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Predictive approach for assessment of physicochemical properties, toxicities and adverse effects of structurally similar organophosphate insecticides monocrotophos and dicrotophos

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Abstract
Organophosphate insecticides are widely used for crop protection. Monocrotophos and Dicrotophos are systemic organophosphate insecticides and are vinyl phosphates derivatives. Monocrotophos is used to control insect pests like aphids, caterpillars, common mites, spiders, ticks. Dicrotophos is used to control boring, chewing, sucking pests, aphids, leafhopper. These are low cost, highly effective insecticides and are widely used in agriculture. The excessive and uncontrolled use of these insecticides in agriculture has been a threat to environment and living organisms. Both Monocrotophos and dicrotophos inhibit acetylcholinesterase enzyme. The inhibition of Acetylcholinesterase results in the accumulation of acetylcholine, which can cause a range of symptoms, including muscle twitching, weakness, and paralysis. Due to their high toxicity monocrotophos is completely banned worldwide and dicrotophos has been added to the pesticide list of refused registration. These two insecticides are structurally similar, except that monocrotophos is N-methyl substituted amide whereas dicrotophos is N, N-dimethyl substituted amide. The presence of an additional methyl group on nitrogen in dicrotophos compared to monocrotophos prompted us for relative study of their physicochemical properties namely solubility and lipophilicity across a range of pH using ChemAxon chemicalize (licenced version) online web server. The biological activities for possible adverse and toxic effects were also studied using Prediction of Activity Spectra for Substances (PASS) online web server.

Keywords: Monocrotophos, dicrotophos, acetylcholinesterase inhibitor, toxicity, health risk, PASS online web server, ChemAxon chemicalize (licenced version)

Introduction
Pesticides are widely used in agriculture for the elimination of pests and to control crop losses. The high effectiveness along with low cost of organophosphorus pesticides makes them a popular choice with farmers. The excessive use and improper handling of these pesticides pose severe risks to the environment and human health [1-2]. Heavy rainfall, surface runoff and irrigation can cause pesticide flow from agricultural lands to water bodies and infiltration can also degrade the groundwater quality [3-4]. Monocrotophos and Dicrotophos are organophosphate insecticides and are dialkyl phosphate derivatives.

Structurally monocrotophos is (2E)-3-[(dimethoxyphosphoryl) oxy]-N-methylbut-2-enamide and dicrotophos is (2E)-3-[(dimethoxyphosphoryl) oxy]-N, N-dimethylbut-2-enamide (Figure 1).

These have broad-spectrum insecticidal activities and are systemic insecticides. Monocrotophos and dicrotophos are vinyl phosphates. Monocrotophos is used to control insect pests like aphids, caterpillars, common mites, spiders, ticks. It is used for a wide range of crops, such as citrus, cotton, maize, peanuts, potatoes, rice, sugar cane, soyabeans, olives, vegetables, ornamental plants and tobacco. Dicrotophos is used to control boring, chewing and sucking pests, aphids and leafhopper. It is used for various crops like apple, coffee, cotton, rice, soyabean, tea, grains and vegetables.

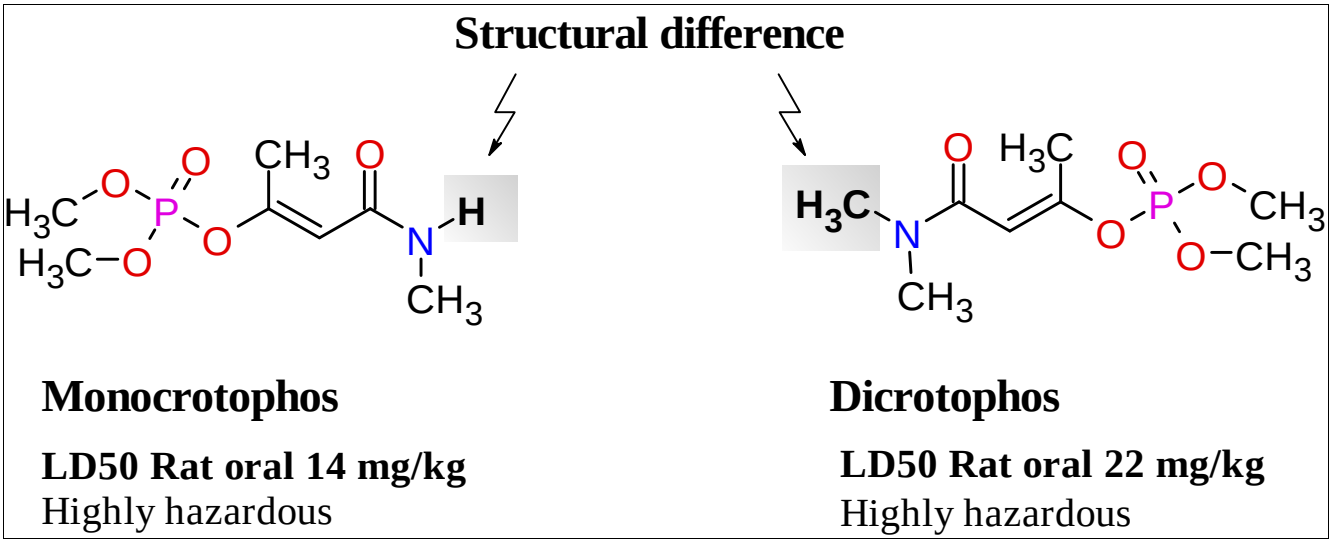

Fig 1: Structures of organophosphate insecticides monocrotophos and dicrotophos

Toxicity and side effects: The oral toxicity LD_{50} for Monocrotophos and Dicrotophos has been reported as 14 mg/kg and 22 mg/kg respectively. These are categorised by WHO as highly hazardous (Class Ib) pesticides. Insecticide Resistance Action Committee (IRAC) has classified insecticides having mode of action as Acetylcholinesterase (AChE) inhibitors in Group-1. Further, organophosphates have been placed in Sub-group-1B. Inhalation of these organophosphate causes some predominant side effects like muscle cramp, nausea, sweating, vomiting, excessive salivation, headache, pupillary constriction, muscle twitching, weakness, laboured breathing, convulsions and unconsciousness. Inhalation or accidental consumption of these insecticides has led to several deaths [5-7]. Monocrotophos is reported to be the contaminant responsible for the death of 23 schoolchildren in Bihar, India [8]. The children ate state-provided school lunch, which was prepared in oil kept in the container of this insecticide. The high toxicity of these insecticides has led to banning of monocrotophos worldwide including India [9] and dicrotophos has been put in the list of "Pesticides Refused Registration" [10].

Inhibitory action on enzymes: Both Monocrotophos and dicrotophos inhibit acetylcholinesterase (EC 3.1.1.7) enzyme. Acetylcholinesterase acts on acetylcholine that serves as neurotransmitter. The inhibition of Acetylcholinesterase results in the accumulation of acetylcholine, leading to overstimulation of cholinergic receptors. This overstimulation results in a range of symptoms, including muscle twitching, weakness, and paralysis. Monocrotophos also inhibits the Cholinesterase (EC 3.1.1.8) enzyme and Monoamine oxidase enzyme (EC 1.4.3.4). Cholinesterase enzyme breaks down acetylcholine. Inhibition of cholinesterase enzyme causes neurotoxicity. Monoamine oxidase enzyme is responsible for the degradation of serotonin, dopamine and norepinephrine in the central nervous system. Inhibition of this enzyme produces symptoms like nausea, drowsiness, dizziness and insomnia. Since dicrotophos is N, N-dimethyl derivative and nitrogen is tertiary in nature, it does not inhibit monoamine oxidase enzyme. Both Monocrotophos and Dicrotophos inhibit arylformamidase enzyme (EC 3.5.1.9**)** Figure 2. The arylformamidase enzyme is responsible for the metabolism of amino acid tryptophan. The kynurenine pathway of tryptophan metabolism converts the amino acid tryptophan into a number of biologically active metabolites. Inhibition of this enzyme may impact immune responses and brain function. Monocrotophos and dicrotophos has been reported to be potent teratogen [11-12] as tested in *Gallus gallus*. The Kd value for Monocrotophos and Dicrotophos is 5.4 mM and 3.2 mM respectively. This indicates dicrotophos has high inhibition activity for arylformamidase enzyme (EC 3.5.1.9) compared to monocrotophos (BRENDA Ids 209247 and 733741) [13]. Monocrotophos and dicrotophos were tested on rats at specific developmental stage of post-natal day (PND17 and PND11) and as adults to study motor activity and neurotoxicity [14].

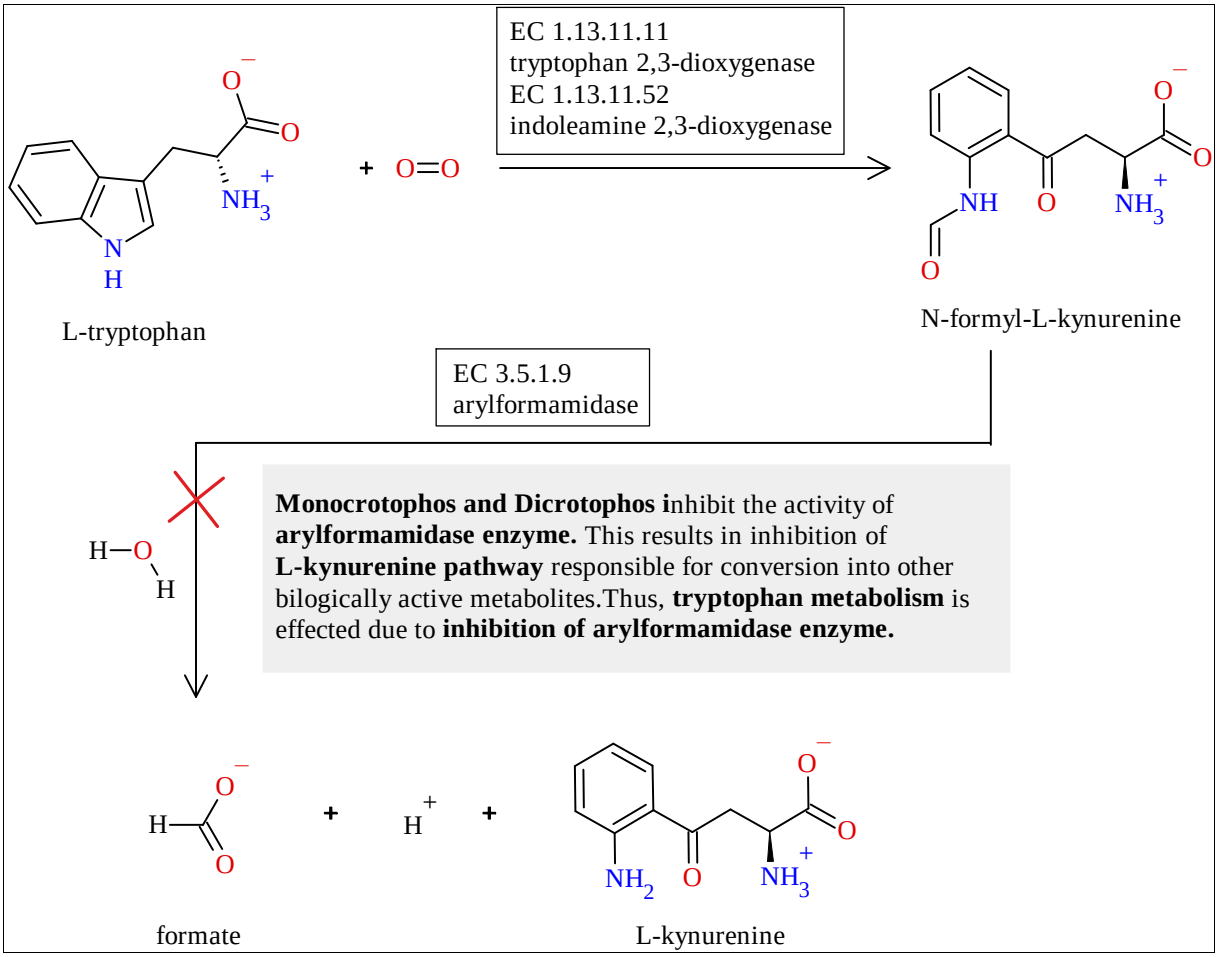

Fig 2: Representation of inhibitory action of Monocrotophos and dicrotophos on arylformamidase enzyme and kynurenine pathway in tryptophan metabolism.

Literature data is consolidated for monocrotophos and dicrotophos in Table 1 and Table 2 with reference to human and environmental toxicity and sourced from PubChem database [15-16] and Pesticides Properties Data Base (PPDB) [17-19] respectively.

Table 1: Literature data for Monocrotophos and Dicrotophos sourced from Pub Chem database for human and environmental toxicity.

Organophosphate pesticides	Monocrotophos	Dicrotophos
Pub Chem database CID	5371562	5371560
Toxicity: LD50 Rat mg/kg bw		
*LD50 oral Rat *(*Source*: WHO (Toxicity Category: highly hazardous: Class Ib)	14 mg/kg	22 mg/kg
LD50 dermal Rat	126 mg/kg	43 mg/kg
GHS Hazard Statement: Health		
H300: Fatal if swallowed [Danger Acute toxicity, oral]	Yes	Yes
H311: Toxic in contact with skin [Danger Acute toxicity, dermal]	Yes	Yes
H330: Fatal if inhaled [Danger Acute toxicity, inhalation]	Yes	No data found
H341: Suspected of causing genetic defects [Warning Germ cell mutagenicity]	Yes	No data found
GHS Hazard Statement: Environment		
H400: Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard]	Yes	Yes
H410: Very toxic to aquatic life with long lasting effects [*Warning* Hazardous to the aquatic environment, long-term hazard]	Yes	Yes

Table 2: Literature data for Monocrotophos and Dicrotophos sourced from Pesticides Properties Data Base (PPDB) for human and environmental toxicity.

Pesticides Properties Data Base (PPDB)		
Organophosphate pesticides	Monocrotophos	Dicrotophos
PPDB: Ref no.	ENT 27129	OMS 253
Acute oral LD_{50} (mg kg^{-1}) Rat	14 High	17 High
WHO Classification for both is Ib	Highly hazardous	Highly hazardous
Carcinogen	N.A.	(Possible)
Genotoxic	X	X
Endocrine disruptor	No data found	(Possible)
Reproduction / development effects	(Possible)	No data found
Acetyl cholinesterase inhibitor	Yes	Yes
Neurotoxicant	Yes	Yes
Respiratory tract irritant	X; (N.A.)	No data found
Skin irritant	Yes	(Possible)
Skin sensitiser	No data found	No data found
Eye irritant	Yes	(Possible)
Photo toxicant	No data found	No data found
Soil degradation (days) (aerobic) DT50(typical) in days (Interpretation	7 (Non-persistent)	28 (Non-persistent)
Aqueous hydrolysis DT50 (days) at 20 °C and pH 7	134 Persistent	N.A.

Monocrotophos and dicrotophos have similarity in structure but differ in their toxicity profile. In monocrotophos one methyl group is present on nitrogen (N-methyl amide) whereas in dicrotophos two methyl groups are present on nitrogen (N, N-dimethyl amide) (Figure 1). The difference in the presence of number of methyl group(s) on nitrogen prompted us for relative study of their physicochemical properties namely solubility and lipophilicity across a range of pH using ChemAxon chemicalize (licenced version) online web server [20]. The biological activities for possible adverse and toxic effects were also studied using Prediction *of Activity Spectra for Substances* (PASS) online web server [21].

Results and Discussion

Physicochemical Properties

Physicochemical Properties like TPSA, log P, strongest acidic pKa, strongest basic pKa, intrinsic solubility (logS), Hydrophilic-lipophilic balance (HLB) and solvent accessible surface area (SASA) were determined for monocrotophos and dicrotophos using ChemAxon chemicalize (licenced version) online web server [20]. The computational data has been given in Table 3. Both monocrotophos and dicrotophos have similar solvent accessible surface area (SASA) of 440.83 $Å^2$ and 440.55 $Å^2$ respectively. Thus, they show similar exposure and interaction with solvent molecules. However, other physicochemical properties have been studied to depict the solubility and lipophilicity behaviour across a range of pH.

Table 3: Physicochemical Properties of monocrotophos and dicrotophos (*source*: ChemAxon-Chemicalize data)

IUPAC Name: Monocrotophos (2E)-3-[(dimethoxyphosphoryl)oxy]-N-methylbut-2-enamide		
IUPAC Name: Dicrotophos (2E)-3-[(dimethoxyphosphoryl) oxy]-N,N-dimethylbut-2-enamide		
Insecticide	**monocrotophos**	**dicrotophos**
Formula	$C_7H_{14}NO_5P$	$C_8H_{16}NO_5P$
Molar mass	223.165	237.192
Isoelectric point	7.96	-
Strongest acidic pKa	15.73	-
Strongest basic pKa	0.2	0.55
Intrinsic solubility (logS)	-1.142	-1.171
logP	-0.466	-0.243
HLB	18.455	18.229
Solvent Accessible Surface Area (SASA), $Å^2$	440.83	440.55
Topological Polar Surface Area (TPSA), $Å^2$	73.86	65.07

Strongest acidic and basic pKa values

Monocrotophos is N-methyl amide. The loss of hydrogen (attached to nitrogen) as proton imparts acidic character to monocrotophos. However, strongest acidic pKa is very high (pKa=15.73), so it is a very weak acid. Dicrotophos is N, N-dimethyl amide. Since, no hydrogen is available on nitrogen, it does not show acidic character (Figure 3). Both monocrotophos and dicrotophos show basicity. The basicity is due to ability of carbonyl oxygen to accept a proton (Figure 3). The strongest basic pKa of monocrotophos (pKa=0.2) is less than the strongest basic pKa of dicrotophos (pKa=0.55), so monocrotophos is stronger base than dicrotophos.

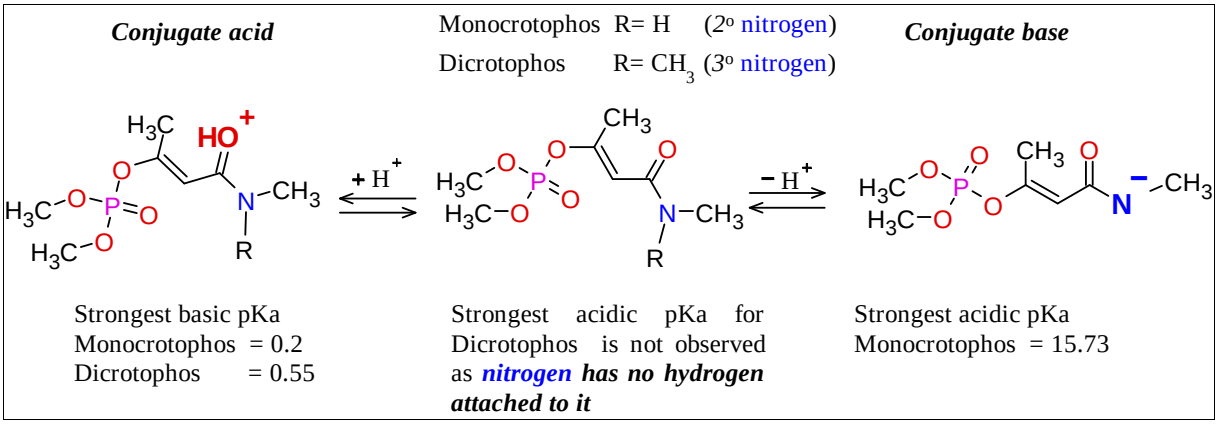

Fig 3: Structures of conjugate acid and conjugate base for monocrotophos and dicrotophos and their Strongest acidic and basic pKa values.

pH dependent variation in Solubility and Lipophilicity

Both monocrotophos and dicrotophos show good solubility. The computational data for solubility at variable pH has been summarized in Table 4. At low pH dicrotophos shows very high solubility compared to monocrotophos. At higher pH (6-14) monocrotophos and dicrotophos show consistent solubility value of 16.1057 mg/L and 15.9875 mg/L respectively (Figure 4).

The logD values at various pH for monocrotophos and dicrotophos has been summarized in Table 4. At very low pH both monocrotophos and dicrotophos have high negative logD values which indicates their highly hydrophilic character. This also indicates their high solubility. At higher pH (5 onwards) monocrotophos and dicrotophos show consistent logD values of -0.4663 and -0.2427 respectively (Figure 5). The higher negative value of monocrotophos with respect to dicrotophos indicates that monocrotophos is highly hydrophilic than dicrotophos.

Table 4: Data indicating pH dependent solubility (mg/mL) and lipophilicity (as logD) at selected pH values

Properties at pH	pH dependent solubility (mg/L vs pH)		pH dependent lipophilicity (logD vs pH)	
	Monocrotophos	Dicrotophos	Monocrotophos	Dicrotophos
0	41.587	72.1706	-0.896	-0.8777
1	18.6538	21.6058	-0.3733	-0.5301
2	16.3605	16.5493	-0.2576	-0.4731
3	16.1311	16.0436	-0.2442	-0.467
4	16.1077	15.9919	-0.4664	-0.2428
5	16.1059	15.988	-0.4663	-0.2427
6	16.1057	15.9875	-0.4663	-0.2427
7	16.1057	15.9874	-0.4663	-0.2427
8	16.1057	15.9874	-0.4663	-0.2427
9	16.1057	15.9874	-0.4663	-0.2427
10	16.1057	15.9874	-0.4663	-0.2427
11	16.1057	15.9874	-0.4663	-0.2427
12	16.1057	15.9874	-0.4664	-0.2427
13	16.1057	15.9874	-0.4671	-0.2427
14	16.1057	15.9874	-0.4735	-0.2427

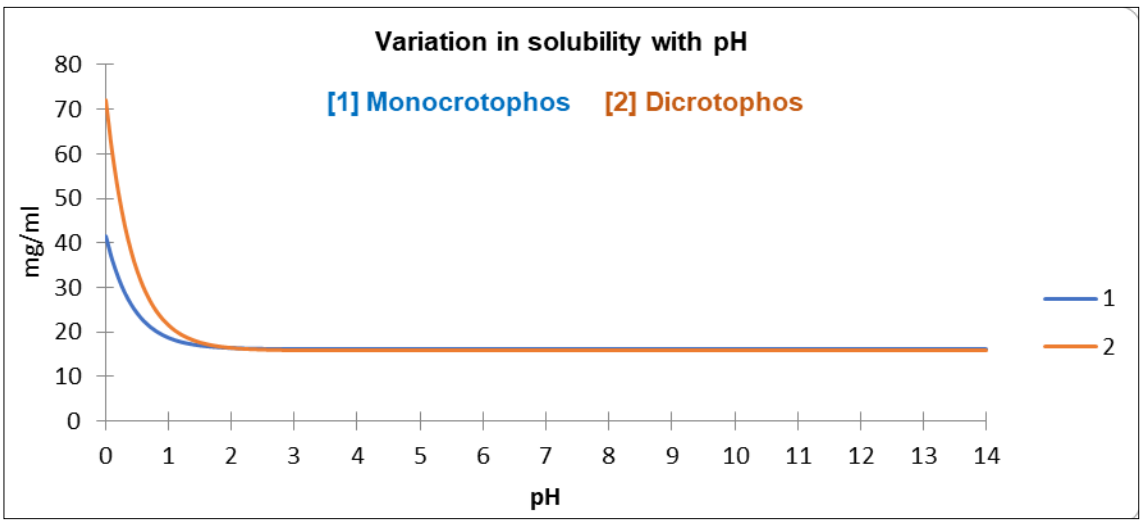

Fig 4: Change in solubility of monocrotophos and dicrotophos with variation in pH

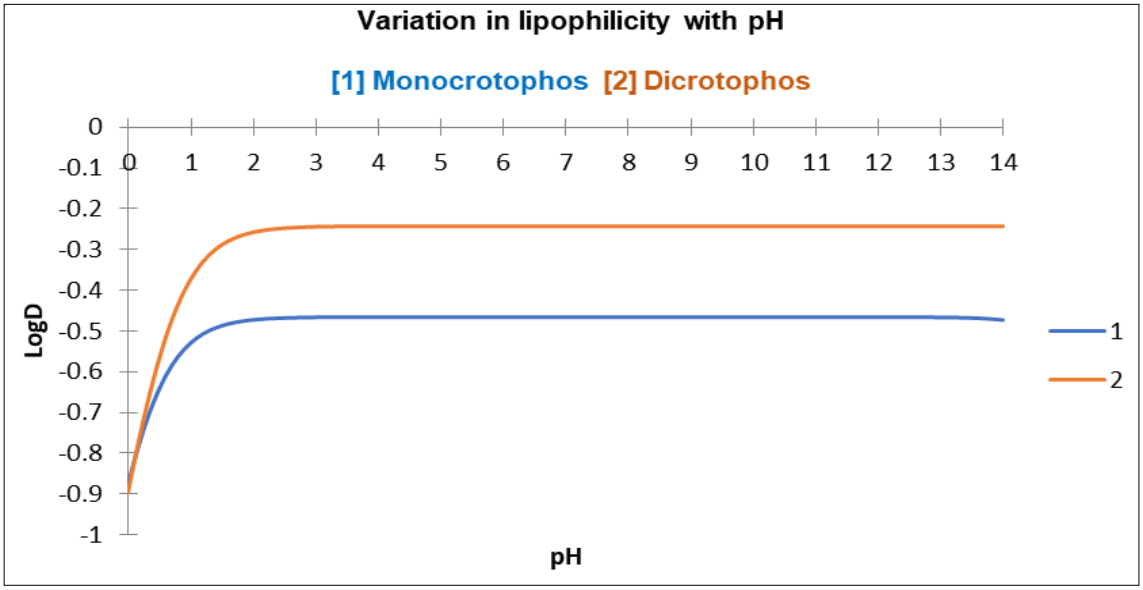

Fig 5: Change in distribution coefficient logD – an indicator of lipophilicity with variation in pH for monocrotophos and dicrotophos

Predictive biological activities for possible adverse and toxic effects

Biological activities of monocrotophos and dicrotophos for possible adverse and toxic effects were predicted using PASS (Prediction of Activity Spectra for Substances) [21] software tool http://www.way2drug.com/passonline. The prediction for selective adverse and toxic effects, as Pa (probability to be active), are summarised in Table 5.

Both monocrotophos and dicrotophos are predicted to have similar probabilities of exhibiting neurotoxicity, hematotoxicity, general toxicity, ocular toxicity, teratogen activity and causing Ataxia (impaired coordination or poor muscle control). Monocrotophos is predicted to be more embryotoxic and has higher probability for causing anemia and respiratory failure as compared to dicrotophos. The dicrotophos has high probability for causing tremor, dyspnea (shortness of breath), gastrointestinal toxicity and mutagenicity as compared to monocrotophos (Figure 6). Both monocrotophos and dicrotophos have been predicted to be of group 3 having moderately carcinogenic nature.

Table 5: Predictive activity data for selective possible adverse and toxic effects of monocrotophos and dicrotophos.

	Pa (probability to be active)				Pa (probability to be active)		
	Monocrotophos	**Dicrotophos**	**Adverse and Toxic Effects**		**Monocrotophos**	**Dicrotophos**	**Adverse and Toxic Effects**
1	0.913	0.926	Neurotoxic	8	0.771	0.926	Dyspnea
2	0.895	0.849	Hematotoxic	9	0.710	0.671	Respiratory failure
3	0.846	0.681	Embryotoxic	10	0.698	0.712	Ataxia
4	0.839	0.846	Toxic	11	0.665	0.67	Teratogen
5	0.765	0.860	Tremor	12	0.608	0.906	Toxic, gastrointestinal
6	0.736	0.756	Ocular toxicity	13	0.285	0.685	Mutagenic
7	0.74	0.487	Anemia	14	0.337	0.315	Carcinogenic, group 3

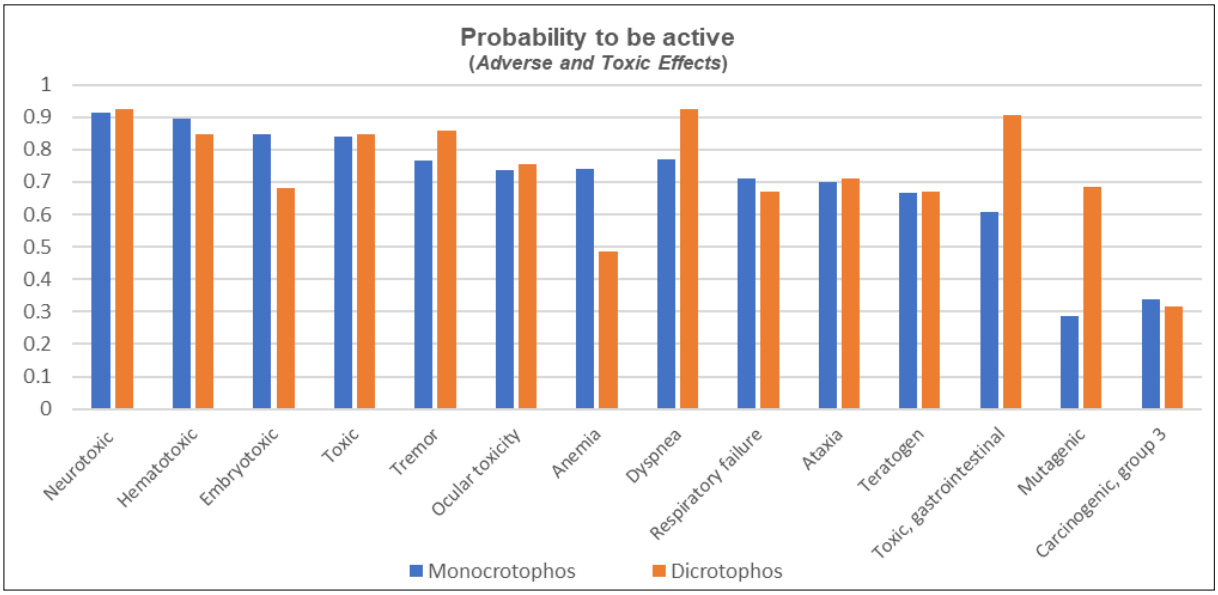

Fig 6: Graphical representation of possible adverse and toxic effects of monocrotophos and dicrotophos.

Conclusion

Relative study of monocrotophos and dicrotophos was carried out in view of physicochemical properties and biological activities, for possible adverse and toxic effects, using computational tools. Graphical representations have been used for broad view of relative study. These are structurally similar insecticides except that monocrotophos is N-methyl amide and dicrotophos is N, N-dimethyl amide. The presence of an additional methyl group in dicrotophos compared to monocrotophos attributes to difference in their properties. Both have similar solvent accessible surface area (SASA) and thus show similar exposure and interaction with solvent molecules. Monocrotophos is stronger base than dicrotophos. Monocrotophos is a very weak acid but dicrotophos has tertiary nitrogen and does not show acidic character. Both show high and consistent water solubility across a wide range of pH. However, at low pH dicrotophos shows higher solubility than monocrotophos. Due to high solubility these are easily leached away from soil to water bodies resulting in contamination of water. Both monocrotophos and dicrotophos have high, consistent negative logD values across a wide range of pH, an indicative of their highly hydrophilic character. At higher pH, monocrotophos is more hydrophilic than dicrotophos. Both are predicted to have similar neurotoxicity, hematotoxicity, general toxicity, ocular toxicity and teratogen activity. Monocrotophos is predicted to show higher embryotoxicity, whereas dicrotophos is predicted to show higher gastrointestinal toxicity and mutagenicity. Both monocrotophos and dicrotophos have been predicted to have moderately carcinogenic nature.

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