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A relative predictive study of structurally similar chlorophenyl urea herbicides: Monuron and Diuron

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Abstract
Herbicides have been an integral and important part of agricultural practices. Herbicides are phytotoxic chemicals that are routinely used for unwanted plants and weed control. Herbicides vary in their chemical structure and thus have very distinct difference in toxicity, associated toxicity, mechanism of action, and use. Monuron and diuron belong to phenyl urea class of herbicides these are non-selective systemic herbicides and inhibit photosynthesis. These two herbicides are structurally similar, except number of chlorine(s) in phenyl ring. The presence of an additional chlorine in diuron compared to monuron has prompted for their relative study. This paper involves the relative study of physicochemical properties of monuron and diuron like pKa, microspecies, logP, Hydrophilic-lipophilic balance (HLB), pH dependent solubility, lipophilicity, charge range which affect their herbicidal properties. These studies are carried out using Chemaxon-Chemicalize and their persistence using QSAR identifier: VEGAHUB and Toxtree on line web server.

Keywords: Monuron, Diuron, pH dependent physicochemical properties, pKa, logP, intrinsic solubility (logS) microspecies, HLB, persistence, on line web servers

Introduction
Herbicides are used for control of unwanted plants and weeds. They are phytotoxic chemicals and their mode of action on plants depends on their structure and the chemical class they belong to. The phenyl urea herbicides are an important class of herbicides [1] which have been extensively used in agriculture to protect variety of crops from weeds. The herbicidal action of phenyl urea derivatives is based on their ability to inhibit photosynthesis, and they cause the inhibition of photosystem II pathway in plants causing chlorosis. Photosystem II (PSII) is a water- plastoquinone oxidoreductase, that involves enzyme EC 1.10.3.9, and captures photons of light to energize electrons that are then transferred through a variety of coenzymes and cofactors to reduce plastoquinone to plastoquinol (Figure 1). The energized electrons are replaced by oxidizing water to form hydrogen ions and molecular oxygen. By replenishing lost electrons with electrons from the splitting of water, photosystem II provides the electrons for photosynthesis to occur [2]. The phenyl urea class of herbicides block the electron flow at PS II by attaching themselves to plastoquinone and inhibiting the activity of enzyme
EC 1.10.3.9. The activity of enzyme has been curtailed through links from Rhea, the reaction knowledgebase [3].

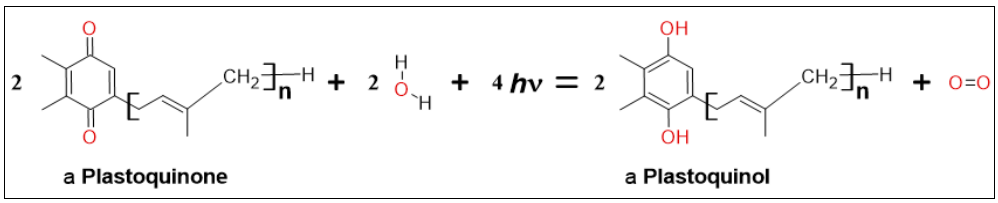
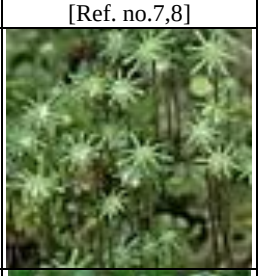


Fig 1: Photosystem II oxidoreductase process: a conversion of plastoquinone to plastoquinol in presence of light: Phenyl urea herbicides inhibit the activity of enzyme EC 1.10.3.9 involved in PS II process.

In the present paper our main aim is to carry out the relative study of two chlorinated phenyl urea herbicides monuron and diuron which are structurally very similar (Figure 2.). Both herbicides monuron and diuron are broad-spectrum non-selective, pre-emergent and post-emergent systemic herbicide used to control various annual and perennial broadleaf and grassy weeds in variety of crops.

These herbicides are photosynthesis inhibitor. Monuron is *N*'-(4-chlorophenyl)-*N*,*N*-dimethylurea also known as CMU. It is used in cotton, asparagus, sugar beet etc, and in non-crop areas. Similarly, diuron is *N*'-(3,4-dichlorophenyl)-*N*,*N*-dimethylurea, also known as DCMU, is used for general weed control and to kill emerging weeds in sugarcane, citrus, pineapple, cotton, and asparagus crops.
Further inhibitory action of phenyl urea derivatives monuron and diuron on PS-II, Photosystem Q(B) protein, for species Marchantia polymorpha (ChEMBL-Id: CHEMBL 2366463) and Spinacia oleracea (ChEMBL-Id: CHEMBL 2366481) has been reported [4, 5]. The inhibitory concentration (IC50) values of two herbicides shows significant difference [6] and their relative comparison has been given in Table 1.

Table 1: Inhibitory concentration (IC50) of Monuron and Diuron.

Herbicides Species Target ChEMBL-Id	**Monuron chembl467623**	**Diuron chembl278489**	Photograph of the species (Source: Wikipedia) [Ref. no.7,8]
	Inhibitory concentration for Photosystem Q(B) protein		
	IC50 std	**IC50 std**	
Marchantia polymorpha CHEMBL 2366463	5011.87 nM	1584.89nM	
Spinacia oleracea CHEMBL 2366481	398.11nM	50.12nM	
Interpretation	Inhibitory concentration values indicate Higher Inhibitory Action of Diuron compared to Monuron.		

In literature, diuron has been reported to be carcinogenic, mutagenic [9] and endocrine disruptor [10]. Some other common herbicide toxicities in animals have also been reported [11]. The literature data is consolidated for these two herbicides in Table 2. The data in Table 2, is with reference to environmental and human toxicity and has been curtailed from the universal databases, PubChem database [23, 13] (Available
Online: https://pubchem.ncbi.nlm.nih.gov/) and Pesticide properties data base [14, 15, 16] (PPDB; Available
Online: http://sitem.herts.ac.uk/aeru/ppdb/en/).

Table 2: Literature data on toxicity for Monuron and Diuron.

	Monuron	**Diuron**
Pub Chem database		
LD50 oral mg/kg Rat	3600	3400
GHS Hazard Statements		
H302: Harmful if swallowed [Warning Acute toxicity, oral]	✓	✓
H351: Suspected of causing cancer [Warning Carcinogenicity]	✓	✓
H400: Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard]	✓	✓
H410: Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]	✓	✓
H373: Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]	✗	✓
Pesticides Properties Data Base (PPDB)		
Carcinogen	not classifiable (suspected carcinogen)	not classifiable (suspected carcinogen)
Reproduction / development effects	No data found	No data found
Respiratory tract irritant	✓	✓
Skin irritant	✓	✓
Skin sensitiser	No data found	✗
Eye irritant	✓	✗
Endocrine disruptor	No data found	✓
Acute oral LD_{50} (mg kg^{-1}) Rat	> 1053	> 2000
DT50(typical) in days *Interpretation*:	170 Persistent	229 Persistent

Although monuron and diuron share some similarity in their structures but differ in their toxicity profiles towards environment and human beings. The difference in the presence of number of chlorines in aromaticring structure has prompted for relative study of physicochemical properties, of monuron and diuron herbicides.

This paper involves the *In-silico* analysis of monuron and diuron herbicides and their relative study in view of various aspects using Chemaxon-chemicalize (licensed version) [17], QSAR identifier: VEGAHUB platform [18, 19] and Toxtree-Toxic Estimation by decision tree approach [20] on line web server.

Results and Discussion

The herbicides Monuron and Diuron belong to the phenyl urea class of herbicides and are structurally very similar. But in case of diuron an additional chlorine is present in phenyl ring as compared to monuron. Structurally in monuron chlorine is present at position 4 in the aromatic ring while in case of diuron chlorine is present at position 3 and 4 in the aromatic ring (Figure 2.). The physiochemical properties and soil adsorption coefficient data (Table 3.) indicate the difference in their lipophilicity (logP), HLB, strongest acidic pKa, intrinsic solubility water solubility and soil persistence.

Physicochemical properties using predictive tools

Toxicity and Persistence Using Toxtree

(Rule Based Interpretation)

Threshold of Toxicological Concern indicate both monuron and diuron belong to Cramer Class III (High toxicity) as per structure alert Rule ID 3**.** According to Rule ID 3 the compound containing elements other than C, H, O, divalent S may be of toxicity concern. The presence of chlorine(s) attached to aromatic ring has triggered this alert "Yes" for monuron and diuron (Figure 2a.) Structural Alert (Rule ID 14) indicate persistence for monuron and diuron to be of class II (persistent chemical). As per Rule ID 14, chemicals with an Iodine, Chlorine or Fluorine attached to an aromatic atom are associated with low biodegradability (Figure 2b.). Consistency has been observed in this prediction and literature data for persistence, which indicates higher soil persistence for diuron as compared to monuron (Table 2 and Table 3).

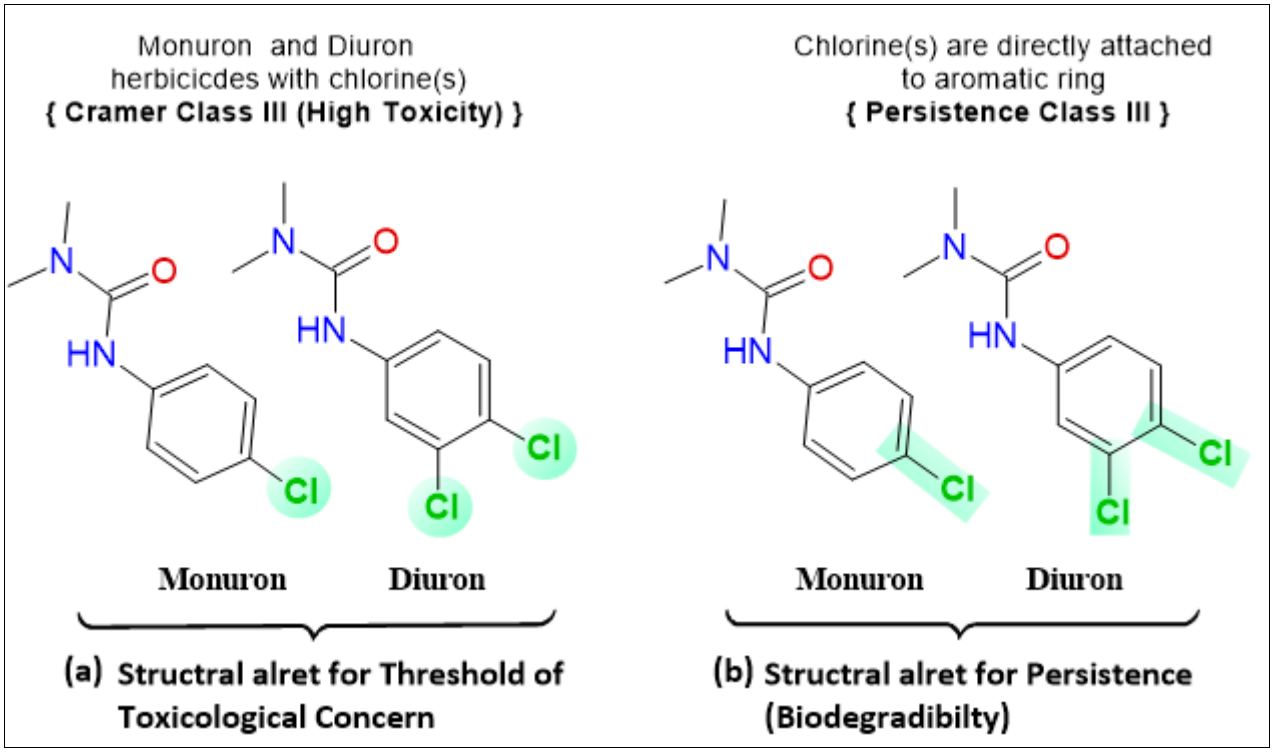


Fig 2: Structure and Prediction of differentiation in Structure Alerts for (a) Toxicological concern and (**b**) Persistence, using Toxtree for monuron and diuron.

QSAR identifier: VEGAHUB platform

QSAR identifier: VEGAHUB platform was used for water solubility and Soil adsorption coefficient (Koc) determination. The water solubility of monuron is higher than diuron. The Soil adsorption coefficient (Koc) of diuron is higher than monuron. It indicates that monuron has higher mobility in soil compared to diuron.

The Koc values predict monuron to be mobile and diuron to be moderately mobile in the soil (Table 3).

Chemaxon-Chemicalize Prediction

The Chemaxon-Chemicalize prediction were used for TPSA, logP, strongest acidic pKa, Intrinsic solubility and hydrophilic-lipophilic balance (HLB) determination. The TPSA values for both monuron and diuron were found to be low (32.34 Å). The logP value of Diuron is relatively higher than monuron.

The high value indicates high lipophilicity and thus high permeability for diuron. A high strongest acidic pKa (>13.0) indicate both herbicides to be very weak acids. Both Monuron and diuron are in the moderately-high solubility category. The HLB values indicate both herbicides to be hydrophilic in nature.

Table 3: Physiochemical properties and soil adsorption coefficient data for monuron and diuron.

Properties	Herbicides	
	Monuron	**Diuron**
General properties [@]		
Molecular formula	$C_9H_{11}ClN_2O$	$C_9H_{10}Cl_2N_2O$
Molecular Mass	198.65	233.09
IUPAC name	*N*'-(4-chlorophenyl)-*N*,*N*-dimethylurea	*N*'-(3,4-dichlorophenyl)-*N*,*N*-dimethylurea
Topological polar surface area; TPSA (Å^2)	32.34	32.34
logP	1.929	2.533
HLB	12.737	12.488
Equilibrium constant (pKa) and other relevant data at pKa) [@]		
Strongest acidic pKa	13.44	13.18
Percentage of Microspecies MS-1 (***Acid***)	46.31	48.85
Percentage of Microspecies MS-2 (***Conjugate Base***)	53.69	51.15
Solubility and Soil Adsorption Coefficient		
Intrinsic solubility (logS) [@)]	-2.351	-3.113
Water solubility [#]	Experimental value is 229.65 mg/L. Model prediction is 1021.77 mg/L	Experimental value is 41.95 mg/L. Model prediction is 629.28 mg/L
Koc [#]	Experimental value is 1.95 log(L/Kg). Model prediction is 1.8726; log(L/Kg)	Experimental value is 2.4 log(L/Kg). Model prediction is 2.2804log(L/Kg)
Koc[$]	82.27	136
Log Koc[$]	1.915	2.134

@ : Chemaxon-Chemicalize- data identifier: TPSA, logP, HLB, pKa and % of microspecies, logS (*Reference no*. **17**)
 # : QSAR identifier: VEGAHUB platform: Water solubility model (IRFMN) 1.0.1; (MODERATE reliability) and KOC model (OPERA) 1.0.1: Model prediction (Good reliability for monuron and Moderate reliability for diuron). (*Reference no*. **18,19**)
$: Data from: www.chemspider.com (*Reference no*. **21**)

pH dependent variation in solubility, lipophilicity and charge (Chemaxon-Chemicalize Prediction)

Monuron and diuron show consistency in their solubility over a long range of pH (Table 4, Figure 3). Their solubilities in water are moderately high. Monuron has higher solubility than diuron as evident from logS vs pH plot (Figure 3). These herbicide residue dissolve in eroding soil water and ultimately reach water bodies. Thus, monuron and diuron are identified as water pollutants [22]. These two herbicides show consistency in their lipophilicity over a long range of pH as evident from the plot logD vs pH (Table 4, Figure 4). Diuron has higher lipophilicity compared to monuron. The octanol-water partition coefficient, logP (Kow) properties of phenyl urea herbicides affect their adsorption to soils, their mobility and thus possibility of reaching water environments. With an increase in the number of chlorine atoms on the phenyl group, an increase in the logP (Kow) is observed.

A higher logP value of diuron (Table 3) indicate high lipophilicity and thus an increased adsorption to soil. As a result, Diuron is most frequently detected in contaminated soils.

Table 4: Data indicating pH dependent solubility (as logS) and lipophilicity (as logD) at selected pH values.

Properties / pH	pH dependent solubility (logS vs pH)		pH dependent lipophilicity (logD vs pH)	
	Monuron	**Diuron**	**Monuron**	**Diuron**
0	-2.3507	-3.113	1.9285	2.5326
1	-2.3507	-3.113	1.9288	2.5328
2	-2.3507	-3.113	1.9288	2.5328
3	-2.3507	-3.113	1.9288	2.5329
4	-2.3507	-3.113	1.9288	2.5329
5	-2.3507	-3.113	1.9288	2.5329
6	-2.3507	-3.113	1.9288	2.5329
7	-2.3507	-3.113	1.9288	2.5329
8	-2.3507	-3.113	1.9288	2.5328
9	-2.3507	-3.113	1.9288	2.5328
10	-2.3506	-3.1128	1.9287	2.5326
11	-2.3491	-3.1102	1.9273	2.5301
12	-2.3351	-3.0853	1.914	2.5065
13	-2.2151	-2.8927	1.801	2.3266
14	-1.6818	-2.2318	1.3327	1.7752

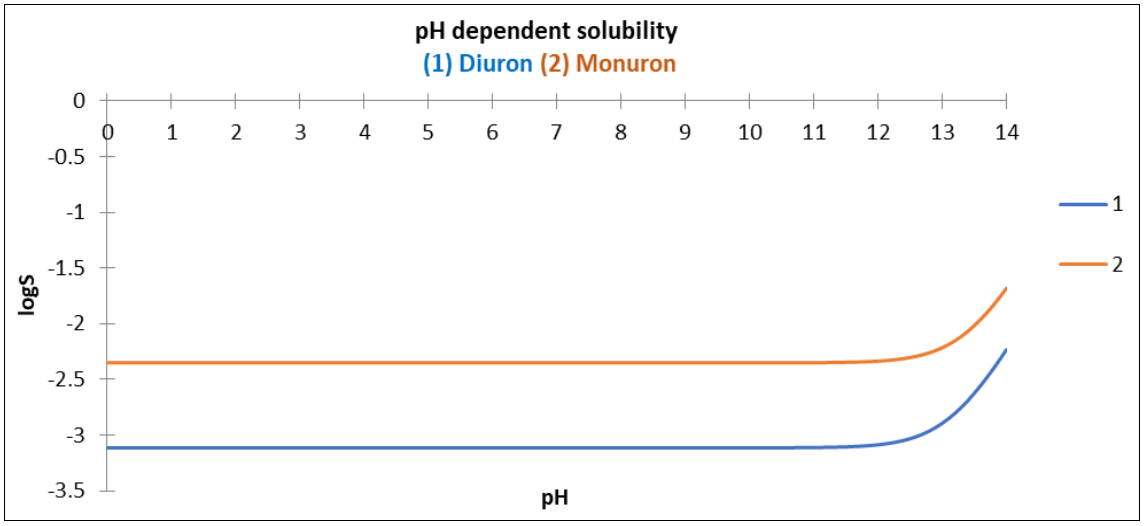


Fig 3: Change in the solubility (mg/ml) (given as log S) –with variation in pH for herbicides Monuron and Diuron

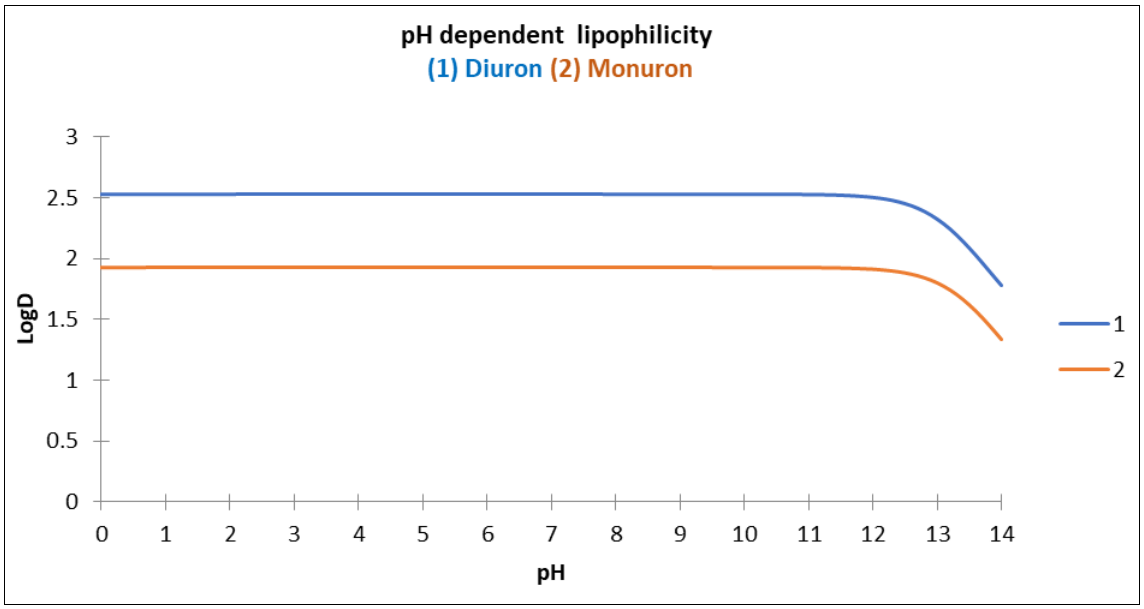


Fig 4: pH dependent lipophilicity (logD vs pH): Change in distribution coefficient – an indicator of lipophilicity with variation in pH for herbicides Monuron and Diuron.

Computationally other properties like pKa and charges on these herbicides has been determined through Chemaxon-Chemicalize (licensed) software. The strongest acidic pKa for monuron is 13.44 and for diuron is 13.18. At pKa the acid (microspecies referred as MS1) and the conjugate base (microspecies referred as MS2) exist in equilibrium for monuron and diuron (Figure 5).

In general soil pH varies from pH 4 to pH 8 depending upon geographical area. Herbicideal properties depend on the change of charge on herbicide with variation in pH.

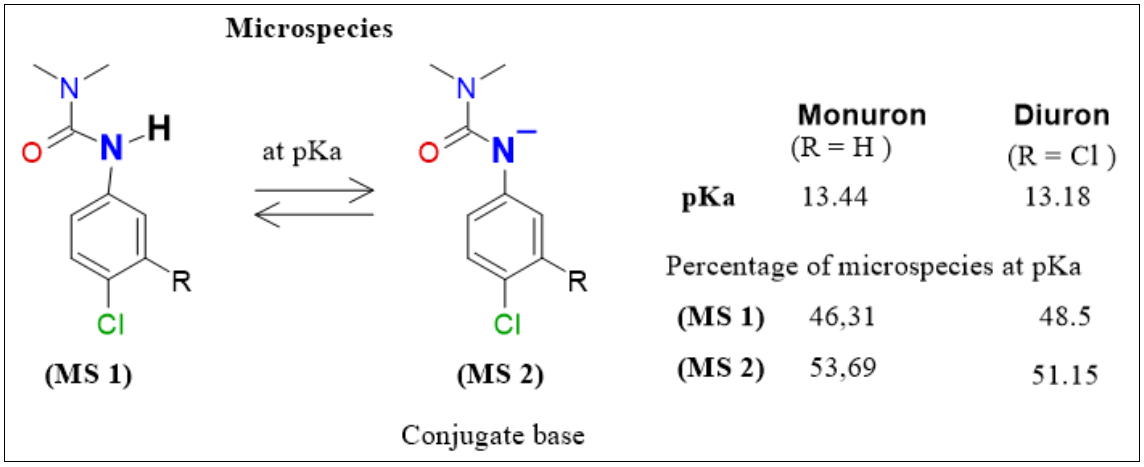


Fig 5: Monuron and diuron as acid and their corresponding conjugate base.

Both herbicides show consistently low charge over pH range of 0 to 12 (Table 5). A sharp change in the charges (negative charge) was observed after pH 12 in both herbicides (Figure 6). The probability of interaction with the charged particles in soil will be low. Due to their moderate solubility, they will be leached away from soil to the water-bodies.

Table 5: Variation in charge with pH (For selected range of pH) for monuron and diuron.

Variation in charge with pH (For selected range of pH)					
Positive to zero charge 0-8 pH Range				Zero to negative charge 9-14 pH Range	
pH	Monuron	Diuron	pH	Monuron	Diuron
0	0.0007	0.0006	9	0	-0.0001
1	0.0001	0.0001	10	-0.0004	-0.0007
2	0	0	11	-0.0037	-0.0066
4	0	0	12	-0.0354	-0.062
7	0	0	13	-0.2683	-0.3979
8	0	0	14	-0.7857	-0.8685

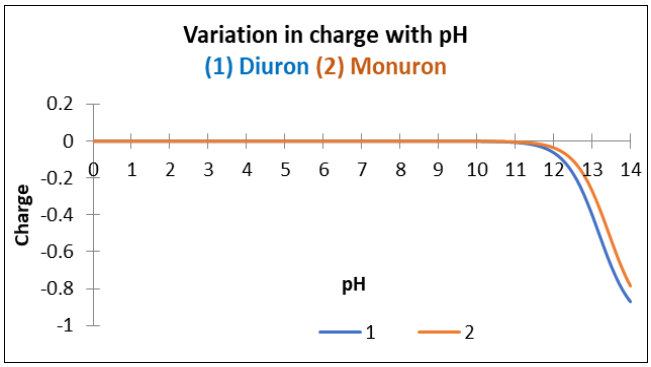


Fig 6: Variation in charge with pH for herbicides Monuron and Diuron.

Conclusion

Relative study of monuron and diuron was carried out in view of various aspects using Chemaxon-Chemicalize along with other online webservers. A broad view of the relative study is given in the form of graphical representations, for both herbicides, depicting variation in solubility, lipophilicity and charge in the pH range 0-14. Both monuron and diuron have low TPSA values. Both herbicides are very weak acids (pKa >13). Further diuron is reported to have higher inhibitory action (IC50) on PS-II, Photosystem Q(B) protein, as compared to monuron, which may be due to structural difference. Diuron has higher lipophilicity (high logP value) and thus higher permeability and higher adsorption to soil as compared to monuron. The soil adsorption coefficient (Koc) of diuron is higher than monuron and indicate higher mobility of monuron in soil than diuron. Both monuron and diuron have moderately high solubility in water. A low charge on both herbicides makes them to have low interaction with charged particles in soil. This causes leaching away of herbicides to water bodies. Diuron has higher soil persistence compared to monuron. The higher lipophilicity and soil persistence of diuron is attributed to presence of an additional chlorine in its phenyl ring compared to monuron.

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