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Probabilistic ecotoxicological risk assessment of imidazolium ionic liquids with amino acid and halide anions

Muhammad Ishaq Khan[1], Dzulkarnain Zaini[1,*], Azmi Mohd Shariff[1] and Muhammad Moniruzzaman[1]

[1] Centre of Advanced Process Safety (CAPS), Chemical Engineering Department,
Universiti Teknologi Petronas, 32610 Bandar Seri Iskandar,
Perak Darul Ridzuan, Malaysia.
Phone: +605 - 368 7588; Fax: +6053656176
[*]Email: dzulkarnain.zaini@utp.edu.my

ABSTRACT

Ionic liquids (ILs) are chemical substances with good solubility and low vapor pressure because they are ionized and therefore charged. ILs may damage ecosystem due to their good water solubility. Toxicological studies for individual ILs. Major constraint in ILs ecotoxicology is that risk cannot be quantified by risk quotient methods because of unavailability of exposure assessment data. At present, only limited information is available about the impacts of ILs to aquatic ecosystems. The main objective of the current work is to use statistical methods to available literature on acute toxicity data of ILs to assess potential ecotoxicological risks when the ILs do come into industrial use. Probabilistic ecotoxicological risk assessment (PETRA) method was adopted by using Chemical Toxicity Distributions (CTDs) and Species Sensitivity Distributions (SSDs). SSDs has been used to derive threshold values below which the ecosystem and its biotic components could be protected from the adverse effect of ILs. CTDs has been used to estimate the probability of finding ILs with an effect below a calculated concentration which is considered to be safe environmental concentration. Acute toxicity data were collected from the literature on the acute toxicity of four bacterial pathogens *Aeromonas hydrophila*, *Escherichia coli*, *Listeria monocytogenes* and *Staphylococcus aureus*. CTD method was applied to assess the distribution of toxicities of group of IL to individual species. The SSD method was applied to estimate guideline values (GVs) to estimate different level of protection of bacterial species from ILs. Imidazolium chloride and bromide ILs were reported to pose more than 5 % risk towards bacteria. Out of the four bacterial strains, *E coli* was reported to be potentially at higher risk because of highest sensitivity when exposed towards ILs. The risk posed was five percent which is acceptable level of risk.

Keywords: Ionic liquids; Ecotoxicity; Species Sensitivity Distributions; Chemical Toxicity Distributions; Probabilistic Risk Assessment.

INTRODUCTION

ILs are chemical substances with the capabilities to replace the conventional organic solvents. They have good solubility and low vapor pressure because they are ionized and therefore charged [1]. Potential applications may range from separation processes, catalytic activity, and synthesis, as well as in the research area of emerging chemicals [2-8]. ILs do not contribute to air pollution as like the

gases or other industrial chemicals because of lower vapor pressure, but they may harm the ecosystem due to good solubility [9-12]. ILs are toxic towards biotic components of ecosystems, including aquatic species[13]. Conventional toxicological research on ILs focused only on the toxicity assessment. There are a lot of species on individual ILs available in the literature [14]. Since ILs are not still used in industries, therefore there is a lack of industrial data. At present only limited information is available about the impacts of ILs on the environment[15], so it is difficult to get exposure data for ecotoxicological risk.

Conventionally, ecological risk assessment (ERA) methodologies are adopted to estimate the probability and the extent of the adverse effect of exposure to toxic chemicals towards ecosystems[16]. The ERA is characterized by effect and exposure assessment [17]. Effect assessment is carried out by performing acute toxicity testing and then NOEC or PNEC are estimated from the toxicity results by using appropriate assessment factors[18]. However, NOECs have been criticized for a variety of reasons [19]. As ILs are new class of chemicals having no major industrial data of leakage into aquatic ecosystems. Therefore, only the effect assessment is carried out either by experimental studies or by modeling techniques to predict toxicity of new ILs[20]. As individual species are not the representatives of cumulative aquatic population, therefore only the effect assessment is not enough to assess ecotoxicological risks of ILs. Another major issue in the assessment of ecotoxicological impacts of ILs on aquatic ecosystem is the limitation in chronic toxicity data. [21].

Traditionally, the toxicity was either evaluated by experimental the acute toxicity studies or predicted by various techniques amongst which QSAR is one of the best techniques[22]. However, it is impossible to test the impacts of all ILs on all species. Laboratory generated data of single species is considered for the hazard ranking only in the ecotoxicological assessment of ILs. Conventionally, the toxic effect of a single ILs is tested on individual organism representatives of various species of ecosystems. Although the results produced are usually accurate and a lot of information on the toxicity of ILs towards individual species are validated through a number of acute toxicity tests, it is desirable to assess the cumulative impacts of ILs to the environment, especially aquatic ecosystems. Even though there are no evidence of exposure of the aquatic organism to ILs in real life, but the use of analytical techniques to translate laboratory acute toxicity data can help to develop tools for the potential ecotoxicological risk assessment. The objective of current work is the extrapolation of the results from a relatively small set of acute toxicity data to assess the distribution of toxicities of ILs to a range of species and the sensitivities of these species towards imidazolium ILs by statistical methods.

In recent years, Species Sensitivity Distributions (SSDs) have become the preferred method of determining PNECs [23]. Different species may react to toxicants in differ way because of a number of reasons. Hence SSD provide a better assessment method to cover this gap [24]. However, no one of the SSD methods had been allied to imidazolium ILs. Furthermore, exposure assessment is carried out by monitoring some real exposure data (measure environmental concentrations, MEC) or from modeling approaches (Predicted Environmental Concentrations, PEC) [25]. The ERA could have been applied only if ILs have some real exposure data. Since ILs didn't have any major industrial applications so far, a method of risk assessment which would not require exposure data is adopted in the current research. Therefore, only available toxicity data are used to calculate CTDs and SSDs. CTDs method has been used in environmental risk assessment for assessment of pharmaceutical effects on aquatic plants but this methods had never been use d for ILs risk assessment [19, 26, 27]. To address the problem of unavailability of release data of ILs the probabilistic techniques may provide best solution. As, CTD gives the probability of finding a toxic chemical below a certain concentration of the tested organisms. Therefore, probabilistic risk assessment methodology incorporating CTD and SSD methods might be one of the best solutions for ecotoxicological risk assessment of imidazolium ILs.

MATERIALS AND METHODS

Selection of Ionic liquids

ILs are emerging solvents and the family of ILs based on imidazolium has the potential for many industrial processes and applications[28]. A number of acute toxicity data are available for the imidazolium ILs. In all toxicological publications on ILs until 2015, 48 % ILs are the Imidazolium ILs[29]. This show that amongst all ILs, Imidazolium ILs are important because of their potential industrial applications. This data may be used for the alternative methods to assess the ecotoxicological risk of ILs as traditional toxicological studies of ILs do not account for risk assessment. Therefore, imidazolium ILs with different alkyl chain and two types of anions (halide, and amino acids) were selected for to apply PETRA method.

Data Selection

As ILs are still new liquids with no industrial use, only laboratory toxicity data were available. The data for the current work were obtained from the published experimental studies on the toxicity of ILs performed by Ghanem et al. 2015 [30]. In their work, they used four species of pathogenic bacteria, *Listeria monocytogenes, Staphylococcus aureus, Escherichia coli* and *Aeromonas hydrophila*. Antimicrobial test were performed by them using standard micro-broth dilution test [31, 32]. Toxicity data obtained from their work are presented in Table1.

Table 1. Toxicity of Imidazolium ILs towards bacteria

Ionic Liquids	EC50 (mmol/L) [30]			
	A hydrophila	*E coli*	*L monocytogenes*	*S aureus*
[C4mim][Cl]	75.83	80.05	85.75	69.19
[C2OHmim][Ser]	76.99	76.6	85.46	73.86
[C2OHmim][Pro]	49.56	43.84	48.88	43.19
[C4mim][Br]	47.17	43.21	42.5	42.85
[C2OHmim][Gly]	34.92	34.72	33.71	33.69
[C2OHmim][Ala]	25.64	23.86	26.37	22.47
[C6mim][Br]	12.73	11.23	11.25	9.91
[C6mim][Cl]	8.53	11	13.05	11.81
[C8mim][Ser]	4.72	4.74	4.68	5.03
[C8mim][Pro]	4.07	3.33	3.72	4.09
[C8mim][Gly]	2.82	2.72	2.72	2.49
[C8mim][Ala]	2.75	2.73	2.62	2.72
[C8mim][Asn]	2	2	2.05	2.07
[C8mim][Cl]	1.48	1.66	1.63	1.41
[C8mim][Br]	1.25	1.12	1.24	1.05
[C10mim][Br]	0.1	0.1	0.11	0.1
[C12mim][Br]	0.05	0.05	0.06	0.06

The results obtained from their work were according to accepted trends in ILs toxicology. The effect of alky chain length, amino acid anions and functional group were good enough as they reflect common trends found in peer literature review [33, 34].

Chemical Toxicity Distributions (CTDs) and Species Sensitivity Distributions (SSDs)

Chemical Toxicity Distributions

Chemical toxicity distribution method is applied when a group of chemicals with the same mode of actions are used and there is a need of assessment of the group towards the environmental species [19, 35, 36]. In CTDs method, For each species, the EC50 data for all ILs (Table 1) were used to calculate CTDs according to the methods outlined by Williams et al 2011[27]. CTDs based on EC50 were used since there were no EC10 data available. The EC50 data for all compounds for a given species were ranked in Excel. The ranks were converted to % ranks (j) using the Weibull formula [37] :

$$J = \frac{100 \times i}{n+1} \qquad (1)$$

Where *j* is percent rank *i* is the rank and *n* is the total number of compounds. The CTDs were graphed in Excel by plotting the probit of the % rank, calculated as =NORMINV((j),5,1) where NORMINV returns the normal cumulative distribution function, against the EC50 of the compounds. A linear regression was then performed in Excel. The threshold values were calculated from the CTDs curves which provided the concentrations of the group of ILs towards individual species.

Species Sensitivity Distributions

Species sensitivity distribution is a statistical distribution method which describes the sensitivity of a toxicant towards a set of species[38]. As there are a large number of species in our ecosystem, therefore we may not know the true distribution of toxicity endpoints. Hence, SSD is used to estimate the sensitivity by using toxicity data of the individual chemicals towards a set of species and visualized as cumulative distribution function [39]. SSDs are presented in curves which are is basically cumulative distribution function of toxicity data performed at laboratory level using a single species. These curves derive Guideline values (GVs) to quantify ecotoxicological risk. Only limited research had been carried out using SSDs for ILs toxicity [40] but these results could not provide a way to assess ecotoxicological risks of ILs.

For each IL, the package BurrliOz 2 was used to derive an SSD using EC50 data for all four bacterial species. Because there were four species, the package fitted a log-logistic curve to the data [41]. BurrliOz produced a graph of the SSD and calculated the GVs to protect 80%, 90%, 95%, and 99%. GVs were taken as toxicity threshold values for the assessment of ecotoxicological risks [42]. SSD analysis evaluated the effects of individual ILs on a range of selected organisms. GVs were used as Predicted Environmental Concentrations (PECs) which can be compared with PNECs to quantify risk by hazard quotient method[43].

RESULTS AND DISCUSSION

Chemical Toxicity Distributions

For the sake of proper data processing, we divided the data into three groups, namely type-I (imidazolium Chloride and Imidazolium Bromide ILs), type-II (Amino acids Imidazolium ILs with C2OH) and type-III ILs (Amino acids Imidazolium ILs with C8 alkyl chain). Williams et al 2011 have defined 1st and the 5% values as their Screening Point Values (SPVs)[27]. To estimate the concentrations expected to have no effect, SPVs referring to 1st and 5th centiles were divided by an assessment factor of 1000 to obtain the Screening Predicted No Effect Concentration (SPNEC) [44, 45]. The CTD plots of imidazolium chloride and imidazolium bromide ILs for all four species were shown in Figure 1. Similarly, the CTD plots for amino acids Imidazolium ILs were shown in Figure 2 and Figure 3.

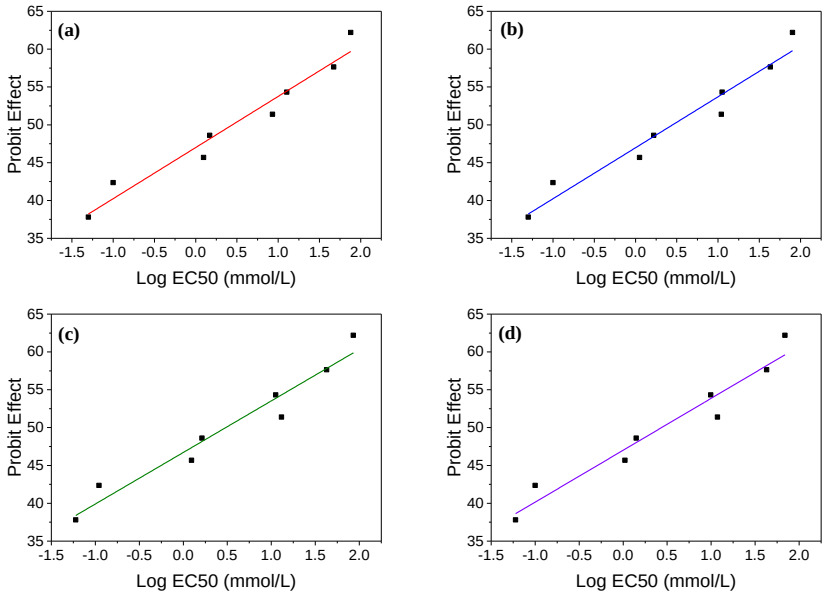

Figure 1. Probit effect of Type-I ILs towards *A hydrophila* (a), *E coli* (b), *L monocytogenes* (c), *S aureus* (d)

SPVs were calculated based on CTD curves. SPENCs were calculated by dividing an assessment factor of 1000 to SPVs to compensate uncertainties in the toxicity data. The concentration against 5th percentile was considered to be a safe concentration [3] for the selected species. It is indicated that if the selected ILs were exposed to one of four bacteria *A hydrophila*, *E coli*, *L monocytogenes* and *S aureus*, the SPNEC will be considered as safe concentration. Exceeding to SPNEC values will exceed risk to four bacteria of the inhabitant of that environmental compartment. The acceptable risk of the toxicants towards the selected species of an ecosystem by SSD is 5 %. If the exposure concentration is less than SPNEC, there will be risk to the species under studied. The SPNECs estimated from CTD analysis are tabulated in Table 2, 3 and 4.

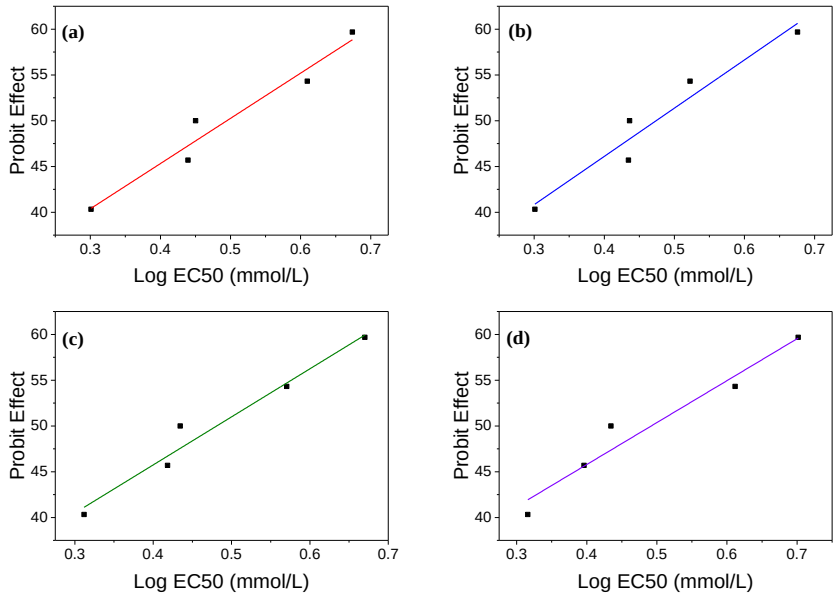

Figure 2. Probit effect of Type- II ILs towards *A hydrophila* (a), *E coli* (b), *L monocytogenes* (c), *S aureus* (d)

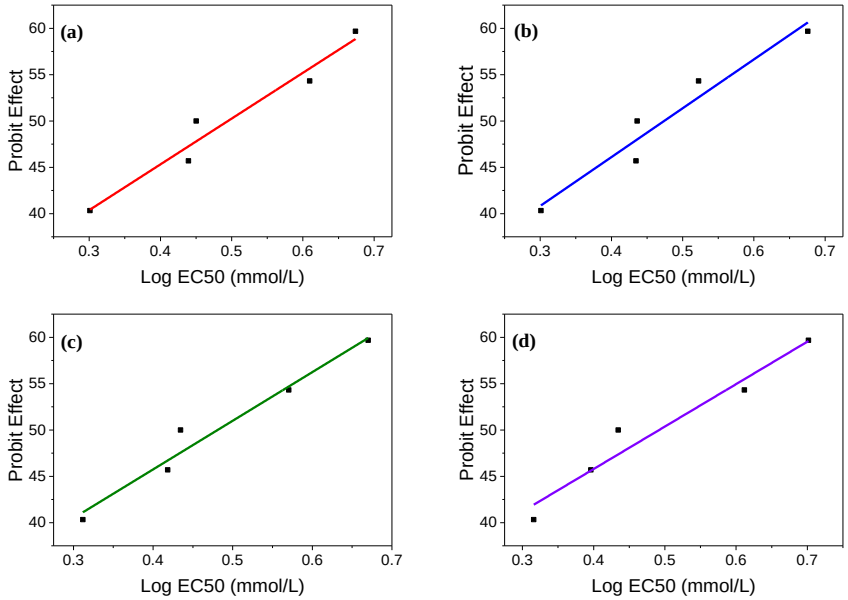

Figure 3. Probit effect of Type-III ILs towards *A hydrophila* (a), *E coli* (b), *L monocytogenes* (c), *S aureus* (d)

Table 2. Screening Predicted No-Effect Concentrations Based on Chemical Species Distributions screening: Type-1 ILs

Organism	No. of ILs	Centile	SPV (mmol/L)	SPNEC (mmol/L)
A hydrophila	8	1st	0.0094169	94.2 x 10-5
		5th	0.0452276	4.52 x 10-5
E coli		1st	0.0009908	9.91 x 10-5
		5th	0.0101807	1.02 x 10-5
L monocytogenes		1st	0.0011937	119.37 x 10-5
		5th	0.0118663	1.19 x 10-5
S aureus		1st	0.0011371	11.4 x 10-5
		5th	0.0111187	1.11 x 10-5

PNECs for the selected imidazolium ILs were observed to have 0.000009414 to 0.0004522 mmol/L of concentration for type-1 ILs safe environmental range for *A hydrophila* at very low risk level (1st centile) and acceptable risk level (5th centile) consecutively.

Table 3. Screening Predicted No-Effect Concentrations based on Chemical Species Distributions screening: Type-II ILs

Organism	No. of ILs	Centile	SPV(mmol/L)	SPNEC (mmol/L)
A hydrophila	4	1st	9.242303284	924.2 x 10-5
		5th	14.49952114	1449.9 x 10-5
E coli		1st	8.245450458	825.0 x 10-5
		5th	13.17572828	1317.5 x 10-5
L monocytogenes		1st	8.142992623	814.3 x 10-5
		5th	13.33889725	1333.8 x 10-5
S aureus		1st	7.76790771	776.80 x 10-5
		5th	12.50126708	1250.1 x 10-5

From SSDs analysis it was revealed that the Type-II ILs have SPNEC from 924.2 x 10-5 to 1449.9 x 10-5 mmol/L for *A hydrophila* at very low risk level to acceptable risk level.The results of SSD of Type-III ILs were presented in Table 4. Type-III ILs were observed to have SPNEC from 105.6 x 10^{-5} mmol/L to 119.9 x 10^{-5} mmol/L for *A hydrophila* which indicated an acceptable risk (5 %) at 119.9 x 10^{-5} mmol/L.

SPNECs indicated that amongst three different groups of ILs with the same mode of action, Type-I ILs had a potential to pose high risk to the selected species as the PNEC of type-II ILs were three order of magnitude. Similarly, the PNEC type-III ILs was also greater than one order of magnitude. Furthermore, it was concluded that if an ecosystem containing *A hydrophila*, *E coli*, *L monocytogenes* and *S aureus* will be exposed to three groups of imidazolium ILs studied in current work, Type-II and type-III ILs would be at comparatively less risk. The comparison is witnessed by the fact that amino acids ILs were less toxic [30]. The different concentrations of the group of ILs

highlighted the important of sensitivities of the species. The sensitivity of the species in response to toxic effects of ILs was analysed by SSD method.

Table 4. Screening Predicted No-Effect Concentrations Based on Chemical Species Distributions screening: Type-III ILs

Organism	No. of ILs	Centile	SPV(mmol/L)	SPNEC (mmol/L)
A hydrophila	5	1st	1.056551327	105.6 x 10-5
		5th	1.199705734	119.9 x 10-5
E coli		1st	1916.514866	19165 x 10-5
		5th	16509.82906	165098 x 10-5
L monocytogenes		1st	1.091175626	109.10 x 10-5
		5th	1.47137974	147.10 x 10-5
S aureus		1st	0.964015497	96.40 x 10-5
		5th	1.357931023	135.70 x 10-5

Species Sensitivity Distributions

Burrlioz2.0 is one of the software used for SSD analysis [46]. Species sensitivities distributions were calculated using the Burrlioz2.0 package to obtain guideline values (GVs) for different levels of protection SSD plots from each group for all 4 bacteria were generated and shown in figures 4, 5 and 6. The SSD data provided different guideline values for all four bacteria at different levels of protection for each of the ILs.

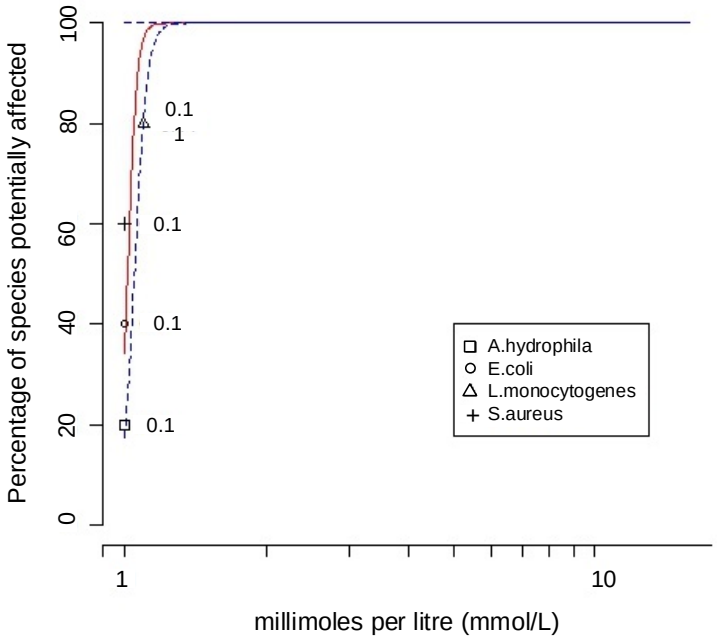

Figure 4. SSD curve for C10mimBr (type-1 ILS)

SSD for type-I ILs indicated that C10mimBr had the worst effect on all four microbes. Estimated 5% of species will have an EC50 of less than 0.095 mmol/L (0.091-0.10 mmol/L) or less at 95 % protection level.

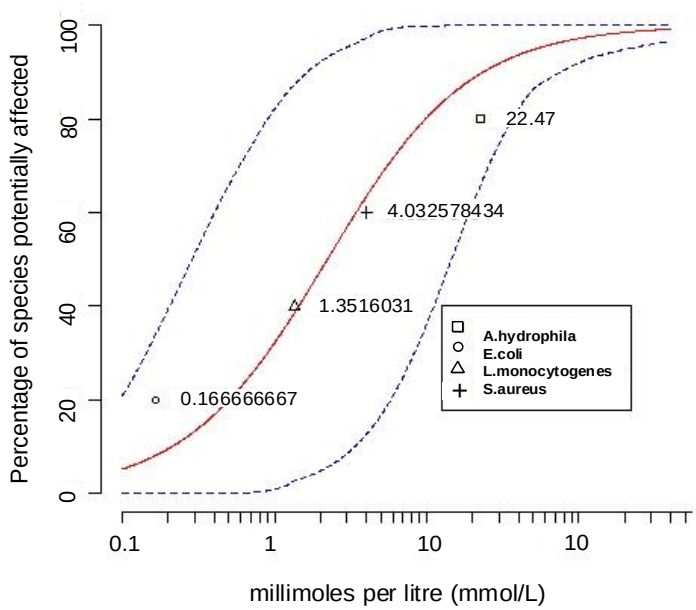

Figure 5. SSD curve for C2OHmimAla (type-II ILs)

SSD for type-II ILs indicated that C2OHmimAla had the worst effect on all four microbes. Estimated 5% of species will have an EC50 of less than 22 mmol/L (21-25 mmol/L) or less at 95 % protection level.

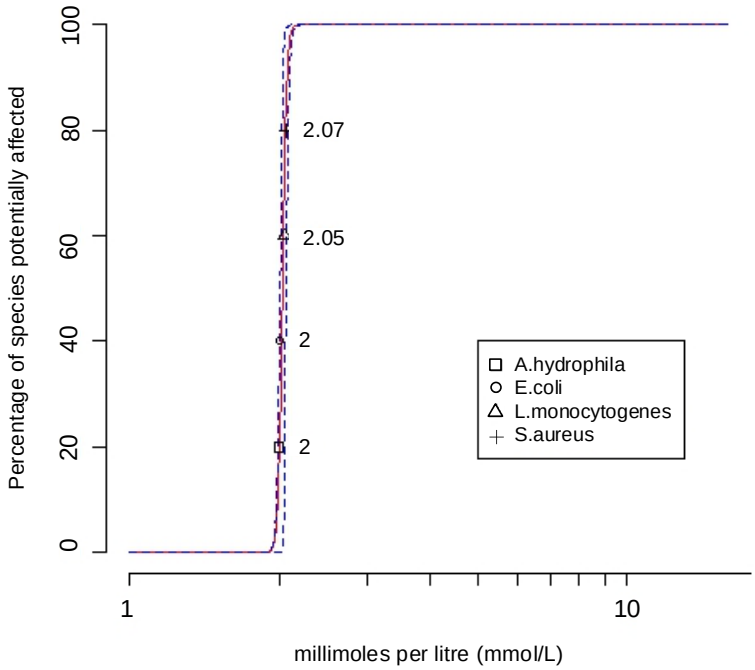

Figure 6. SSD curve for C8mimAs (type—III ILs)

SSD for type-III ILs indicated that C8mimAs had the worst effect on all four microbes. Estimated 5% of species will have an EC50 of less than 2 mmol/L (CI 2-2 mmol/L) or less at 95 % protection level.

SSD analysis performed for three groups of ILs provided an understanding of how we can prioritize the use of chemicals into a specific environment. Especially aquatic compartment of ecosystem which are represented by four bacterial strains studied in current research. For example, amongst the studied ILs, C10MIMBr ILs having GV of 0.095 mmol/L were proved to be riskier as compared to C8MIMAs with GV of 2 mmol/L and C2OHMIMCl with 22 mmol/L as GV. The major reason for the higher sensitivity of selected bacteria towards ILs is the fact that amino acids IL were less toxic as compared to bromide or chloride ILs. Similarly, the higher sensitivity of imidazolium chloride is because of the combination of cation and anion in such a way that this cationic anionic interaction proved to be more toxic amongst other ILs of the same and other type of families.

CONCLUSIONS

The PETRA methodology presented an idea to assess the effect of individual ILs to a range of an organism or species along with the assessment of effects of a group of ILs to a single organism or species. Although not enough quality data was utilized in applying PETRA, this methodology still provided an idea for probabilistic measures for ecotoxicological assessment of ILs. SPNECs from CTDs indicated that amongst three sets of ILs with the same mode of action Type-I ILs are potentially risky toward the selected species.

Type-II and type-III ILs were noted to be at comparatively potentially less risky towards species under investigations in current research. This is because of amino acids ILs are considered to have low toxicity effect, hence low risk to the species Similarly the SSDs provided Guideline values for all three groups towards four species. Type-1 ILs having 0.095 mmol/L as Guideline Value was declared most risky toward selected species as compared to type-II (GV 22 mmol/L) and type-III ILs (GV 2 mmol/L).

Amino Acids ILs are considered to have low toxicity because of which in current research Amino acids ILs (type-II and type-III) were proved to be less risky for selected species. ILs are replacing many industrial chemicals, therefore the methods applied for the ecotoxicological risk assessment on ILs in current work will directly affect industrial chemicals. As a result, environmental safety can be improved which will increase the importance of the use of probabilistic methodologies for newly synthesized industrial chemicals.

The major contribution of the current work is the assessment of ecotoxicological risk estimation even without the availability of exposure assessment data. In current work we have used EC50 values to calculate CTDs and SSDs, however more sensitive concentrations like EC20 could provide better risk assessment. Furthermore, the success of this methodology will enable risk assessors to integrate exposure end effect assessment methods to quantify ecotoxicological risk associated with the applications of ILs.

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