genetic Algorithm (MOGA)), researchers [131] obtained the model with R^2 values of 0.82-0.96.

Discussion

In summary, analysis of existing predictive QSAR toxicity models and biodegradation of ILs assists in better interpretation of mechanisms underlying their toxicity and behavior in environment. In general, toxicity of ILs depends on both ions (cation and anion) as well as on their interaction. In the published models, it was established that toxicity of ILs mainly depends on the nature of the cation and increases with the cation alkyl chain length [68,114], whereas the anion exerts in general a more limited impact on the overall toxicity [4,38,51,63]. The important role of the alkyl chain length in the cation in the contribution to ecotoxicity of ILs is in good agreement with literature data [36,39,104].

The effect of the anion, cation core, and presence of functionalized groups in the cation chain on toxicity of ILs is less important as compared to the alkyl chain length in the cation substituent [63,68]. According to the literature [16,37,39,104], ILs with the same cation and different anions do not show any statistical difference in toxicity. With respect to the cation structure, it was proven that more branched cations with long alkyl chains are more toxic than smaller ILs with linear alkyl chains [63]. Toxicity of ILs is reduced by the presence of a polar group in the cation substituent chain.

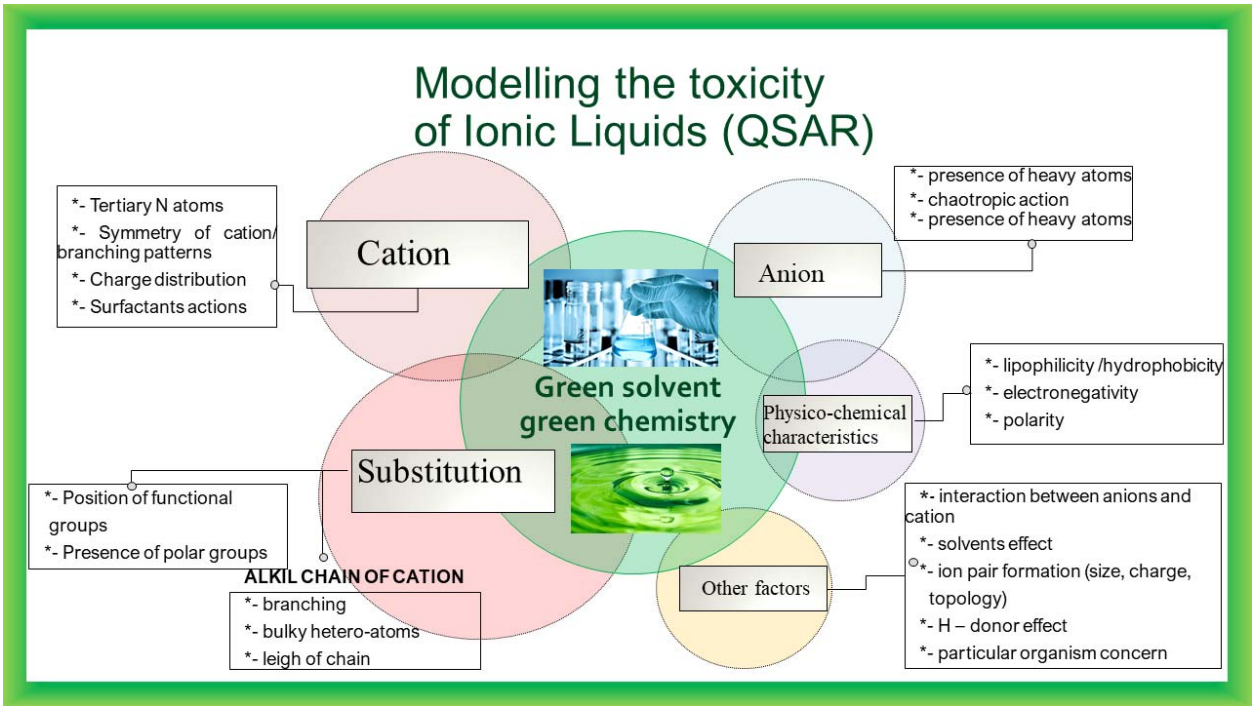

Figure 3. Generalization of the role of different factors in affecting the toxicity of ILs based on the state-of-the-art of the published models.

Toxicity of ILs is moreover strongly correlated with their lipophilicity [70,142] since the hydrophobic character of ILs allows them to be easily incorporated into biological membranes [38,114]. Some key properties such as molecular size, branching, presence of hydroxyl groups (making a molecule hydrophilic), induce lipophilicity of ILs and govern their toxicity. As discussed above, the nature of the cation and substituent are vital for the interaction of ILs with cells and biotic species, as determined by lipophilicity, hydrogen bonding capacity, electronegativity, and size of ILs. This overview is of broad interest as it not only provides useful information about the structural patterns of ILs responsible for toxicity and biodegradation of ILs, but also by shedding light on selecting and designing greener ILs based on published QSAR models.

Conclusions

In this contribution, we presented the current state of the art in the area of design of computational models of ILs toxicity towards different species and cell lines. A general overview of the database and datasets used in QSAR studies for ILs toxicity modeling is given. With respect to the published models, it was concluded that toxicity of ILs mainly depends on the cation and increases with the cation alkyl chain length and for the more branched cation chain groups. With the knowledge of the structures that are responsible for the toxicity of ILs, it is possible to control toxicity of chemicals. In case of ILs, it is reasonable to synthesize a morpholinium head group as it shows the least toxicity towards several test subjects [40]. The overview shows that the presence of a polar group like e.g. hydroxyl or nitrile groups in the cationic substituent chain reduces the toxicity and increases the efficiency of biodegradation. The same tendency was observed for short polar side-chains linked to the cations of ILs. Meanwhile the effect of the anion was shown to play mostly an insignificant role in toxicity of ILs. Thereby from a toxicological point of view it is clear that in order to obtain eco-friendly ILs one needs to use morpholinium or pyridinium cations with short linear and polar alkyl chains and avoid fluorine-containing and hydrophobic anions with cations containing positively charged atoms and N atoms. As mentioned above, the ILs structure is essential for their interaction with cell membranes. The cell membrane in general has a total negative charge and thereby ILs with nucleophilic properties have a higher tendency to interact with biomembranes.

Development of reliable QSAR/QSTR models of toxicity of ILs is essential for reducing the time and cost of experimental research and thus can lead to understanding the strategy in synthesis of green ILs. Even considering the promising benefit from QSAR models for ILs toxicity, most of the publications on this topic used a limited number of test species and only several ILs. To evaluate the total assessment of ILs for regulatory purposes, it is important to expand the number of species and ILs. The information about the state of ILs during the experiments is limited. It will be a good practice to look over the ILs state under experimental conditions. Meanwhile, linking the structure of ILs to their environmental behavior and degradation is of great interest. Such research will provide further understanding of the mechanisms of toxicity and biodegradation of ILs.

Analysis of descriptors discussed in published QSAR studies assists in providing a proper interpretation of possible mechanisms of ILs toxicity on the basis of the structures that mainly drive adverse effects. Thus, this brief overview of modeling studies related to toxicity prediction of ionic liquids manifests applicability of a number of different models allowing for achieving high correlation coefficients. Researchers recommend considering the structure of the cation and the anion separately. Most of the studies so far are based on a variety of modeling techniques such as regression (MLR, EVM, PLS), SVM, ANN, GPA, GCM, and LFER approaches. To

have better understanding of the IL structure – toxicity relationship is important for known and new emerging ILs.

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Competing interests

The authors have no competing interests to report

Abbreviations

a_LUMO – lowest unoccupied molecular orbital energy of anion
ACO - ant colony optimization
ANN – Artificial Neural Network
ASNN - Associative Neural Networks
c_FPSA - Fractional Polar Surface Area of cation
c_HOMO – cation ionization energy
CA - cluster analysis approaches
CART - Classification and Regression Tree
COSMO-RS theory is a continuum solvation model
C08AL is CATS (Chemically Advanced Template Search) 2Dacceptor-lipophilic at lag 08, encode the pairwise topological relationship of potential pharmacophore points patterns based on the cross-correlation of generalized atom types in a molecular graph by a vector of fixed size
CNN - cascade correlation network
CPCM - Conductor-like Polarizable Continuum Solvation Model
CSM - conductor-screening model
DisPm - geometrical descriptor represents displacement value/weighted by mass
Dipole – Dipole moment in [Debye] of the molecule
DFT - density functional theory
ETA - Extended topochemical atom
ELM - Extreme learning machine
GCM - Group contribution method
GFA - genetic function approximation
GMTI - Gutman molecular topological index
GMTIA - Gutman molecular topological index
GRNN - generalized regression neural networks
GSFrag calculates the occurrence numbers of certain special fragments on the vertices in a molecular graph.
HAC - heavy atom count (all atoms except hydrogen) in the anions
HATSv represents leverage-weighted total index/weighted by van der Waals volume
InertiaZ - Principal component of the inertia tensor in z-direction in [Da.Å^2].
k-NN – k Nearest Neighbors method
k-NNCA - k-nearest neighbor cluster algorithm
LDA - Linear discriminant analysis
LFER - linear free energy relationship
LOC - lopping centric information index
LOCC - The lopping centric information index
LSSVM - Least squares support vector machine
MACCS structural keys are substructure-based fingerprints representing a dictionary of predefined structural fragments of fixed format and length
MLP - Multilayer perceptron neural network
MLP NN - multilayer perceptron neural net work
MLR - Multiple linear regression
Mor16u, as a 3D-MoRSE descriptor (Molecular Representation of Structures based on Electron diffraction), describes the signal16/unweighted.
MW - represents molecular weight, which is a constitutional indices descriptor.
NAtoms - Number of all atoms in the molecules (including H atoms).
nOC - the number of oxygen atoms
NSG – network like similarity graph

OCHEM - Online Chemical Modeling Environment database
PCA - principal component analysis
Polariz - Mean molecular polarizability in [$Å^3$] of the molecule
PLS - partial least squares regression
PNN - probabilistic neural network
Q^2 - predictive squared correlation coefficient
Q^2_{cv} – robustness/ internal validation
Q^2_{ext} - predictive ability/ external validation
QSAR – quantitative structure-activity relationship
QSPR – quantitative structure-property relationship
QSTR - quantitative structure-toxicity relationship
QSTTR – quantitative structure–toxicity–toxicity relationship
QTMS - quantum topological molecular similarity
R^2 - determination coefficient
R^2_{pred} - determination coefficient for test set prediction
R3uþ - (R maximal autocorrelationoflag 3/unweighted) and RARS - two GETAWAY descriptors, which try to match 3D-molecular geometry with chemical information by using different atomic weightings.
RDF descriptors - descriptors are based on the distance distribution in a three-dimensional representation of the molecule.
RDF095m - Radial distribution function—9.5/weighted by atomic masses; one of RSD descriptors
S_{EP} - electrostatic potential surface area
$S_{\sigma\text{-profile}}$ - distribution area of the σ-profile
SMILES - simplified molecular input line entry system
RMSE - root mean square error
Span - Radius of the smallest sphere centered at the center of mass, which completely encloses all atoms in the molecule in [Å].
SVR - support vector regression
TPSA - Topological polar surface area in [$Å^2$] of the molecule.
T_SAR - Thinking in Structure-Activity Relationships
WEKA –RF – WEKA Random Forest
XLogP - Octanol/water partition coefficient in logarithmic units of the molecule following the atomic contribution approach

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