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Original Research

Role of Hydrophobicity in Bio-Accessibility of Environmental Pollutants Among Different Organisms

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Abstract

This study concerns the relationship between hydrophobicity and bio-accessibility of environmental pollutants among *Tetrahymena pyriformis* (protozoan), *Daphnia magna* (water flea) and the fish *Poecilia reticulata*. The toxicological data of 55 chemicals in terms of 50% effect concentration (EC_{50}) was selected toward these three biological objects along with their hydrophobic potential (octanol-water partition coefficients (log K_{ow})). Overall, a significant correlation was recorded among all test systems, with the highest between *Tetrahymena pyriformis* and *Poecilia reticulata* (R = 0.93). The acute toxicity results revealed substantial difference in the sensitivity of the three test systems but at a certain level of hydrophobicity (log K_{ow} values 0.5 to 2.5), where all environmental pollutants have the utmost ability to reach biological compartments as cytosole and target sites within the membranes, to interfere with normal cell functioning by effecting normal enzymatic activity and directly to biological macromolecules.

Keywords: hydrophobicity, toxicity, protozoan, water flea, fish

Introduction

In the modern world, organic chemicals have extensively been used in a variety of industries, including pharmaceuticals, fuels, beverages, foods and agricultural products [1-3]. However, limited information is available about their potential risk to the environment – especially in developing countries because of time and economic constraints [4-6]. In aquatic systems, it is often difficult to make relationships of cause and consequences for aquatic life [7]. So far, different efforts have been made to look into other avenues, i.e., physico-chemical properties, different biological barriers and modelling of existing data to address the toxic potential of pollutants [8-12]. Among different physico-chemical properties (e.g., adsorption forces at surface, solubility, hydrogen bonding, lone-pair electrons, chemical polarity and polarizability among different atoms and molecules)

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of organic pollutants, hydrophobicity plays a substantial role in the bio-availability/bio-accessibility of these chemicals [13-16].

According to the mode of action, chemicals are classified into two main classes: chemicals with a non-specific mode of action and chemicals with a specific mode of action [17-19]. Chemicals having non-specific toxicity usually interact with lipids of membranes in bio-molecules, and therefore toxic effects are highly associated with their hydrophobicity. In contrast, chemicals with a specific mode of action have not only specific target-oriented effects (based on the specific receptors), but the non-specific components (due to the hydrophobic nature) also contribute to the overall toxic effects [18]. Hydrophobic potential of environmental pollutants can be calculated from octanol-water partition coefficients (log K_{ow}) [20-22]. In an aqueous environment, the concentration of highly hydrophobic chemicals remains quite low, and therefore their specific toxic effects may not be obvious [23]; whereas non-specific toxic effects will remain due to hydrophobicity and will be additive [24, 25].

Daphnia magna (water flea), *Vibrio fischeri* (Marine bacterium), *Tetrahymena pyriformis* (protozoan), green algae and fish are the most commonly used laboratory species [26-32]. A large amount of toxicity data obtained by reliable and robust methods is available for these test systems [33-38]. It still remains unclear whether the linear relationship between hydrophobicity and toxicity exists for all environmental pollutants [39]; therefore, for better understanding, it is imperative to work in this area. In the present study, we aim at identifying the toxicological diversity with respect to different hydrophobicity levels among *Tetrahymena pyriformis*, *Daphnia magna* and *Poecilia reticulata*. The sensitivities of these three bio-indicators with reference to their hydrophobicity was analysed in order to obtain a wide range of hydrophobicity with clear difference in their pertinent sensitivity toward different chemicals.

Materials and Methods

In the present study we conducted bibliographical research. We obtained toxicity data of 55 organic contaminants including narcotic compounds from literature toward three different test systems by using *Tetrahymena pyriformis*, *Daphnia magna* and *Poecilia reticulate*. The molecular descriptor (log K_{ow} values = octanol/water partition coefficient) has been determined using the EPI suite (USEPA, 2009). The mortality of a guppy (*P. reticulata*) after 96 hours and the growth impairment of ciliate (*T. pyriformis*) population in terms of LC_{50} and IGC_{50} data (secured from TETRA-TAX) for these chemicals with toxic effects were selected from an appendix by Seward et al. [33] as the source of data. The protocol details for *T. pyriformis* population growth impairment are given in a study reported earlier [38]. The presented toxiciare value for *Daphnia magna* and the median lethal concentration (LC_{50}) for essays of 48-h were collated from an appendix by Von der Ohe et al. [37] as the source of data.

Results and Discussion

The research performed resulted in three systemized toxicity test systems with relevance to their hydrophobicity. The toxicity database contains 55 organic chemicals with different hydrophobicity levels ranging from −0.24 to 3.93. For all three test systems, the interspecies toxicity correlation was carried out for the toxicity values illustrated in Table 1. Overall, a significant correlation was recorded among all three test systems. The interspecies toxicity correlation was highest between *Tetrahymena pyriformis* and *Poecilia reticulata* (R = 0.93). Whereas, the correlation was slightly weaker between the toxicity toward *Tetrahymena pyriformis* and *Daphnia magna* (R = 0.73) and between the toxicity toward *Daphnia magna* and *Poecilia reticulata* (R = 0.74).

The main objective of the present study was to identify toxicological differences of various chemicals at different hydrophobicity levels among three test organisms, i.e., *Tetrahymena pyriformis*, *Daphnia magna* and *Poecilia reticulata*. The sensitivity of these bio-indicators with their hydrophobicity data is illustrated in Table 1. The results obtained suggest that the hydrophobic property of chemicals has a strong influence on chemical uptake by organisms as translated into different toxicity levels. The acute toxicity results reveal substantial differences in the sensitivity of the three test systems, but at certain level of hydrophobicity (log K_{ow} values 0.5 to 2.5) as shown in Fig. 1.

In general, toxicological data suggests that all organisms sensitivity to these organic chemicals lay on the same order of the magnitude. Analysing the acute toxicity bio-assays separately for these chemicals, we cannot see any toxicological difference at very low (*Tetrahymena* vs *Poecilia*) and very high (*Daphnia* vs *Poecilia*) hydrophobicity levels. The hydrophobic potential of chemicals is suggested to be a major driving force for intake of xenobiotics in aquatic species. Consequently, it leads to the accumulation of hydrophobic residues in the cellular membranes causing narcotic effects. However, the concentration of the chemicals in the aqueous cytosole is decreased, which results in less availability to reaction targets such as protein sites in the hydrophilic environment of the cell contents of the aquatic species. Furthermore, chemical capabilities of a compound to interact and modify proteins and other macromolecules like DNA depend on its hydrophobicity (log K_{ow}) and reactivity (the presence of reactive moieties) [40].

The majority of industrial organic chemicals (about 60%) are considered to act as baseline contaminants (i.e., acts via narcosis). Their toxicities are quantitatively

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Table 1. Set of 55 organic chemicals with information about their hydrophobicity and toxicity toward the protozoan water flea and fish.

Sr. No.	Chemical	CAS	log K_{ow}	*Tetrahymena pyriformis*[a] (M)	*Daphnia magna*[b] (M)	*Poecilia reticulata*[c] (M)
1	Acetone	67-64-1	-0.24	-0.8	-0.62	-0.9
2	Ethanol	64-17-5	-0.14	-0.69	-0.59	-0.56
3	2-Methyl-2,4-pentanediol	107-41-5	0.58	-1.04	-1.22	-1.04
4	Isobutanol	78-83-1	0.77	-1.63	-1.82	-1.71
5	Aniline	62-53-3	1.08	-2.77	-5.33	-2.91
6	2,2,2-Trichloroethanol	115-20-8	1.21	-2.54	-3.00	-2.69
7	Phenol	108-95-2	1.51	-2.54	-3.44	-3.45
8	3-Methoxyphenol	150-19-6	1.59	-2.67	-3.48	-3.22
9	2-Methylaniline	95-53-4	1.62	-2.45	-5.31	-3.12
10	3-Methylaniline	108-44-1	1.62	-2.58	-5.17	-3.47
11	1,3-Dinitrobenzene	99-65-0	1.63	-3.76	-3.59	-4.64
12	2-Chloroaniline	95-51-2	1.72	-2.75	-5.19	-4.31
13	3-Chloroaniline	108-42-9	1.72	-3.01	-6.11	-3.98
14	4-Chloroaniline	106-47-8	1.72	-4.35	-6.41	-3.67
15	Nitrobenzene	98-95-3	1.81	-3.14	-3.48	-2.97
16	2-Methylphenol	95-48-7	2.06	-2.71	-4.05	-3.77
17	3-Methylphenol	108-39-4	2.06	-2.97	-3.04	-3.48
18	4-Methylphenol	106-44-5	2.06	-2.79	-3.68	-3.74
19	2-Ethylaniline	578-54-1	2.11	-2.65	-4.18	-3.21
20	4-Ethylaniline	589-16-2	2.11	-3.05	-6.13	-3.52
21	2-Chloro-4-nitroaniline	121-87-9	2.12	-3.75	-4.49	-3.93
22	Quinoline	91-22-5	2.14	-3.09	-3.53	-3.63
23	4-Chlorophenol	106-48-9	2.16	-3.54	-4.42	-4.18
24	2,4-Dinitrotoluene	121-14-2	2.18	-3.64	-3.72	-4.16
25	1-Chloro-2,4-dinitrobenzene	97-00-7	2.27	-4.98	-5.4	-6.19
26	2-Nitrotoluene	88-72-2	2.36	-3.05	-4.14	-3.59
27	3-Nitrotoluene	99-08-1	2.36	-3.05	-4.04	-3.65
28	4-Nitrotoluene	99-99-0	2.36	-3.17	-4.01	-3.67
29	2,5-Dichloroaniline	95-82-9	2.37	-3.58	-4.74	-4.99
30	3,5-Dichloroaniline	626-43-7	2.37	-3.71	-5.16	-4.62
31	2,4-Dichloroaniline	554-00-7	2.37	-3.56	-5.43	-4.41
32	3,4-Dichloroaniline	95-76-1	2.37	-4.37	-5.95	-4.39
33	Tetrachloromethane	56-23-5	2.44	-2.71	-3.64	-3.36
34	2-Chloronitrobenzene	88-73-3	2.46	-3.39	-3.64	-3.72
35	3-Chloronitrobenzene	121-73-3	2.46	-3.63	-3.84	-4.01
36	4-Chloronitrobenzene	100-00-5	2.46	-3.21	-4.31	-4.42
37	Toluene	108-88-3	2.54	-2.5	-2.8	-3.13
38	2,4-Dimethylphenol	105-67-9	2.61	-2.96	-4.43	-3.86
39	Chlorobenzene	108-90-7	2.64	-2.87	-3.77	-3.77

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Table 1. Continued.

40	4-Chloro-3-methylphenol	59-50-7	2.70	-3.8	-4.85	-4.33
41	2,3-Dimethylnitrobenzene	83-41-0	2.91	-3.56	-4.56	-4.39
42	3,4-Dimethylnitrobenzene	99-51-4	2.91	-3.59	-3.98	-4.21
43	2-Chloro-6-nitrotoluene	83-42-1	3.00	-3.68	-4.61	-4.52
44	4-Chloro-2-nitrotoluene	89-59-8	3.00	-3.82	-4.27	-4.44
45	2,3,4-Trichloroaniline	634-67-3	3.01	-4.35	-5.43	-5.15
46	2,4,5-Trichloroaniline	636-30-6	3.01	-4.3	-4.76	-4.92
47	4-Xylene	106-42-3	3.09	-3.12	-3.52	-3.48
48	3,5-Dichloronitrobenzene	618-62-2	3.10	-4.13	-4.46	-4.63
49	2,3-Dichloronitrobenzene	3209-22-1	3.10	-4.07	-4.62	-4.66
50	2,4-Dichloronitrobenzene	611-06-3	3.10	-3.99	-4.66	-4.46
51	2,5-Dichloronitrobenzene	89-61-2	3.10	-4.13	-4.26	-4.59
52	3,5-Dichloronitrobenzene	618-62-2	3.10	-4.13	-4.46	-4.58
53	1,2-Dichlorobenzene	95-50-1	3.28	-3.53	-4.81	-4.4
54	2-Phenylphenol	90-43-7	3.28	-4.09	-5.38	-4.76
55	1,2,4-Trichlorobenzene	120-82-1	3.93	-4.08	-4.16	-4.83

Log K_{ow} = decadic logarithm of the octanol/water partition coefficient calculated with EPISuite [21], LC_{50} [mol/L] / IG_{50} [mol/L] = effective concentration yielding 50% inhibition. [a,c]96-h guppy (*P. reticulata*) mortality (LC_{50}) and the 40-h ciliate (*T. pyriformis*) population growth impairment (IGC_{50}) data was collated in an Appendix by Seward (2002). [b]Medium Lethal Concentrations (LC_{50} Immobilization) for essays of 48-h, were collated in an Appendix by Von der Ohe (2005)

associated with their partitioning into biological membranes [19, 41]. Certain chemicals, however, may interact through more specific mechanisms. For example, weak organic acids lower the electro-chemical gradient and impair the cellular energy transduction by membrane. On the other end, compounds with specific functional groups may interact with different enzymes and receptor sites in the membrane [42].

The impact of environmental contaminants can be estimated by studying the toxicological effects or

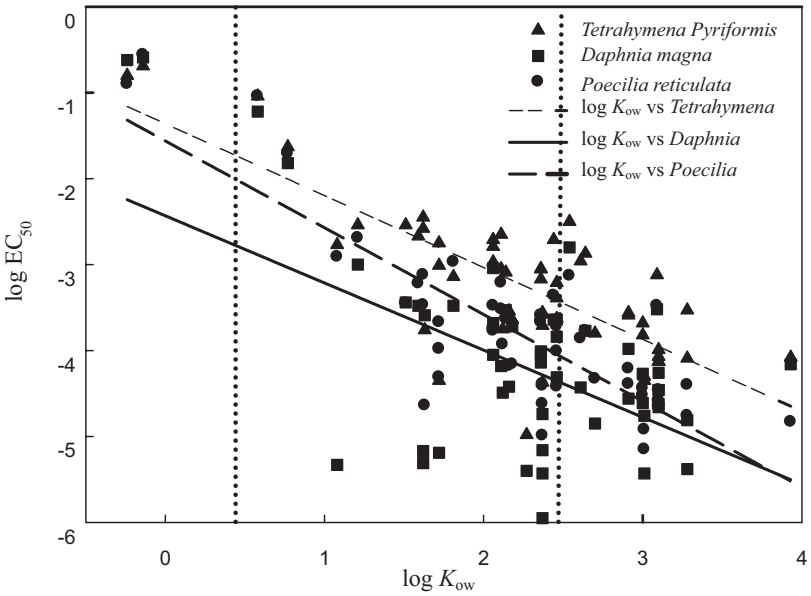

Fig. 1. Acute toxicity of 55 organic chemicals toward protozoan *Tetrahymena pyriformis*, water flea D*aphnia magn*a and fish *Poecilia reticulata* vs. their hydrophobicity values (*log* K_{ow}); the two vertical lines represent the area with distinguish toxic response among all three bio-tests.

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quantifying the bio-accumulation of contaminants in exposed organisms. It is well established that substances with log $K_{ow} \geq 3$ can easily accumulate biological tissues [43]. However, in the case of pharmaceuticals, lipid partitioning processes are insufficient to explain bio-accumulation. It is therefore important to consider the depuration kinetics of ionized organic compounds while assessing bioaccumulation potential. To evaluate the toxicity of chemicals in an aqueous environment, it is important to discriminate the absolute concentration of a contaminant, bioaccessible fraction and its final concentration that interacts with target site(s). It is suggested that the bioaccumulation of organic compounds in an aquatic environment is more related to partitioning coefficients than their absolute exposure concentrations. Furthermore, the fate of the environmental contaminants is not only affected mainly by their physio-chemical characteristics, but also biological processes including environmental parameters that play a critical role in the uptake of these chemicals [44-47]. Biological factors including individual size, life cycle, feeding type, lipid content, respiration strategy, habitat and metabolic processes may affect the uptake and sensitivity of individuals to the contaminants [48-50]; however, the available information is still limited [51].

Numerous synthetic aromatic compounds such as phenolic pesticides, pentachlorophenate, benzene sulfonates, naphthalene mono- and disulfonates are known as hydrophobic ionizable organic compounds (HIOCs) [52, 53]. In case of HIOCs, speciation may strongly affect the fate of contaminants. It is suggested that the charged species show less bioaccumulation in comparison to the neutral species [54]. However, sorption contaminants to organic matter reduce their availability. Predominantly, the freely dissolved fraction of a contaminant can be available for uptake. The hydrophobic ionizable compounds such as phenolic pesticides may destroy the electro-chemical gradient of protons through interaction with the energy cycle. The process is achieved via short-circuiting, which in response may affect their bio-availability and bio-accumulation, which further enhances their sorption in organic molecules [21]. Therefore, the compounds with hydrophobic properties have the ability to change membrane energization causing membrane perturbation that in response exerts narcotic-level effects that reflect baseline toxicity. Since the cellular membranes are composed of phospholipids, the lipophilic compounds can easily penetrate to the membrane, where cytochrome P-450 enzymes are embedded. While interacting with these enzymes, hydrophilic compounds produce a specific mode of action. In the case of less hydrophobic organic compounds (e.g., log $K_{ow}<2$), partitioning into the lipid phases is not considerable; it is therefore the internal effective concentration that should be calculated considering the concentration of a toxicant in liquid phase cellular compartments of an organism [55].

Several agricultural pesticides are weak acids (low to moderate) in nature. Toxicants with a strong acidic nature have the ability to completely ionize at ambient pH. Some banned herbicides with acidic potential (i.e., trifluoroacetic and chloroacetic acids) still exist as solvent degradation products [56-58]. Since polar compounds have strong H-donor/H-acceptor ion interactions [21], they exhibit quite low IEC (ionization energy compounds) values as compared to non-polar compounds. The polar narcotic compounds exert toxicity (in terms of 50% internal lethal concentration (ILC_{50})) in a range of 0.6 to 2 mmol/kg (based on body weight) [19]. However, the effective concentration in the membrane matrix was indistinguishable in an in-vitro test among the polar and non-polar compounds; specifically, where the dependency is only on an energy-transducing membrane in different biological testing units, as the chemicals target lipid protein embedded in the membrane matrix [19]. However, the most important factor related to whole body concentration in both (polar and non-polar) compounds is the distribution of the environmental pollutants between target and non-target compartments [21].

Time of exposure has significant influence on the response of hydrophobic pollutants. Since the narcotic effect (baseline toxicity) is a reversible process in which the response to toxicants in the cellular membrane is directly associated with their concentration, effect of time is determined by the time required for equilibrium between the internal and surrounding aqueous phases. The bio-accumulation of hydrophobic compounds in the cellular compartments increases with increasing exposure time. Therefore, the importance of time of exposure couldn't be ruled out. In most acute toxicity tests, short exposure time is insufficient to reach equilibrium in hydrophobic chemicals. Therefore, the obtained effect concentrations from short-term experiments could not be time independent, and prolonged time duration is recommended [18, 19].

Furthermore, it is observed that the LC_{50}-values of electrophilic compounds with higher hydrophobic potential generally show less deviation from baseline models as compared to the electrophilic compounds with a hydrophilic nature. Although many factors influence the bio-accessibility of environmental pollutants, hydrophobicity has a substantial effect among physico-chemical properties. The potential chemicals could only meet the classification of toxic compounds while reaching the target site (by crossing all physico-chemical and biological barrier) in such quantity that can pose an adverse effect on the exposed population. The quantity of potential chemicals translated into response may vary from species to species and from chemical to chemical, as shown in Fig. 1. At a certain scale of hydrophobicity (log K_{ow} values 0.5 to 2.5), all environmental pollutants have the utmost ability to reach biological compartments such as cytosole and target sites in membranes, to interfere with normal cell functioning by effecting

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normal enzymatic activity and directly to biological macromolecules.

Conclusions

A significant relationship was found among physico-chemical (hydrophobicity) parameters and toxicity. It was demonstrated that the toxic response of all three bio-tests was distinguished at a certain level of hydrophobicity (log K_{ow} values 0.5 to 2.5). There seems to be no obvious reason, but possibly at this level of hydrophobicity of all environmental pollutants have the utmost ability to reach biological compartments to react with target sites. Secondly, the presence of proper aqueous concentrations of chemicals ensures the continuous availability of chemicals to target sites that lead to wider biological action spectra and are translated in a distinguished toxic response. Further, due to proper dose administration, all chemicals get an appropriate time to reach equilibrium between the inner and outer environments in order to follow the chemo-availability concept. For future study, along with hydrophobicity, additional factors such as steric hindrance, rate of hydrolysis, charge, mono- versus polyfunctionality, and molecular size should be considered.

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Conflict of Interest

All the authors declare no conflict of interest.

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