South Asian Journal of Agricultural Sciences

E-ISSN: 2788-9297
P-ISSN: 2788-9289
https://www.agrijournal.org
SAJAS 2023; 3(1): 159-162
Received: 17-04-2023
Accepted: 30-05-2023

Bhupinder Mehta
Department of Chemistry,
Swami Shraddhanand College
University of Delhi,
Alipur, Delhi, India

Correspondence Author:
Bhupinder Mehta
Department of Chemistry,
Swami Shraddhanand College
University of Delhi,
Alipur, Delhi, India

Comparative study of physicochemical properties and biological activities through cheminformatics for two auxinic herbicides 2,4,5-T and Triclopyr with same substitutive pattern of chlorines on aromatic system

Bhupinder Mehta

Abstract
Herbicides are of immense importance in agricultural practices. Herbicides are phytotoxic chemicals used for control of unwanted plants and weeds. Herbicides differ in their chemical structure and that results in distinct difference in their properties, toxicity, mechanism of action and use. The 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) and 3,5,6-trichloro-2-pyridinyloxyacetic acid (Triclopyr) are synthetic auxinic herbicides, that belong to aryloxy acetic acid class of herbicides. They produce their herbicidal effects by over stimulating plant growth. These are effectively used against broadleaf weeds. These two herbicides are structurally similar, having similar substitutive pattern for three chlorines present on aromatic ring system, except that in case of 2,4,5-T the aromatic system is phenyl ring whereas the triclopyr has heterocyclic aromatic system as pyridyl ring. It was of interest to study how the difference in aromatic system affects the physicochemical properties and biological activities of the two herbicides. Their physicochemical parameter, pharmacokinetics and biological activities for possible adverse and toxic effects are compared through computational approach. Biological activities for possible adverse and toxic effects were predicted using *PASS (Prediction of Activity Spectra for Substances)* software tool.

Keywords: Auxinic herbicides, 2,4,5-T, Triclopyr, physicochemical properties, biological activities

Introduction
Herbicides are important and integral part of agricultural practices. Herbicides are phytotoxic chemicals used for control of unwanted plants and weeds [1, 2].
The 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) and 3,5,6-trichloro-2-pyridinyloxyacetic acid (Triclopyr) are synthetic auxinic herbicides that produce their effects by over stimulating plant growth. The synthetic auxin herbicides were the first selective organic herbicides developed and being used in agriculture for over 50 years, for the selective control of broadleaf weeds in cereal crops. The 2,4,5-T and Triclopyr herbicides are aryloxy acetic acid derivatives [1] and are systemic foliar herbicides, effectively used against broadleaf weeds in forests, lawns, industrial sites, along roadside and railway tracks. The 2,4,5-trichlorophenoxyacetic acid has low volatility, moderate solubility in water, and tendency to be persistent in soil systems. It has a high potential for leaching to groundwater. 2,4,5-T when applied to soil is reported to show rapid degradation rate and is thus widely used [3,4]. Triclopyr has limited mobility and is moderately persistent in soil systems [5, 6]. It is non persistent in surface water. Triclopyr is reported to be well absorbed from the oral route in numerous species and shows low toxicity [7]. These herbicides are known to exhibit skin and eye irritation. Prolonged exposure may cause allergic skin reaction. 2,4,5-T and Triclopyr are toxic to aquatic life [8] and Hazardous to the aquatic environment. The LD50 for herbicides 2,4,5 T and Triclopyr is 500 mg/kg and 630 mg/kg respectively (PubChem CID 1480 and PubChem CID 41428 respectively).
In the present paper comparative study has been carried out for 2,4,5 T and Triclopyr herbicides which are aryloxy acetic acid derivatives. The 2,4,5-T and Triclopyr herbicides are structurally similar, except that in case of 2,4,5-T the aromatic system is phenyl ring and in triclopyr the aromatic system is pyridine ring. Both have similar substitutive pattern for three chlorines present on aromatic system (Figure 1).

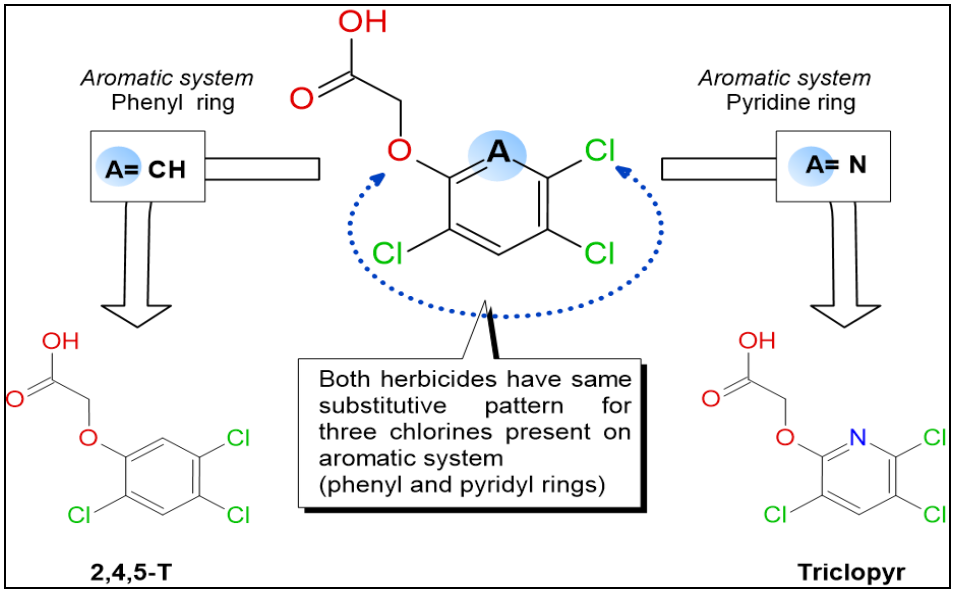

Fig 1: Structure of auxinic herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 3,5,6-trichloro-2-pyridinyloxyacetic acid (Triclopyr)

It was of interest to study how the presence of phenyl ring in 2,4,5-T and pyridine ring system in triclopyr affects their physicochemical properties and biological activities.

Results and Discussion

Physicochemical properties

The herbicides 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) and 3,5,6-trichloro-2-pyridinyloxyacetic acid (Triclopyr) exhibit moderate intrinsic solubility with logS values -3.79 and -3.87 respectively. The TPSA value for triclopyr and 2,4,5-T were predicted to be 59.42 Å² and 46.53 Å² respectively.

The higher logP and logD values of 2,4,5-T indicate its high lipophilicity compared to Triclopyr. The acidic pKa values indicate high acidic strength of Triclopyr compared to 2,4,5-T (Table 1).

Table 1: Physicochemical properties and Pharmacokinetics of Triclopyr and 2,4,5-T

IUPAC Name: Triclopyr: [(3,5,6-trichloropyridin-2-yl)oxy] acetic acid 2,4,5-T: (2,4,5-trichlorophenoxy) acetic acid		
Physicochemical properties		
Traditional /common name	Triclopyr	2,4,5-T
Formula	$C_7H_4Cl_3NO_3$	$C_8H_5Cl_3O_3$
Molecular mass	256.47	255.48
Intrinsic solubility Log S	-3.87	-3.79
LogP	2.70	3.11
Log D (pH7.4)	-0.82	-0.40
Strongest acidic pKa	2.28	2.56
TPSA Å²	59.42	46.53
Pharmacokinetics		
GI absorption	High	High
BBB permeant	Yes	Yes
P-gp substrate	No	No
CYP1A2 inhibitor	Yes	Yes
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	No
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	No
Log K_p (skin permeation)	-5.76 cm/s	-5.51 cm/s
Note: The predictive data for Physicochemical properties and Pharmacokinetics of Triclopyr and 2,4,5-T has been evaluated using Chem Axon and Swiss ADME cheminformatic tools. Swiss ADME computational tool: GI-Gastrointestinal Absorption, BBB-Blood Brain Barrier Permeant, P-gp-P-Glycoprotein, CYP-Human Cytochrome, log K_p - Skin Penetration coefficient in logarithmic scale.		

Predictive Pharmacokinetics

The pharmacokinetics of Triclopyr and 2,4,5-T has been predicted using Swiss ADME [9].

Both Triclopyr and 2,4,5-T exhibit high gastrointestinal absorption and predicted to be permeable to blood brain barrier and thus have potential to affect the central nervous system. Permeability -glycoprotein (P-gp) is a cell membrane protein to protect the central nervous system from xenobiotics. Both Triclopyr and 2,4,5-T do not show the probability of being substrate of Permeability -glycoprotein (P-gp).

Cytochrome P450 1A2 (CYP1A2) enzyme is involved in metabolism of xenobiotics in the human body. The CYP1A2 enzyme, is responsible for removing toxic chemicals from

body and processing metabolic products. Both Triclopyr and 2,4,5-T were found to be inhibitor of CYP1A2 enzyme contributing to their toxic effects. Prediction indicates that both Triclopyr and 2,4,5-T did not show inhibition activity for CYP2C19, CYP2C9, CYP2D6 and CYP3A4 isoenzymes for their metabolic activities. The skin permeation values (Log K_p) of -5.76 cm/s and -5.51 cm/s for Triclopyr and 2,4,5-T respectively, indicate moderate skin permeability.

Predictive biological activities for possible adverse and toxic effects

Biological activities of Triclopyr and 2,4,5-T for possible adverse and toxic effects were predicted using *PASS* (Prediction of Activity Spectra for Substances) [10] software tool 'http://www.way2drug.com/passonline'. The prediction for selective adverse and toxic effects, as probability to be active (Pa), are summarised in Table 2 and represented graphically (Figure 2).

Table 2. A comparative view of predictive activity data for selective possible adverse and toxic effects of trichlopyr and 2,4,5-T

Pa (probability to be active) Probability for Individual herbicide to be active for adverse effect (A Comparison)		
Adverse and Toxic Effects	**Herbicides**	
	Triclopyr (Pa)	**2,4,5-T (Pa)**
Muscle weakness	0.923	0.938
Weakness	0.922	0.931
Diarrhea	0.904	0.869
Respiratory failure	0.891	0.851
Anemia	0.885	0.822
Gastrointestinal disturbance	0.859	0.585
Weight loss	0.848	0.802
Hepatotoxic	0.81	0.791
Reproductive dysfunction	0.805	0.733
Consciousness alteration	0.797	0.599
Nephrotoxic	0.771	0.66
Sleep disturbance	0.757	0.498
Teratogen	0.729	0.785
Embryotoxic	0.712	0.785
Hematotoxic	0.713	0.631

Both Triclopyr and 2,4,5-T are predicted to have similar probabilities of exhibiting muscle weakness, weakness and hepatotoxicity. Triclopyr is predicted to exhibit higher probability of consciousness alteration, gastrointestinal and sleep disturbance as compared to 2,4,5-T. The probability of causing anaemia and being hematotoxic is more in case of Triclopyr. The probability to be embryotoxic and teratogen has been predicted to be more in case of 2,4,5-T [11] compared to Triclopyr. The relative predictive activity data for selective adverse and toxic effects of Triclopyr and 2,4,5-T has been tabulated (Table 2) and represented graphically (Figure 2). The data indicates that probability to be active for adverse effect is more for Triclopyr compared to 2,4,5-T herbicide.

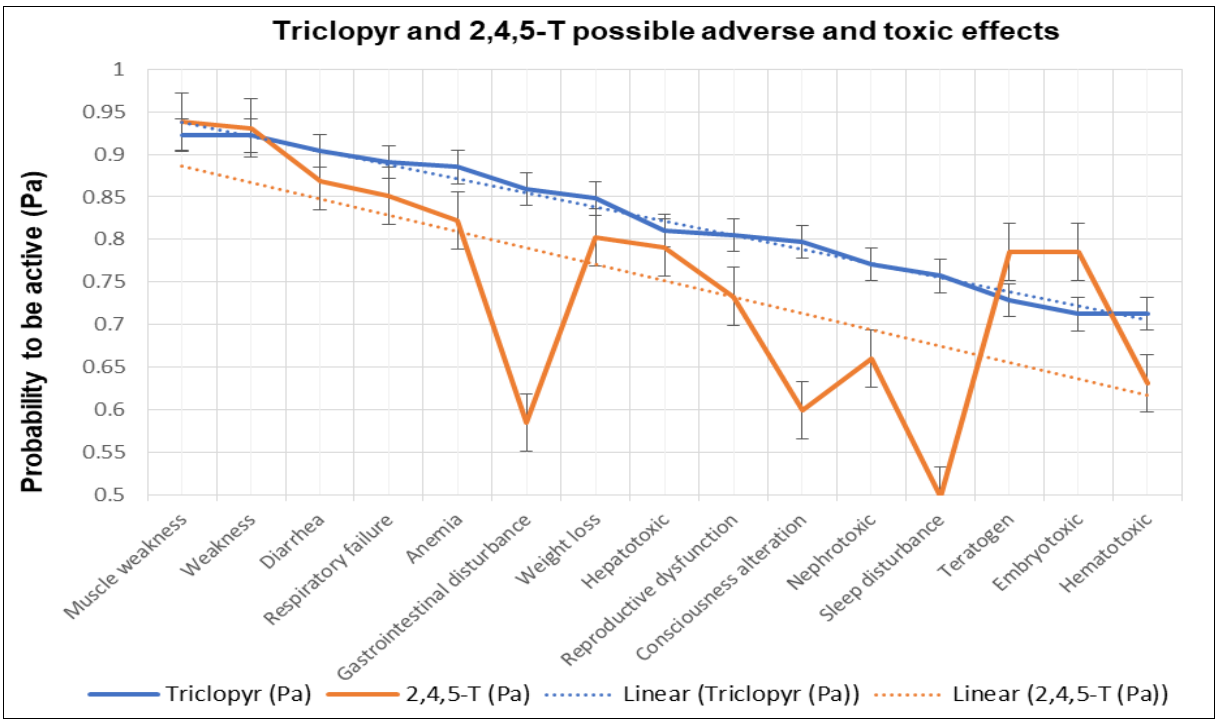

Fig 2: Graphical representation of possible adverse and toxic effects of Triclopyr and 2,4,5-T and their linear trendlines

Conclusion

The herbicides 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T) and 3,5,6-trichloro-2-pyridinyloxyacetic acid (Triclopyr) are synthetic auxin and belong to aryloxy acetic acid class of herbicides. These are systemic foliar herbicides, effectively used against broadleaf weeds. The 2,4,5-T and Triclopyr herbicides are structurally similar, except that in case of 2,4,5-T the aromatic system is phenyl ring and in triclopyr the aromatic system is pyridine ring. Both have similar substitutive pattern for three chlorines present on aromatic system. The study was carried out that how the presence of phenyl ring in 2,4,5-T and pyridine ring system in triclopyr affects their physicochemical properties, pharmacokinetics and biological activities. The computational studies predicted 2,4,5-T and Triclopyr to have moderate solubility in water. The 2,4,5-T has higher lipophilicity whereas Triclopyr has higher TPSA and higher acidic character. Both are predicted to penetrate blood brain barrier. Both are predicted to have moderate skin permeability. Triclopyr and 2,4,5-T were found to be inhibitor of CYP1A2 enzyme. Biological activities of Triclopyr and 2,4,5-T for possible adverse and toxic effects indicate 2,4,5-T to be more embryo toxic and teratogen. Triclopyr is predicted to exhibit higher probability of consciousness alteration, gastrointestinal disturbance, sleep disturbance, of being hematotoxic and of causing anaemia. From data it can be concluded that probability to be active for adverse effect is more for Triclopyr compared to 2,4,5-T herbicide.

References

1. Büchel KH, editor. Chemistry of Pesticides. A Wiley-Interscience publication; c1983. ISBN: 0471056820.
2. Hassall KA. The Chemistry of Pesticides: Their Metabolism, Mode of Action and Uses in Crop Protection. Verlag Chemie; c1982.
3. Suskind RR, Hertzberg VS. Human health effects of 2,4,5-T and its toxic contaminants. JAMA. 1984;251(18):2372-80.
4. Lavy TL, Shepard JS, Mattice JD. Exposure measurements of applicators spraying 2,4,5-trichlorophenoxy acetic acid in the forest. Journal of Agricultural and Food Chemistry. 1980 May;28(3):626-30.
5. Cessna AJ, Grover R, Waite DT. Environmental fate of triclopyr. Reviews of environmental contamination and toxicology: Continuation of Residue Reviews. 2002;19-48.
6. Johnson WG, Lavy TL, Gbur EE. Sorption, mobility and degradation of triclopyr and 2,4-D on four soils. Weed Science. 1995 Dec;43(4):678-84.
7. Bartels M, Brown C, Chung G, Chan M, Terry C, Gehen S, *et al*. Review of the pharmacokinetics and metabolism of triclopyr herbicide in mammals: Impact on safety assessments. *R*egulatory toxicology and pharmacology. 2020 Oct 1;116:104714. DOI: 10.1016/J.YRTPH.2020.104714
8. Kreutzweiser DP, Holmes SB, Behmer DJ. Effects of the herbicides hexazinone and triclopyr ester on aquatic insects. Ecotoxicology and Environmental Safety. 1992 Jun 1;23(3):364-74. DOI: 10.1016/0147-6513(92)90071-K
9. Daina A, Michielin O, Zoete V. Swiss ADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci. Rep. 2017;7:42717. DOI: 10.1038/SREP42717
10. Filimonov DA, Lagunin AA, Gloriozova TA, Rudik AV, Druzhilovskii DS, Pogodin PV, *et al*. Prediction of the biological activity spectra of organic compounds using the PASS online web resource. Chemistry of Heterocyclic Compounds. 2014;50(3):444-57. DOI: 10.1007/S10593-014-1496-1
11. Båge G, Cekanova E, Larsson KS. Teratogenic and embryotoxic effects of the herbicides di- and *trichlorophenoxyacetic* acids (2,4-*D* and 2,4,5-T). Acta Pharmacologica ET Toxicologica. 1973;32(6):408-16. DOI: 10.1111/J.1600-0773.1973.TB01864.X