Journal of Science and Technology
ISSN: 2456-5660 Volume 7, Issue 08 (October 2022)
www.jst.org.in *DOI:https://doi.org/10.46243/jst.2022.v7.i08.pp01-08*

In Silico study using Toxtree (TT) Cramer decision tree scheme for different Isomers of Resmethrin -a Type-I Synthetic Pyrethroid

Manju Mehta, Bhupinder Mehta

Chemistry Department, Maitreyi College (University of Delhi), Chanakyapuri, Delhi-110021, INDIA.
Chemistry Department, Swami Shraddhanand College (University of Delhi), Alipur, Delhi-110036, INDIA
Corresponding Author Email: bhupindermehta@ss.du.ac.in

To Cite this Article

Manju Mehta, Bhupinder Mehta**, In Silico study using Toxtree (TT) Cramer decision tree scheme for different Isomers of Resmethrin -a Type-I Synthetic Pyrethroid "***",Journal of Science and Technology, Vol. 07, Issue 08,-October 2022, pp*01-08

Article Info

Received: 25-08-2022 Revised: 9-09-2022 Accepted: 17-10-2022 Published: 27-10-2022

ABSTRACT

Synthetic pyrethroids are widely used in household, public places and agriculture as insecticides but have harmful effect on human and the environment. The Cramer classification scheme (decision tree) is the best-known approach to estimate the Threshold of Toxicological Concern for a chemical substance based on its chemical structure. In present article we have used *In silico* tool Toxtree to get the Cramer class for isomers of Resmethrin. The stereochemical relationships and toxicologic and environmental effects are also discussed.

Key Words: Pyrethroids, Resmethrin , Toxtree , Cramer decision tree **,** Threshold of Toxicological Concern (TTC)

INTRODUCTION

Natural pyrethrum extracted from the *Chrysanthemum cinerariaefolium* has been widely used as a natural insecticide [1,2]. In general, it is considered to be less harmful to humans and the environment. Its low toxicity may be due to a fast biotransformation in higher species. Its readily/rapid degradation in sunlight does not allow it to be used commercially for agricultural and other applications.

Chemically synthetic pyrethroids [3,4] are esters of chrysanthemic acid and alcohols. The asymmetric centre may be present in acid or / and alcohol moiety. Synthetic pyrethroids are not easily degraded by sunlight and this makes them more stable and more effective as insecticides compared to natural pyrethrums. Their toxicity is attributed to their functioning as an insecticide, which makes them harmful for humans and the environment [5].

Synthetic pyrethroids can be classified into two broad categories: Type-I and Type-II pyrethroids. Resmethrin belongs to category of Type-I pyrethroids as it does not contain a cyano group in its structure. Few examples of Type-I pyrethroids are permethrin, bifenthrin and tetramethrin. Type-II pyrethroids contain a cyano group in their structure, for example, cypermethrin, deltamethrin, fenpropathrin, fenvalerate.

Synthetic pyrethroids have a complex chemical structure and can have two to eight optical isomers. Synthetic pyrethroids are used as household sprays (allethrin, bioresmethrin, cyhalothrin) against flies, mosquitoes, and cockroaches and also in agricultural uses as insecticidal sprays (cypermethrin, deltamethrin, fenvalerate, permethrin). Some synthetic pyrethroids (allethrin and permethrin) are also used in shampoos and pet sprays.

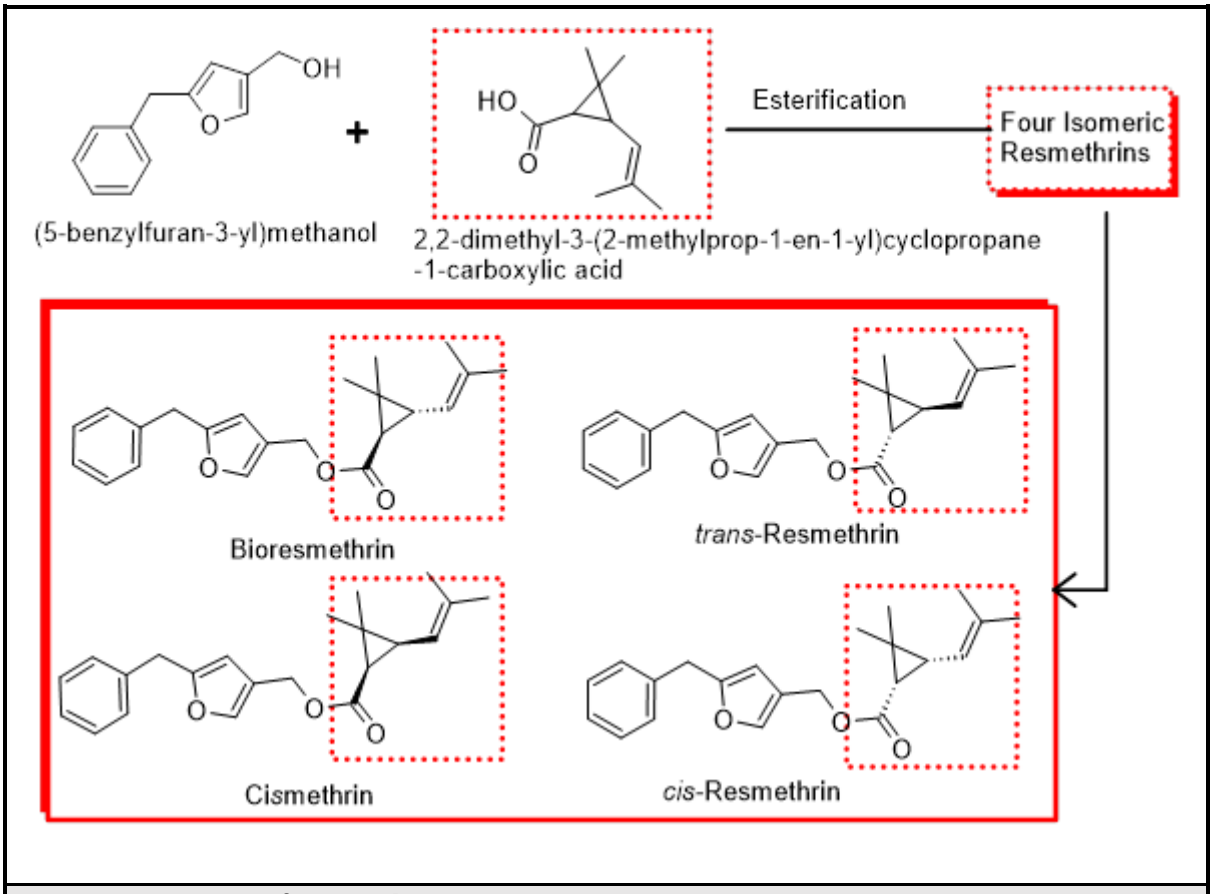


Figure-1: Isomers of Resmethrin (Molecular Formula: $C_{22}H_{26}O_3$)

Resmethrin a Type-I pyrethroid is chemically an ester of chrysanthemic acid, 2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylic acid, and (5-benzylfuran-3-yl)methanol. It is a racemic mixture of four optical isomers [1R, *trans*], [1R, *cis*], [1S, *trans*], [1S, *cis*]. Resmethrin is a mixture of 70% (+/-) trans and 30% (+/-) cis [6,7]. Commercially available resmethrin has bioresmethrin and cismethrin as major components. Its chemical name is written as 5-benzyl-3-furylmethyl(1RS)-cis-trans-3-(2-methylprop-1-enyl)cyclopropane carboxylate.

Pesticide products containing resmethrin are classified in **Class III toxicity**, which requires a cautious label to sell in the market. The resmethrin is primarily used as an insecticide in households as well as public places. It is available in aerosol, oil formulation and emulsifiable concentrate forms.

Bioresmethrin and Toxicity: Bioresmethrin is [1R, *trans*]-isomer of resmethrin [7]. It is soluble in most organic solvents but insoluble in water. Bioresmethrin is used to control 'whiteflies' in stored grains and is also used for pest management, contemplating public health [8,9]. It is a sodium channel modulator and has contact action acting on the nervous system of insect [10]. It can be absorbed into the body by inhalation of its aerosol and by ingestion. It is very toxic to aquatic organisms. This substance does enter the environment under normal use [5]. However, it should be disposed in an appropriate manner to avoid any additional release. Acute oral LD_{50} in rats is 8000 mg/kg and intravenous LD_{50} is 340 mg/kg [11-14].

Cismethrin and Toxicity: Cismethrin is the [1R, cis]-isomer of resmethrin. It can be absorbed into the body by inhalation of its aerosol and by ingestion. It is very toxic to aquatic organisms. It is mildly irritating to the eyes and skin. Cismethrin may cause effect on the nervous system. This substance does enter the environment under normal use [5]. However, it should be disposed in an appropriate manner to avoid any additional release. Acute oral LD_{50} in rats is 63 mg/kg and intravenous LD_{50} is 4.5 mg/kg [15-17].

Bioresmethrin and Cismethrin are equally potent as insecticides, but cismethrin is much more toxic to rats than bioresmethrin [18]. The low toxicity of bioresmethrin is possibly due to the inability of this isomer to interact with the site of action in the central nervous system [19-21].

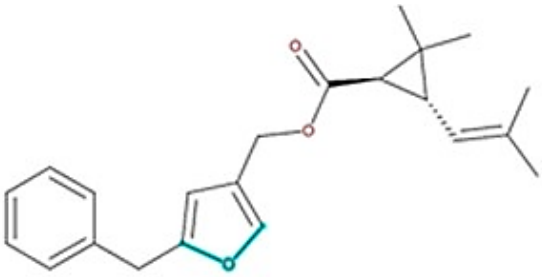
IN SILICO STUDY USING TOXTREE (TT) CRAMER DECISION TREE SCHEME

The Toxtree [22-24] is useful tool that enable effective implementation of the Cramer decision tree. The Cramer classification scheme (decision tree) is the best-known approach to estimate the Threshold of Toxicological Concern (TTC) for a chemical substance based on its chemical structure. The in-silico performances are thus chemical class-dependent. The chemical structures of isomers of Resmethrin were represented using the simplified molecular-input line-entry system (SMILES). The SMILES were used as input for Toxtree (TT), Version 3.1.0. The Cramer class of each isomer was determined by the Cramer rule decision tree feature in ToxTree. The data for Bioresmethrin is summarized in Table-1 as per Cramer decision tree and Table-2 as per revised Cramer rule decision tree (see conclusion).

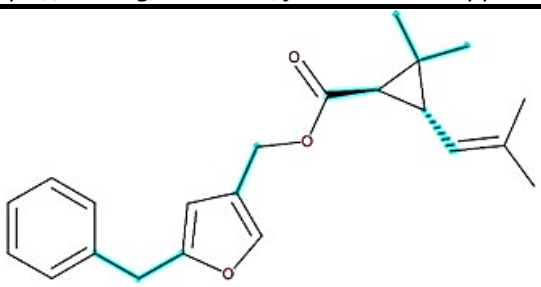
Table-1: Toxtree: Estimation of toxic hazard for Bioresmethrin as per Cramer decision tree approach

Available structure attributes	
IUPAC Name: (5-benzylfuran-3-yl)methyl (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-1-carboxylate	
Cramer Rules	High (Class III) **Toxicity**
SMILES	O=C(OCc1cc(Cc2ccccc2)oc1)[C@@H]1[C@@H](/C=C(\C)C)C1(C)C
Toxtree, Cramer	1N,2N,3N,5N,6N,7Y,10N,11N,12Y,13Y,14Y,15N,33N
Q1.Normal constituent of the body **No**	
Q2.Contains functional groups associated with enhanced toxicity **No**	
Q3.Contains elements other than C,H,O,N,divalent S **No**	
Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate **No**	
Q6.Benzene derivative with certain substituents **No**	
Q7. Heterocyclic **Yes** Q8.Lactone or cyclic diester **No**	
Q10.3-membered heterocycle **No**	
Q11.Has a heterocyclic ring with complex substituents. **No**	
Q12.Heteroaromatic **Yes**	
Q13.Does the ring bear any substituents? **Yes**	
Q14.More than one aromatic ring **Yes**	
Q15.Readily hydrolised **No**	
Q33.Has sufficient number of sulphonate or sulphamate groups **No** Class High (Class III)	

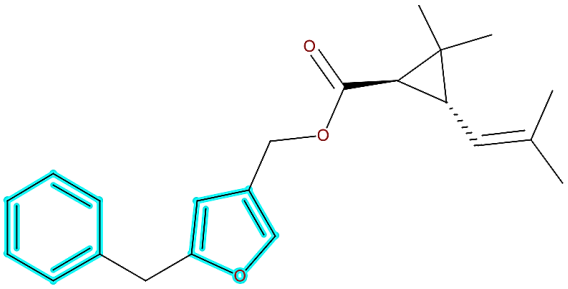
Highlighted Structural alerts for Bioresmethrin as per Cramer decision tree are picked up as individual screen shot and are consolidated in Figure -2.



Structure-1



Structure-2



Structure-3

Structural alerts for Bioresmethrin:
Structure-1: Q7, Q12
Structure-2**:** Q13
Structure-3**:** Q14

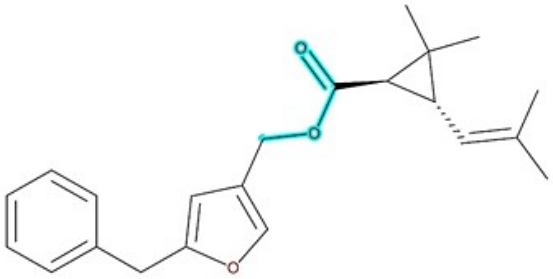
Figure-2: Structural alerts for Bioresmethrin as per Cramer decision tree

The data for Bioresmethrin is summarized in Table-2 as per revised Cramer rule decision tree.

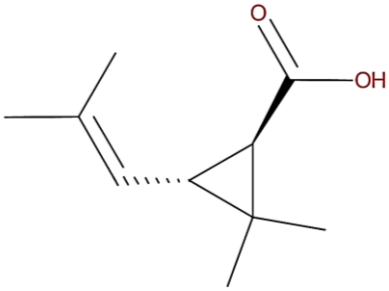
Table-2: Toxtree: Estimation of toxic hazard for Bioresmethrin as per *revised* Cramer decision tree approach	
Available structure attributes	
IUPAC Name: (5-benzylfuran-3-yl) methyl(1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-1-carboxylate	
***Revised* Cramer Rules**	High (Class III) **Toxicity**
SMILES	O=C(OCc1cc(Cc2ccccc2)oc1)[C@@H]1[C@@H](/C=C(\C)C)C1(C)C
Toxtree , *Revised* Cramer	1Y,2N,3N,4N,6N,7Y,8N,15N,19N,20Y,21N,22Y,17N,18N,18(J-M),9A N,10N,11N,12Y,13N,14A N, ,29N
Q1.Does the structure contain a functional group (...) that is hydrolyzed or reduced? **Yes** **Q2**.Is the structure a linear, unsubstituted aliphatic alcohol, aldehyde, carboxylic acid or derivative (ester, acetal or orthoesters) or an L-amino acid? **No** **Q3**.Does the substance contain any of the following functional groups? **No** **Q4**.Does this structure contain elements other than specified? **No** **Q6**.Is the substance hydrocarbon, carbohydrate or terpene as specified? **No** **Q7**.Is the substance heterocyclic? **Yes** **Q8**.Is the substance heterocyclic because it contains a cyclic hemiacetal, acetal, hemiketal, ketal, or cyclic carbonate? **No** **Q15**.Is the structure acyclic (open chain)? **No** **Q19**.Is the substance aromatic? **No** **Q20**.Is the carbocyclic mono-, bi-, or tricyclic ... **Yes** **Q21**.Does the cyclic substance contain as its only functional group a ring ketone with an alpha isopropylidene or isobutylidene group **No** **Q22**.Is the substance, monocyclic, bicyclic, or tricyclic with ring carbons totalling	

≤C12? **Yes**
Q17.Does the structure contain four or more different functional groups? **No**
Q18.one or more of the following carbon moieties or functional groups **No**
Q18(J-M).one or more of the following carbon moieties or functional groups **No** Class Low (Class I)
Q9A.Is the substance a cyclic diester or lactone? **No**
Q10.Does the substance contain any three membered heterocyclic rings containing O, or S, or N? **No**
Q11.Is the heterocyclic ring substituted by groups OTHER than specified ? **No**
Q12.Is the substance heteroaromatic? **Yes**
Q13.Is the heteroaromatic substance thiophene or a substituted thiophene? **No**
Q14A. Considering both fused and unfused substitutents, does the heteroaromatic ring have more than one aryl substituent? **No**
Q29.Does the substance bear on every major structural entity at least one sulfonate or sulfamate salt as specified? **No** Class High (Class III)

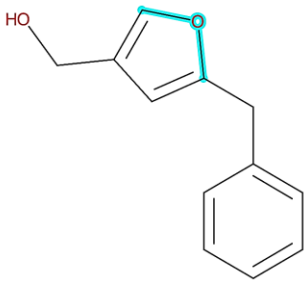
Highlighted Structural alerts for Bioresmethrin as per Revised Cramer decision tree are picked up as individual screen shot and are consolidated in Figure -3.



Structure-1



Structure-2



Structure-3

Structural alerts for Bioresmethrin:
Structure-1**: Q1, Q12,Q22**
Structure-2**: Q20**
Structure-3**: Q7,Q12**

Figure- 3: Structural alerts for Bioresmethrin as per Revised Cramer decision tree

CONCLUSION

The Cramer Rule decision tree feature in Toxtree was applied for all the four isomers of resmethrin. The structure alerts for all the isomers were found to be same. Thus, details of only Bioresmethrin are summarized in Table -1 and Table-2. As per in silico prediction, to estimate the Threshold of Toxicological Concern (TTC) for a chemical substance based on its chemical structure, all isomeric resmethrins belong to Cramer Class -III. The Cramer Class -III depicts high toxicity (1.5 µg/kg bw/d) and is described as substances with chemical structures that permit no strong initial impression of safety and may even suggest a significant toxicity.

Thus, stereochemical aspects of resmetherins have no impact on structural alerts in Toxtree.

REFERENCES

[1] Casida J.E., Pyrethrum, the Natural Insecticide, Academic Press, New York-London (1973).

[2] Elliott, M. (1989). The pyrethroids: early discovery, recent advances and the future. *Pesticide Science*, *27*(4), 337-351.

[3] Elliott M., Janes N. F.,Chem Soc. Reviews 7,473 (1971)

[4] La Forge F.B., Barthel W.F., J. Org Chem 12,199 (1947)

[5] Hartley D, Kidd H, Agrochemicals Handbook, with updates; Nottingham, Royal Soc of Chemistry, 1983-86, A362 (1983).

[6] M. Elliott *et al.*, *Nature* **213,** 493 (1967)

[7] Soderlund, D. M. (2015). Resmethrin, the first modern pyrethroid insecticide. *Pest management science*, *71*(6), 801-807.

[8] *Idem, et al., Pestic. Sci.* **2,** 243 (1971)

[9] Chadwick P. R *et al.*, Control of cockroaches, *J. Med. Entomol.* **13,** 625 (1977).

[10] Soderlund, D. M. (2008). Pyrethroids, knockdown resistance and sodium channels. *Pest Management Science: formerly Pesticide Science*, *64*(6), 610-616.

[11] T. B. Gaines, R. E. Linder, *Fundam. Appl. Toxicol.* **7,** 299 (1986).

[12] Review of toxicology and human exposure: *Toxicological Profile for Pyrethrins and Pyrethroids* (PB2004-100004, 2003) 332 pp.

[13] Pesticide Manual., 9(80), 1991

[14] EHP, Environmental Health Perspectives., 14(15), 1976 [PMID:789062]

[15] Pesticide Biochemistry and Physiology., 2(308), 1972

[16] Pesticide Biochemistry and Physiology., 4(456), 1974

[17] Pesticide Biochemistry and Physiology., 6(491), 1976

[18] Aldridge,W.N.(1983). Toxicology of pyrethroids. In Mode of Action, Metabolism and Toxicology (pp.485-490).Pergamon

[19] Gray, A. J., Connors, T. A., & Hoellinger, H. (1980). The relationship between the pharmacokinetics of intravenous cismethrin and bioresmethrin and their mammalian toxicity. *Pesticide Biochemistry and Physiology*, *13*(3), 281-293.

[20] Wolansky, M. J., & Harrill, J. A. (2008). Neurobehavioral toxicology of pyrethroid insecticides in adult animals: a critical review. *Neurotoxicology and teratology*, *30*(2), 55-78.

[21] White, I. N. H., Verschoyle, R. D., Moradian, M. H., & Barnes, J. M. (1976). The relationship between brain levels of cismethrin and bioresmethrin in female rats and neurotoxic effects. *Pesticide Biochemistry and Physiology*, *6*(5), 491-500.

[22] Cramer G. M., R. A. Ford, R. L. Hall, Estimation of Toxic Hazard - A Decision Tree Approach, J. Cosmet. Toxicol., Vol.16, pp. 255-276, Pergamon Press, 1978 http://toxtree.sourceforge.net/cramer3.html

[23] I.C. Munro, R.A. Ford, E. Kennepohl, and J.G. Sprenger, Correlation of structural class with No-Observed-Effect Levels: A proposal for establishing a threshold of concern, Food Chem. Toxicol. 34 (1996), pp. 829-867.

[24] Patlewicz G, Jeliazkova N, Safford RJ, Worth AP, Aleksiev B. (2008) An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. SAR QSAR Environ Res. ;19(5-6):495-524.