Ecotoxicity of Ionic Liquids Towards *Vibrio fischeri*: Experimental and QSAR Studies

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Abstract

Ionic liquids (ILs) have gained significant attention within the academic and industrial circle owing to their attractive and unique characters. However, the usual green image of the ionic liquids mainly associated with their low vapour pressure has become increasingly doubtful. Several recent studies have highlighted the underestimated ILs toxicity which has not been adequately addressed. Therefore, improving the understanding of the ionic liquids toxicity towards aquatic organisms will undoubtedly lead to formulation of right solutions to address the toxicity problem hence contributing towards the development of green and sustainable ILs-based technology. The chapter provides a collective review of studies conducted on the effect of ILs structure on toxicity, specifically focussing on the various types of cations and anions, and the length of the alkyl chain attached. Based on the qualitative outcome from the review, a discussion on the development of statistical modelling on the impact of ILs structural features towards the overall toxicity is presented. The application of quantitative structure activity relationship (QSAR) for developing the predictive model for toxicity is highlighted.

Keywords: ionic liquids, ecotoxicity, *Vibrio fischeri*, structural features, QSAR

1. Introduction

One of the major developments made on green solvents focuses on the design of new and more environmental friendly solvents. From the green chemistry perspective, green solvent should be non-toxic, readily biodegradable and is synthesized using the environmental friendly synthesis procedure, whilst at the same time able to meet the application target technologically and economically [1, 2]. For several years, ionic liquids (ILs) have been gaining significant attention as the candidate for future ‘green solvents’ from the scientific and indus-
trial community. It has shown several advantages over the volatile organic solvents (VOCs), among others, covering three major aspects namely:

1. Extremely low vapour pressure in comparison to the VOCs resulting in insignificant vaporization losses to the atmosphere.

2. Inflammable as opposed to the flammable VOCs hence easier to handle and store.

3. Non-toxic perception due to minute losses through vaporization into the atmosphere compared to the VOCs.

Whilst most studies have converged opinion on the first two aspects, the third has been increasingly contested. The work presented focuses on addressing the latter in order to provide further clarity pertaining to the issue of ILs toxicity. It has been generally agreed that the unique feature which enables ILs to capture significant interest is the ability to design them for specific application by changing the cation and anion coupling to meet specified physical, chemical and biological properties. To date, significant number of ILs has been developed and most of them are now commercially available. In addition, there are few more millions of possible ILs that could be theoretically synthesized [3].

ILs are mainly designed to be inflammable, non-volatile, and non-explosive media with a high thermal stability [4]. Due to their hardly measurable vapour pressure, they are not expected to contribute towards atmospheric pollution. On the contrary, most of them display high aqueous solubility. Even the supposedly most hydrophobic IL was found to exert some degree of solubility hence allowing their possible dispersion into aquatic systems, raising concerns on their subsequent environmental impact [5, 6]. Given the almost
unlimited combinations of possible ILs that could be developed, the toxicity determination could become highly laborious and extremely costly as well as time consuming. Developing predictive methods would require systematic understanding of the complex interactions between the cation and anion pairings leading to the toxicity properties, which are not easily done.

On another note, recent studies have pointed towards some possible drawbacks on the use of ILs on an industrial scale. One of the major concerns highlighted was from aquatic toxicity studies showing potential drastic impact of some ILs which was considered as being green, on various aquatic organisms. A number of these ILs were found to possess higher toxicity than some of the acute organic solvents. Therefore, evaluating their overall toxicity has become of primary interest to the industries and public at large prior to their bulk application. This necessitates the development of a predictive method to substitute the laborious manual toxicity measurement in light of the increasing interest on ILs applications.

Figure 1. Structures of cations and anions discussed in the study.
It has been known for some time that the structural feature of ILs may have different contributions on the ILs overall toxicity. Hence, a systematic study to assess the variation of the ILs structure on its overall toxicity has to be commissioned separately. The review attempted at investigating the influence of the changes in ILs structural features involves: (i) the cation core and the functional group substituent, (ii) the length of the alkyl chain substituent, and (iii) anion nature, on the ILs toxicity using bioluminescent *Vibrio fischeri*. The effective concentration at 50% i.e. EC$_{50}$ values for 83 ILs were collected from different literature reports in order to configure the effect of changing the functional group and the structure of the ILs on its toxicity. All the various functional group substituents together with their different structures reflected on the cation and anion are shown in Figure 1. The study also introduces some further insight into the recent development pertaining to the quantitative structure activity relationship models (QSAR) which are proposed as the approach for developing models for predicting ILs toxicity based on the *V. fischeri*.

2. Ecotoxicity measurement using *V. fischeri*

The bioluminescent *V. fischeri* is a Gram-negative, rod-shaped bacterium that bioluminesces through a population-dependent mechanism called quorum sensing [7, 8]. The Microtox assay system (MAS) against bioluminescent *V. fischeri* was often chosen as the first sequence in a test battery to evaluate the toxicity of chemicals due to their simple, quick, good sensitivity and cost-effectiveness as well as a widely acceptable method for ecotoxicity assessments [9, 10]. In addition, *V. fischeri* is also sensitive to a wide variety of toxic substances hence making it a popular proxy method for detecting environmental pollutants for ecotoxicity studies. Furthermore, *V. fischeri* is also considered as a common test organism, well published in the Aquatic Toxicity Information Retrieval database (AQUIRE) produced by the US Environmental Protection Agency (EPA). Several other large environmental-based organizations have also recommended these species for aquatic toxicity assessment [11, 12]. It was earlier reported that *V. fischeri* assay yielded fairly replicable results which were comparable to those obtained using the standard tests, with an advantage of only requiring about 5% of the actual work involved in the standard procedures. Therefore, it was suggested that the MAS be used as a pre-screening tool in the hazard assessment of chemicals [13].

In the reported study, the ILs are classified based on their EC$_{50}$ values according to the hazard ranking as described by Passino and Smith [14], shown in Table 1.

| Hazard ranking      | Concentration of ILs in mg L$^{-1}$ |
|---------------------|-------------------------------------|
| Practically harmless| 100–1000                            |
| Moderately toxic    | 10–100                              |
| Slightly toxic      | 1–10                                |
| Highly toxic        | 0.1–1                               |

*Table 1.* Hazard ranking classification for aquatic organisms.
2.1. Effect of the cation core

Numerous cations have been used to create ILs such as imidazolium and pyridinium, which have been appearing mostly in past ILs studies particularly for the room temperature ionic liquids (RTILs). In the study, the influences of the cation core on the ILs toxicity were investigated using imidazolium-, pyridinium-, pyrrolidinium-, piperidinium- and morpholinium-based cations. The structure with regards to the chain length variation on the cation core was kept within 1-butyl-(1 or 3)-methyl (cation) bromide ILs [15], as shown in Table 2, group A.

| Ionic liquid names                      | Abbreviation | EC_{50} in mg L^{-1} |
|-----------------------------------------|--------------|----------------------|
| **Group A**                             |              |                      |
| 1-Butyl-1-methylimidazolium bromide     | [C₄mim][Br]  | 1002                 |
| 1-Hexyl-1-methylimidazolium bromide     | [C₆mim][Br]  | 334                  |
| 1-Octyl-1-methylimidazolium bromide     | [C₈mim][Br]  | 50.9                 |
| 1-Butyl-1-methylpiperidinium bromide    | [C₄mpip][Br] | 3958                 |
| 1-Hexyl-1-methylpiperidinium bromide    | [C₆mpip][Br] | 230                  |
| 1-Octyl-1-methylpiperidinium bromide    | [C₈mpip][Br] | 29.3                 |
| 1-Butyl-1-methylpyrrolidinium bromide   | [C₄mpyrr][Br]| 5525                 |
| 1-Hexyl-1-methylpyrrolidinium bromide   | [C₆mpyrr][Br]| 387                  |
| 1-Octyl-1-methylpyrrolidinium bromide   | [C₈mpyrr][Br]| 50.8                 |
| 1-Butyl-3-methylpyridinium bromide      | [C₄mpy][Br]  | 130.48               |
| 1-Hexyl-3-methylpyridinium bromide      | [C₆mpy][Br]  | 29.99                |
| 1-Octyl-3-methylpyridinium bromide      | [C₈mpy][Br]  | 1.77                 |
| 1-Butyl-1-methylmorpholinium bromide    | [C₄mmor][Br] | 66,729               |
| 1-Methylimidazole                       | [mim]        | 2864                 |
| 1-Methylmorpholine                      | [mmor]       | 2328                 |
| Pyridine                                | [py]         | 867                  |
| 1-Methylpiperidine                      | [mpip]       | 700                  |
| 1-Methylpyrrolidine                     | [mpyrr]      | 493                  |
| 2,3-Dimethylpyridine                    | [2,3mpy]     | 238                  |
| 3,5-Dimethylpyridine                    | [3,5mpy]     | 65.9                 |
| 2,3,5-Trimethylpyridine                 | [2,3,5mpy]   | 43                   |
| **Group B**                             |              |                      |
| 1-Propyl-3-methylimidazolium tetrafluoroborate | [C₃mim][BF4] | 1846.44             |
| 1-Butyl-3-methylimidazolium tetrafluoroborate  | [C₄mim][BF4] | 801.88              |
| 1-Pentyl-3-methylimidazolium tetrafluoroborate | [C₅mim][BF4]| 331.29              |
| Ionic liquid names                                           | Abbreviation                | EC$_{50}$ in mg L$^{-1}$ |
|------------------------------------------------------------|-----------------------------|--------------------------|
| 1-Hexyl-3-methylimidazolium tetrafluoroborate              | [C$_6$mim][BF$_4$]          | 384.44                   |
| 1-Heptyl-3-methylimidazolium tetrafluoroborate            | [C$_7$mim][BF$_4$]          | 73.81                    |
| 1-Octyl-3-methylimidazolium tetrafluoroborate             | [C$_8$mim][BF$_4$]          | 7.25                     |
| 1-Nonyl-3-methylimidazolium tetrafluoroborate             | [C$_9$mim][BF$_4$]          | 1.55                     |
| 1-Decyl-3-methylimidazolium tetrafluoroborate             | [C$_{10}$mim][BF$_4$]       | 0.20                     |
| 1-Ethyl-3-methylimidazolium chloride                      | [C$_2$mim][Cl]              | 3134.68                  |
| 1-Butyl-3-methylimidazolium chloride                      | [C$_3$mim][Cl]              | 515.49                   |
| 1-Hexyl-3-methylimidazolium chloride                      | [C$_4$mim][Cl]              | 164.78                   |
| 1-Octyl-3-methylimidazolium chloride                      | [C$_5$mim][Cl]              | 2.36                     |
| 1-Decyl-3-methylimidazolium chloride                      | [C$_6$mim][Cl]              | 0.15                     |
| 1-Tetradecyl-3-methylimidazolium chloride                | [C$_{14}$mim][Cl]           | 0.22                     |
| 1-Hexadecyl-3-methylimidazolium chloride                  | [C$_{16}$mim][Cl]           | 0.58                     |
| 1-Octadecyl-3-methylimidazolium chloride                  | [C$_{18}$mim][Cl]           | 10.46                    |
| 1-Ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonylamide) | [C$_2$mim][NTf$_2$]         | 330.23                   |
| 1-Propyl-3-methylimidazolium bis((trifluoromethyl)sulfonylamide) | [C$_3$mim][NTf$_2$]         | 240.18                   |
| 1-Butyl-3-methylimidazolium bis((trifluoromethyl)sulfonylamide) | [C$_4$mim][NTf$_2$]         | 141.99                   |
| 1-Pentyl-3-methylimidazolium bis((trifluoromethyl)sulfonylamide) | [C$_5$mim][NTf$_2$]         | 46.87                    |
| 1-Hexyl-3-methylimidazolium bis((trifluoromethyl)sulfonylamide) | [C$_6$mim][NTf$_2$]         | 22.8                     |
| 1-Heptyl-3-methylimidazolium bis((trifluoromethyl)sulfonylamide) | [C$_7$mim][NTf$_2$]         | 19.25                    |
| 1-Octyl-3-methylimidazolium bis((trifluoromethyl)sulfonylamide) | [C$_8$mim][NTf$_2$]         | 6.44                     |
| Tetramethylammonium bromide                               | [N$_{1111}$][Br]            | >15405.0                 |
| Tetraethylammonium bromide                                | [N$_{2222}$][Br]            | 21016.00                 |
| Tetradetylammonium bromide                                | [N$_{4444}$][Br]            | 600.28                   |
| Hexyltriethylammonium bromide                             | [N$_{6222}$][Br]            | 64.65                    |
| Tetrabutylphosphonium bromide                             | [P$_{2222}$][Br]            | 174.03                   |
| Tributylethylphosphonium diethylphosphate                | [P$_{4622}$][Br]            | 451.71                   |
| Trihexyl(tetradecyl)phosphonium bromide                   | [N$_{66614}$][Br]           | 1449.09                  |

**Group C**

| Cholinium bicarbonate                                    | [Chol][Bic]                 | >20000                   |
| Cholinium butanoate                                      | [Chol][But]                 | 884.1                    |
| Ionic liquid names                          | Abbreviation     | EC_{50} in mg L^{-1} |
|--------------------------------------------|------------------|----------------------|
| Cholinium acetate                          | [Chol][Ac]       | 673.21               |
| Cholinium dihydrogenphosphate              | [Chol][DHPhosp]  | 572.72               |
| Cholinium propanoate                       | [Chol][Prop]     | 487.9                |
| Cholinium chloride                         | [Chol]Cl         | 469.34               |
| Cholinium salicylate                       | [Chol][Sal]      | 236.11               |
| Cholinium bitartrate                       | [Chol][Bit]      | 37.9                 |
| Cholinium dihydrogencitrate                | [Chol][DHCit]    | 37.23                |
| 2-Hydroxyethanolamine formate              | [2-HEA][F]       | 700                  |
| 2-Hydroxyethanolamine butanoate            | [2-HEA][B]       | 2239                 |
| 2-Hydroxydiethanolamine formate            | [2-HDEA][F]      | 800                  |
| 2-Hydroxydiethanolamine acetate            | [2-HDEA][ace]    | 1750                 |
| 2-Hydroxydiethanolamine propionate         | [2-HDEA][Pr]     | 650                  |
| 2-Hydroxydiethanolamine butanoate          | [2-HDEA][B]      | 800                  |
| 2-Hydroxydiethanolamine isobutanoate       | [2-HDEA][iB]     | 850                  |
| 2-Hydroxydiethanolamine pentanoate         | [2-HDEA][Pe]     | 350                  |
| 2-Hydroxytriethanolamine butanoate         | [2-HTEA][B]      | 501                  |
| 2-Hydroxytriethanolamine pentanoate        | [2-HTEA][Pe]     | 461                  |
| 1-Ethyl-3-methylimidazolium chloride       | [C_{2}mim][Cl]   | 9213.24              |
| 1-Ethyl-3-methylimidazolium hexafluorophosphate | [C_{2}mim][PF_{6}] | 4250.70           |
| 1-Ethyl-3-methylimidazolium ethylsulphate  | [C_{2}mim][EtSO_{4}] | 2974.71          |
| 1-Ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)amide | [C_{2}mim][NTf_{2}] | 1631.25          |
| 1-Ethyl-3-methylimidazolium triflate       | [C_{2}mim][TiO]  | 1430.13              |
| 1-Ethyl-3-methylimidazolium acetate        | [C_{2}mim][Ace]  | 1321.25              |
| 1-Ethyl-3-methylimidazolium tetrachloroferrate | [C_{2}mim][FeCl_{4}] | 9.99              |
| 1-(2-Hydroxyethyl)-3-methylimidazolium glycinate | [C_{2}OHmim][Gly] | 11649.23          |
| 1-(2-Hydroxyethyl)-3-methylimidazolium alaninate | [C_{2}OHmim][Ala] | 8123.27          |
| 1-(2-Hydroxyethyl)-3-methylimidazolium serinate | [C_{2}OHmim][Ser] | 10526             |
| 1-(2-Hydroxyethyl)-3-methylimidazolium proline | [C_{2}OHmim][Pro] | 14509             |
| 1-(2-Hydroxyethyl)-3-methylimidazolium bis((trifluoromethyl)sulfonyl)amide | [C_{2}OHmim][NTf_{2}] | 4896.94          |
| 1-(2-Hydroxyethyl)-3-methylimidazolium iodide | [C_{2}OHmim][I]  | 1972.20             |

**Group D**

|                         | Abbreviation |                  |
|-------------------------|--------------|------------------|
| Methanol                | MeOH         | 320400           |
| Dimethyl sulfoxide      | DMSO         | 98359.84         |

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Although the EC$_{50}$ values for the five ILs fall under the same category i.e. practically harmless, the impact of the cation variations on the overall toxicity are found to be obvious. The result on EC$_{50}$ values highlighted that the imidazolium-based ILs exhibited about 4–5 magnitude higher toxicity measurement compared to piperidinium- and pyrrolidinium-based ILs respectively. The most toxic IL is the one based on pyridinium cation where a slightly higher toxicity values were observed compared to the imidazolium analogue. Meanwhile the morpholinium cation demonstrates far less toxicity behaviour than the other counterparts with EC$_{50}$ value reaching as high as 66,729 mg L$^{-1}$. The piperidinium and morpholinium exhibited almost similar cationic core structure where the latter can simply be established by replacing the carbon atom located opposite to the amine group in the piperidinium structure, with an oxygen atom. Despite the slight structural differences, the presence of the oxygenated atom in the morpholinium cation led to its significant toxicity reduction in the order of 17 times, compared to the piperidinium-based IL. This finding augurs well with the earlier work reported by Samorì et al. [16, 17].

The toxicity of some starting reactant for the cation used in the ILs synthesized in the study were tested against *V. fischeri*, with results shown in Table 2, group A. The EC$_{50}$ values for 1-methylimidazolium, 1-methylpyrrolidinium, 1-methylpiperidinium, 1-methylmorpholinium, pyridinium, 2,3-dimethylpyridine, 3,5-dimethylpyridine and 2,3,5-dimethylpyridine are found to be 2864 mg L$^{-1}$, 493 mg L$^{-1}$, 700 mg L$^{-1}$, 2328 mg L$^{-1}$, 867 mg L$^{-1}$, 238 mg L$^{-1}$, 65.9 mg L$^{-1}$ and 43 mg L$^{-1}$, respectively. The reported toxicity of these compounds did not show any clear and logical pattern linking the toxicity to the ILs structure. Hence, there were not any structure-toxicity relationships that could be established. As an example, the results show that 1-methylpyrrolidinium and 1-methylpiperidinium cation-based ILs displayed 5.8 and 4 times higher toxicity respectively, when compared to 1-methylimidazolium, which is contrary to the anticipated trend which predicts imidazolium-based to have higher toxicity than the earlier two ILs.

### Table 2. Ionic liquids ecotoxicity against *Vibrio fischeri* expressed in mg. L$^{-1}$.

| Ionic liquid names          | Abbreviation | EC$_{50}$ in mg L$^{-1}$ |
|-----------------------------|--------------|--------------------------|
| Ethanol                     | EtOH         | 34947.67                 |
| 2-Propanol                  | IPA          | 35389.50                 |
| Acetonitrile                | Acn          | 24172.03                 |
| Acetone                     | Ace          | 17140.62                 |
| N,N-Dimethylformamide       | DMAc         | 20130.66                 |
| Dichloromethane             | DCM          | 2877.80                  |
| Chloroform                  | CHCl$_3$     | 671.32                   |
| Cyclohexane                 | CYHEX        | 226.52                   |
| Pyridine                    | py           | 212.90                   |
| Benzene                     | bz           | 102.97                   |
| Toluene                     | TOL          | 19.70                    |

Although, the EC$_{50}$ values for the five ILs fall under the same category i.e. practically harmless, the impact of the cation variations on the overall toxicity are found to be obvious. The result on EC$_{50}$ values highlighted that the imidazolium-based ILs exhibited about 4–5 magnitude higher toxicity measurement compared to piperidinium- and pyrrolidinium-based ILs respectively. The most toxic IL is the one based on pyridinium cation where a slightly higher toxicity values were observed compared to the imidazolium analogue. Meanwhile the morpholinium cation demonstrates far less toxicity behaviour than the other counterparts with EC$_{50}$ value reaching as high as 66,729 mg L$^{-1}$. The piperidinium and morpholinium exhibited almost similar cationic core structure where the latter can simply be established by replacing the carbon atom located opposite to the amine group in the piperidinium structure, with an oxygen atom. Despite the slight structural differences, the presence of the oxygenated atom in the morpholinium cation led to its significant toxicity reduction in the order of 17 times, compared to the piperidinium-based IL. This finding augurs well with the earlier work reported by Samorì et al. [16, 17].
Generally, it was extremely difficult to establish sensible and systematic structure-toxicity relationship with exception to the observation involving relationship between the position and the number of methyl groups attached to the pyridine cation and the effect on toxicity of the ILs as a whole. Also, the result indicates an important general trend which shows that the ILs with the cation structure containing aromatic, are always more toxic than the non-aromatic ones. According to Ventura et al. [6] and Kurnia et al. [18], the aromatic cation are more soluble in water and therefore capable of directly exhibiting its high toxicity effect on the aqua environment compared to the non-aromatic-based ILs which are much less soluble. However, it is worth to note that the toxicity of the non-cyclic cations such as sulphonium, ammonium and phosphonium has not been rigorously studied. Nevertheless, the present study still takes into account of the toxicity involving few ammonium and phosphonium ILs reported earlier and the results are included.

2.2. Effect of alkyl chain length

It is known that the alkyl chain length of the cation has a strong effect on the physical and chemical properties of the ILs. For example, the extension of the cation side resulting from a longer alkyl chain commonly results in lower density and solubility, slower diffusion rate and increases viscosity [19, 20]. In addition, it was also observed that the cation alkyl chain length has a pronounced effect on the ecotoxicity towards microorganisms. Most of the established ecotoxicity data covering not only \textit{V. fischeri} but also other organisms such as cell, green algae, fish, and bacteria employed for investigating the influence of the alkyl chain length on the ionic liquid toxicity. Table 2 group B provides the EC\textsubscript{50} values for different counters to represent the impact of the alkyl chain length associated with different cation type on the ILs toxicity. Viboud et al. [15] have reported the effect of butyl, hexyl and octyl on the toxicity for 1-alkyl-1-methylimidazolium [C\textsubscript{n}mim][Br], 1-alkyl-1-methylpyrrolidinium bromide [C\textsubscript{n}mpyrr][Br] and 1-alkyl-1-methyl piperidinium bromide [C\textsubscript{n}mpip][Br]. It was noticeable that the EC\textsubscript{50} values sharply decreases with the reduction in the alkyl chain length of the cation, indicating clear toxicity relationship.

The type of cation also seems to have an important role in changing the toxicity effect of the ILs when its substituent chain length are further extended. For the shorter alkyl chain (butyl), the pyrrolidinium cation demonstrated lower toxicity compared to piperidinium and imidazolium, respectively. The recorded EC\textsubscript{50} value of [C\textsubscript{4}mpyrr][Br] is 5525 mg L\textsuperscript{-1} and this marked a reduction of 109-fold in the EC\textsubscript{50} value, signifying a tremendous increase in toxicity when the side alkyl chain was extended from four to eight carbon atoms. For the piperidinium type, the recorded effect was even more drastic with the toxicity increased by 135-fold from 3958 mg L\textsuperscript{-1} for [C\textsubscript{4}mpip][Br] to 29.3 mg L\textsuperscript{-1} for [C\textsubscript{8}mpip][Br]. Between the three cations, imidazolium recorded the lowest rate of increase in toxicity with the increase in the alkyl chain length, where the increment was only by 20-fold from 1002 mg L\textsuperscript{-1} for [C\textsubscript{4}mim][Br] to 50.9 mg L\textsuperscript{-1} for [C\textsubscript{8}mim][Br]. The lowest rate of increase in toxicity could be explained by the fact that imidazolium is already possessing highest toxicity even with shorter alkyl chain length compared to the others.

A similar study has been conducted for pyridinium-based ILs by Docherty and Kulpa [21] who studied the effect of butyl, hexyl and octyl substituents on the toxicity of 1-alkyl-3-meth-
ylpyridinium bromide-based ILs. A similar increasing trend in the toxicity associated with increasing alkyl chain length was observed. As expected, the least toxic compound of this cation type is the butyl-based ILs with EC$_{50}$ value of 130.48 mg L$^{-1}$. The EC$_{50}$ value reduces to 29.99 mg L$^{-1}$ through the addition of two carbon atoms to the alkyl chain (hexyl) resulting in a fourfold increase in toxicity. Switching the hexyl substituent to an octyl causes an increase in toxicity i.e. by 17-fold compared to the hexyl-based IL and up to 73-fold compared to the butyl-based IL.

Generally, it can be stated that increase in the side chain for the pyrrolidinium- and piperidinium-based ILs produces more pronounced effect than those of the aromatic-based cation such as imidazolium- and pyridinium-based ILs. Although there were almost zero data reported for much longer alkyl chain except for imidazolium-type ILs which will be further discussed below, the increasing trend of the toxicity with respect to the increase in the side alkyl chain reveals that longer extension on the alkyl chain beyond C$_{9}$ and above, will produce highly toxic ILs and therefore should be avoided.

For the longer alkyl chain, Ranke et al. [22] studied the toxicities for 1-alkyl-3-methylimidazolium tetrafluoroborate with alkyl chain varied from C$_{3}$ to C$_{10}$. Based on their EC$_{50}$ values, as can be seen from Table 2 group B, the tetrafluoroborate-based ILs having alkyl chain length up to heptyl, can still be classified as practically harmless. Further extension of the alkyl chain will lead to more toxic effect on the V. fischeri, with the C$_{5}$- and C$_{6}$-based ILs classified as slightly toxic ILs. A more drastic increase in toxicity was observed when the alkyl chain length reaches decyl with the resultant IL producing a highly toxic one. A similar study has been done by Stolte et al. [23] where they investigated the toxicities for 1-alkyl-3-methylimidazolium chloride with alkyl chain varied from C$_{2}$ to C$_{10}$ with an increment rate of two carbon atoms at a time, and for C$_{14}$, C$_{16}$ and C$_{18}$. It is clear that chloride-based ILs showed a slightly more toxic character than their tetrafluoroborate counter parts which is a result of the contribution from the halide anion. In agreement with what have been discussed above, the toxicity of the chloride-based ILs was found to follow the same trend observed for tetrafluoroborate-based ILs. The alkyl chain length extension of ethyl, butyl and hexyl are categorized as practically harmless, whereas the octyl is found to be slightly toxic. Increasing the alkyl chain from 8 to 10 carbon atoms causes a reduction of 15-fold on the EC$_{50}$ values. The EC$_{50}$ value reduces from 2.36 mg L$^{-1}$ for [C$_{8}$mim][Cl] to 0.15 mg L$^{-1}$ for [C$_{10}$mim][Cl], producing the most toxic IL for [C$_{8}$mim][Cl] ILs. Also for the latter, the toxicity hazard impact increases to highly toxic when compared to the slightly toxic octyl. The reported EC$_{50}$ values of [C$_{14}$mim][Cl] and [C$_{16}$mim][Cl] were 0.22 mg L$^{-1}$ and 0.58 mg L$^{-1}$, respectively.

Despite the above highlighted findings, a temporary reverse effect was observed for the ILs when the alkyl chain reaches decyl, where a noticeable increase in the EC$_{50}$ value indicating reduction in the toxicity of the ILs. The observed effect continues until the chain length reaches C$_{17}$ before reversing back to the earlier trend. As a result, the hazard ranking of [C$_{18}$mim][Cl] changes back to a slightly toxic effect, similar to the earlier hazard ranking for the ILs when the alkyl chain was at C$_{9}$. Hence it can still be concluded that for long alkyl side chains beyond C$_{9}$, the dependence between the chain length and toxicity is still valid.
The toxicity of hydrophobic \([\text{C}_{n}\text{mim}][\text{NTf}_2]\)-based ILs was also discussed by Ventura et al. [6]. For this ILs, the alkyl chain is varied from \(\text{C}_1\) to \(\text{C}_8\) (see Table 2 group B). The reported EC\(_{50}\) values are found to be comparable and it follows a similar trend observed for the chloride and tetrafluoroborate-based ILs. The exception was only observed for the short alkyl chain, where \([\text{NTf}_2]\)-based ILs exhibited higher toxicity than their corresponding \([\text{BF}_4]\) and \([\text{Cl}]\) anions. For instance, the EC\(_{50}\) value for \([\text{C}_2\text{mim}][\text{NTf}_2]\) is 330.23 mg L\(^{-1}\) which is 5.6-fold more toxic than \([\text{C}_3\text{mim}][\text{BF}_4]\) despite having shorter alkyl chain attached to the cation, and 9.5-fold more toxic than \([\text{C}_2\text{mim}][\text{Cl}]\). On the contrary, for the \([\text{C}_{n}\text{mim}]\)-based ILs, much smaller differences in EC\(_{50}\) values were reported for the three different anions, where the values for \([\text{C}_8\text{mim}][\text{Cl}]\), \([\text{C}_8\text{mim}][\text{NTf}_2]\) and \([\text{C}_8\text{mim}][\text{BF}_4]\) were 2.36 mg L\(^{-1}\), 6.44 mg L\(^{-1}\) and 7.25 mg L\(^{-1}\), respectively. This could be explained based on earlier reported work that the \(V.\ fischeri\) organism was less sensitive to the hydrophobic ILs than other organisms such as Folsomia candida [24].

Phosphonium-based ILs also showed a similar behaviour as discussed earlier where its toxicity reduces as the alkyl chain length grew longer than decyl. For instance, the reported EC\(_{50}\) value for trihexyl(tetradecyl)phosphonium bromide is 1449.09 mg L\(^{-1}\), eightfold greater than the EC\(_{50}\) value of tetrabutylphosphonium bromide i.e. 174.09 mg L\(^{-1}\) [25], as presented in Table 2 group B. The phenomenon is well reported in the literature for highly lipophilic substances (log \(K_{ow}\) > 5) known as the cut-off effect. For this phenomenon, different explanations were presented based either on insufficient solubility i.e. nominal concentration deviating from real test concentration, or on kinetic aspects i.e. slower uptake due to steric effects for compounds with a large molecular size [2, 26].

The increasing trend in toxicity with alkyl chain length was also confirmed for quaternary ammonium-based ILs [25]. As can be seen from the tabulated data shown in Table 2 group B, tetramethylammonium bromide and tetraethylammonium bromide show non-toxic behaviour with EC\(_{50}\) values greater than 5000 mg L\(^{-1}\). The toxicity of this ILs increases i.e. EC\(_{50}\) value reduces to 600.28 mg L\(^{-1}\), for tetrabutylammonium bromide. Further noticeable increase in toxicity was observed for hexyltributylammonium bromide with EC\(_{50}\) value reduces to 64.65 mg L\(^{-1}\).

Generally it can also be seen that the quaternary ammonium-based ILs exhibits lower toxicity against \(V.\ fischeri\) than the ILs with cyclic cations (aromatic and non-aromatic).

### 2.3. Effect of the anions

The anion chemistry has a great impact on the alteration of the ILs properties. Most of ILs properties such as melting point, hydrophobicity, chemical and thermal stabilities, ability to dissolve organic and inorganic solutes and miscibility with organic solvent rely mainly on the type of the anion [27–29]. Although there is no clear pattern that could be drawn for the anion influence on the ILs toxicity, recent studies have given more attention towards the impact of anions type on ILs toxicity. The data reported for the anion effect are tabulated in Table 2 group C. Ventura et al. [30] investigated the toxicity of 10 ILs with 9 of them comprising the cholinium cation with different anions. Cholinium-based ILs has received significant attention due to its non-toxic and biocompatible nature [31–33]. Using cholinium as the cation, the study on the impact of various anions on toxicity of the ILs was conducted. The bicarbonate
anion was found to be the least toxic whilst the dihydrogen citrate being the most toxic. In fact, there was no EC₅₀ value reported for cholinium bicarbonate due to its unnaturally high value. The maximum luminescence inhibition caused by this IL was as low as 35% at a very high concentration of 20,000 mg L⁻¹.

Judging on the anion structure, the butanoate anion which corresponds to the addition of propanoate and acetate anions with one and two methyl group, respectively is expected to possess higher toxicity due to longer alkyl chain on its structure. However, the toxicity reported for the cholinium cation did not show any consequence leading to noticeable toxicity increase with increase in the alkyl chain on the anion side. Except for cholinium bitartrate and cholinium dihydrogencitrate which are classified as moderately toxic with EC₅₀ values lower than 100 mg L⁻¹, the other seven compounds reported fell under practically harmless class. The reported eco-toxicity data also demonstrated that some classic ILs, pairing the imidazolium or pyridinium cation with alkyl chain varied from C₁ to C₆ with similar anions, may possess lower toxicity than the one exerted by the cholinium cation. Hence, contrary to the effect of alkyl chain length on the IL cation towards ILs toxicity, the same effect is proven to be inconclusive for the anion.

Overall, the order of toxicity sequence reported in increasing order is bicarbonate < butanoate < acetate < dihydrogenphosphate < propanoate < chloride < salicylate < bitartrate < dihydrogencitrate.

Another recent work concerning the anion impact on IL toxicity is the study conducted by Peric et al. [34] where they investigated the ecotoxicity of compounds based on substituted amines as the cations including monoethanolamine, [2-HEA], diethanolamine [2-HDEA] and triethanolamine [2-HTEA], paired with organic acids with different numbers of carbon atoms (formic, propionic, butanoic, isobutanoic and pentanoic acid) as the anions. From the reported data, it is apparent that the alkyl chain length did show some influence on the ILs toxicity. The 2-hydroxydiethanolamine pentanoate [2-HDEA][Pe] was found to be the most toxic with EC₅₀ values of 350 mg L⁻¹, followed by 2-hydroxytriethanolamine pentanoate [2-HTEA][Pe] with EC₅₀ of 461 mg L⁻¹. The two ILs have pentanoic as its anion, indicating the presence of five carbon atoms in the anion side chain. The toxicity exerted by the two ILs demonstrated stronger influence by the cation structure although [2-HDEA][Pe] displayed a 1.3-fold higher toxicity than the [2-HTEA][Pe] despite the latter having a larger cation size. The lower toxicity of [2-HTEA] is attributed mainly to the presence of three hydroxyl groups (-OH) in the cation structure as opposed to only two in [2-HDEA]. As a matter of fact, the observation agrees well with the conclusion stated earlier on the influence of the oxygenated atom within the cation structure which tends to lower the ILs toxicity. Interestingly, this is not always true for the butanoate anion as the toxicity trend displayed different results. The 2-hydroxydiethanolamine butanoate [2-HDEA][B] was reported to be 1.6-fold less toxic than the 2-hydroxytriethanolamine butanoate (2-HTEAB) despite having more hydroxyl (-OH) group attached to it. In this respect, the authors argued that the noticeable increase in the toxicity is due to the more dominant effect contributed from the longer alkyl chain length of the anion. The argument is rather controversial as it was earlier explained that the trend on the effect of the alkyl chain length of the anion on toxicity is inconclusive and lesser compared to the cation. Nevertheless, all the studied ILs were non-toxic and fell under the class of practically harmless.
It is worthy to highlight that it may be worthwhile to use some of the carboxylic acid anions such as decanoic and undecanoic acid which have longer alkyl chains, to synthesize novel ILs for undertaking the study to confirm the effect of the alkyl chain of the anion to the ILs toxicity.

More recently, Montalbán et al. [35] studied the toxicity of 1-ethyl-3 methylimidazolium-based ILs using six different anions including PF₆, TfO, NTf₂, Cl, Ace and EtSO₄. Due to the short alkyl chain used, the six ILs possess very low toxicity and hence all of them were classified as practically harmless. The reduction in toxicity of these ILs follow the trend of Ace > TfO > NTf₂ > EtSO₄ > PF₆ > Cl. Contrary to the above finding, Alvarez-Guerra and Irabien [36] studied the toxicity of tetrachloroferrate(III) anion with the same cation and found a very low EC₅₀ value i.e. 9.99 mg L⁻¹ indicating highly toxic behaviour. Clearly, the [FeCl₄] anion contributes to the extreme toxicity effect when compared to the earlier six anions and the alkyl chain length used. The [FeCl₄] found to possess toxicity of 132-fold higher compared to [Ace] which was the most toxic among the former anions. According to the QSAR model developed by Alvarez-Guerra and Irabien [36], it was similarly suggested that the highly toxic behaviour exerted by the anion was due to the presence of Fe in its structure, exerting a significant influence on the toxicity.

Based on past reported work, introducing amino acid anion to the structure of the ILs can be considered as a convenient approach to reduce its toxicity. Interestingly, the claim has yet to be experimentally proven. In our recent work [37], the variation of the toxicity of 1-(2-hydroxylethyl)-3-methylimidazolium, [C₂OHmim] by pairing it with four different types of amino acid anions namely glycinate, alaninate, serinate and prolinate was studied towards the V. fischeri. The reported EC₅₀ for the amino acid-based ILs was found to be greater than 5000 mg L⁻¹, which highlighted their non-toxic behaviour. The toxicity of the same cation when paired with [NTf₂] and [I] anions as reported earlier by Alvarez-Guerra and Irabien [36] in EC₅₀ values was 4896.94 mg L⁻¹ and 1972.20 mg L⁻¹, respectively as shown in Table 2 group C. This indicates a marked change in toxicity when changing the anion from amino acid type. Nevertheless, there was a recent report by Egorova et al. [38] contravening the role of the amino acid anion in ILs in lowering the ILs toxicity and the fact that they should not be seen as entirely green compounds for initial design. Nonetheless, the comparison between the EC₅₀ values of 1-(2-hydroxylethyl)-3-methylimidazolium-based ILs has sufficiently indicated a clear impact of the amino acid anions on lowering the toxicity of the ILs compared to the [I] and [NTf₂]-based ILs. Furthermore, the toxicity of [C₂OHmim][Ala] which is the most toxic among the amino acid-based ILs, displayed even lower toxicity than [C₂OHmim][NTf₂] and [C₂OHmim][I] by 1.6 and 4-fold, respectively.

Generally, it can be argued that the impact contributed by the anion on the toxicity did not show any strong systematic relationship involving its structure i.e. alkyl chain length as demonstrated in the case of the cation. However, changing the type of the anion would be crucial as it can change the ILs’ toxicity significantly.

2.4. Toxicity of starting material and organic solvent

Volatile organic solvents (VOCs) are considered as a major source of atmospheric pollution. They exert high vapour pressure hence have high volatility leading to their significant losses to the atmosphere. Their vapour can be highly toxic depending on the type of component
and its respective concentration thus posing toxic exposure to process operators and the surrounding community. This is where ILs, having significantly low volatility, was promoted by many researchers as the ideal replacement to VOCs for many of the industrial application. However, several studies have reported comparable EC$_{50}$ values towards *V. fischeri* for some of the common VOCs (Table 2 group D) compared to several common ILs. Hence, the idea of ILs being a greener alternative to the VOCs has to be carefully evaluated. In fact, most of VOCs displayed lower toxicity to the *V. fischeri* than some of the least toxic ILs discussed earlier.

3. **Quantitative structure activity/property relationship (QSAR/QSPR)**

Quantitative structure activity/property relationships (QSAR/QSPR) are models which can be used to predict the relationship between the chemical compound structure and a desired end measure which could refer to any type of physical, chemical or biological activities/properties [39]. Reliable experimental data is crucial at the model development stage in order to produce good prediction model. However, the more extensive the experimental data used, the more time and resources required causing higher cost.

The main aim of the QSAR development is to develop reliable predictive models with minimum possible experimental data thus reducing the time and resources required. The basic principles of the development of the QSAR/QSPR as outlined by Todeschini and Consonni [40] are;

1. The property of interest of the studied compound must have some strong form of relationship with their molecular structure.

2. Similar compounds judging from the orientation of the molecular structure, must behave in a similar fashion.

As the QSAR/QSPR modelling involves computational work, it reflects the benefits as below;

- low costs and high productivity levels especially dealing with data from large chemical libraries,

- more environmental friendly approach leading to reduction in necessary chemical experiments and/or animal testing, which could be further reduced with selection of good descriptor linking the molecular structure to the property of interest,

- possibility to predict properties of newly synthesized compounds based on its chemical structure without the need to conduct any experimental or test procedure.

In this study, ILs toxicity is the property of interest and an attempt was made to develop efficient relationship with the ILs molecular structure. There have been several QSAR models reported for predicting ILs ecotoxicity against *V. fischeri*. Nevertheless, all the QSAR/QSPR models developed suffer from limitation due to the lack of experimental data involving some specific family of ILs. The main differences between the various QSAR/QSPR models were mainly on the selection of the descriptors used in developing the predictive model, and the algorithm learning methods used to establish the relationships between input descriptor and the identified property of interest.
The evaluation of the model accuracy and stability are highly important. The correlation coefficient ($R^2$) was used mostly as the statistical parameter to evaluate the model accuracy. However, the high $R^2$ value (close to 1) does not necessarily mean that the model is reliable and stable. Therefore, model validation is another important step to ascertain the model stability which signifies the ability to display consistently good prediction for ILs especially for data outside the experimental range used during model development stage. In other words, validation of the QSAR models is a crucial issue for judging its ability in predicting similar properties of new ILs set not included during model development [41].

Different methods were adopted to validate the QSAR/QSPR models such as internal, external and cross-validation [42]. Most of the developed models used the multiple linear regression technique (MLR) which was widely employed due to its simplicity, transparency and reproducibility as well as easy interpretability [43]. It also provides useful statistical parameter for evaluating the significance of the selected descriptors (i.e. $P$-value and $t$-statistic), thus guiding the elimination of insignificant descriptors that have none or insignificant impact on the model performance.

In most cases reported, the end measure for ecotoxicity of ILs towards $V. fischeri$ was expressed as log $EC_{50}$ in $\mu$mol L$^{-1}$. In the extensive literature study conducted, the pioneering work found on QSAR/QSPR model dealing with the toxicity of ILs towards $V. fischeri$ was developed by Couling et al. [25]. The model was developed using four descriptors namely E-state indices, surface area, surface charge density and shadow parameter. This model was able to predict the toxicity with accuracy producing $R^2$ value of 0.78. Luis et al. [44]and [45] later developed novel QSAR models based on multiple linear regression method to predict the ecotoxicity. In their two studies, they proposed the used of group contribution approach i.e. the functional group, as molecular descriptors, in order to assess the contribution of different structural elements on the overall toxicity of ILs. Supposedly, an ionic liquids structure could be divided into three main components namely the cation, the anion and the substitution group, and each group could further be divided into subgroups based on their toxicity effect. In their earlier model, nine descriptors were used to represent a medium dataset obtained for 43 ILs. In their later model, the number of descriptors was increased to 15 as the dataset was expanded to 96 ILs. Despite the effort of increasing the number of descriptors with a larger pool of ILs, the later multiple linear regression models hardly produced improvement compared to the earlier, both displaying only acceptable regression statistics with $R^2 = 0.925$ and 0.924, respectively. This was due to the fact that the group contribution descriptors were used as independent variables for the prediction of a dimensionless toxicity value. Alvarez-Guerra and Irabien [36] proposed a new approach for estimating the ecotoxicity of ILs by means of partial least square-discriminant analysis (PLS-DA) to classify the ecotoxicity for relatively large dataset comprising of 148 ILs. The developed model was able to achieve a high correlation coefficient value of 0.929. The same dataset was used later by Das and Roy [46] to develop their ecotoxicity predictive model. Various two-dimensional chemical descriptors were used to build the input dataset code including constitutional, topological, connectivity, information indices, extended topo-chemical atom (ETA) indices, atom-type E-state indices and molecular properties, using the Dragon™ software. The regression model produced an $R^2$ value of 0.739 when tested using external validation i.e. using data set outside the data range used during
the model development stage. The achievement has led to more QSAR models developed to predict ILs toxicity against \textit{V. fischeri}, which are summarized in Table 3.

| No of IL | Method | Molecular descriptor | Descriptor type | $R^2$ | Ref |
|----------|--------|----------------------|----------------|-------|-----|
| 25       | GFA\(^a\) | 4                    | Electronic, spatial, structural, thermodynamic, and topological descriptors | 0.78 | [25] |
| 43       | MLR    | 9                    | Group contribution | 0.925 | [44] |
| 96       | MLR    | 15                   | Group contribution | 0.924 | [45] |
| 148      | PLS-DA\(^b\) | 94            | Negative or positive effect | $\text{Tr} = 0.963$ $\text{Te} = 0.929$ | [36] |
| 157      | MLR    | 28                   | Topological index | 0.908 | [47] |
| 10 & 19  | MCA\(^c\) | 1                    | Number of aliphatic carbons & number of carbons in the cation | 0.934 & 0.861 | [15] |
| 147      | MLR    | 12                   | DRAGON | $\text{Tr} = 0.936$ $\text{Te} = 0.757$ | [46] |

\(^a\) Genetic function approximation.  
\(^b\) Partial least squares-discriminant analysis.  
\(^c\) Multifactorial analysis.

Table 3. Summary of published QSAR models for predicting the ecotoxicity for \textit{V. fischeri}.

There were two aspects clearly noticeable from the comparison made across all the published models. These are the variation in the dataset size and the number and type of molecular descriptors used. It is worth highlighting that adding new ILs which pair different elements in their structure, not considered in the earlier models, would require new set of descriptors for better molecular representation and good applicability of the QSAR model. For instance, Viboud et al. [15] developed two linear QSAR models for relatively small datasets containing 10 and 19 ILs. The first dataset which comprised pyridinium bromide-based ILs was expanded by the addition of 9 ILs pairing different cations (imidazolium, pyrrolidinium and piperidinium). Although a single descriptor was used in the model construction, good correlation coefficients was achieved i.e. 0.934 and 0.861, respectively. However, it is clear that expanding dataset size would affect the model accuracy resulting in the accuracy drop. Therefore, many QSAR models developed to cover relatively huge dataset were constructed using higher number of molecular descriptors to cover the significant variation in all the molecular structure. So far, the largest dataset used comprised 157 ILs covering 74 cations and 22 anions, studied by Yan et al. [47]. They used linear regression to propose a predictive model with good correlation coefficient i.e. $R^2 = 0.908$, using large number of topological descriptors i.e. 28.

Overall, it can be concluded that the application of proper method for the selection of molecular descriptor, and the model validation method used, become the key factors in influencing the outcome of the QSAR/QSPR model developed. With the right selection of the molecular descriptors, the accuracy and reliability of the predictive models developed could be enhanced significantly.
With such capability, the design of ILs for any application could be made to consider its toxicity thus enabling greener ILs developed for industrial application right from the design stage.

4. Conclusion

The collective study on the relationship between ILs ecotoxicity towards luminescent marine bacterium *V. fischeri* has demonstrated the impact of the ILs structure on the overall toxicity. Although, most of ILs highlighted in the works discussed were practically rated between harmless to moderately toxic towards luminescent marine bacterium *V. fischeri*, few of them were found to be highly toxic with an EC$_{50}$ values lower than 1 mg L$^{-1}$. These ILs are mainly characterized by the presence of a cyclic cation having long alky chain attachment. The extension of the alky side chain leads to increase in the ILs hydrophobicity, and hence increasing the toxicity drastically.

There seems to be consensus from the past literature that the alkyl chain length appeared to be the dominant parameter controlling the ILs toxicity towards different aquatic organisms including *V. fischeri* and other trophic organisms such as cress (*Lepidium sativum*), mammalian cells (IPC-81), limnic unicellular green algae (*Scenedesmus vacuolatus*), enzymes (acetylcholinesterase), wheat (*Triticum aestivum*) and duckweed (*Lemna minor*). Therefore, the focus on the ILs design for low toxicity should be focussed on the ILs structure including the type of chemical elements attached to it. Two useful guidelines that could be applied to consistently design low toxicity ILs are the utilisation of shorter alky chain varied from (C$_1$ to C$_4$) attached to the ILs cation, and functional group containing oxygen paired to its atom on the ILs cation side. Any alky chain used as extension on the ILs cation should be kept at less than C$_4$ since the toxicity increases significantly beyond the limit. Past toxicity studies have also displayed that the non-aromatic cation such as piperizinium, pyrrolidinium and morpholinium, shows lower toxicity compared to the imidazolium and pyridinium cations which contained an aromatic structure.

Besides the above factors highlighted on ILs cation affecting its toxicity, the proper selection of the anion moiety could also have impact on controlling its toxicity. With the exception of the FeCl$_4$ anion which showed very high toxicity behaviour towards *V. fischeri*, the other anion types demonstrated heterogeneous and diverse effect on the ILs toxicity. It was difficult to ascertain an identifiable pattern that could explain the toxicity variation. Even the effect of the side alky chain length for the carboxylic acids-based anions does not show any clear trend relating to the changes in the corresponding ILs toxicity. Also, for some of the anions possessing more than one oxygenated atom in their structure, the expected reduction in toxicity as seen in the cations’ effect, was not evidenced. Hence, it can be concluded that although changing the anions’ structure and content can alter the chemical and physical properties of the ionic liquids but the effect on ILs toxicity remained uncertain.

Overall, from the aquatic toxicity point of view, ILs may not seem to necessarily perform better when compared to the organic solvent, which it supposed to replace for many industrial applications. However, considering their negligible impact on the atmosphere as a result of extremely low vapour pressure as well as being non-flammable, and coupled with the unique
tuning ability to meet specific industrial requirements, ILs can still be largely considered as promising class of greener material. In view of the need to perform the toxicity assessment to confirm fully green behaviour, the QSAR/QSPR method can be the key towards providing the predictive ability which could guide the design of novel greener ILs for industrial application.

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