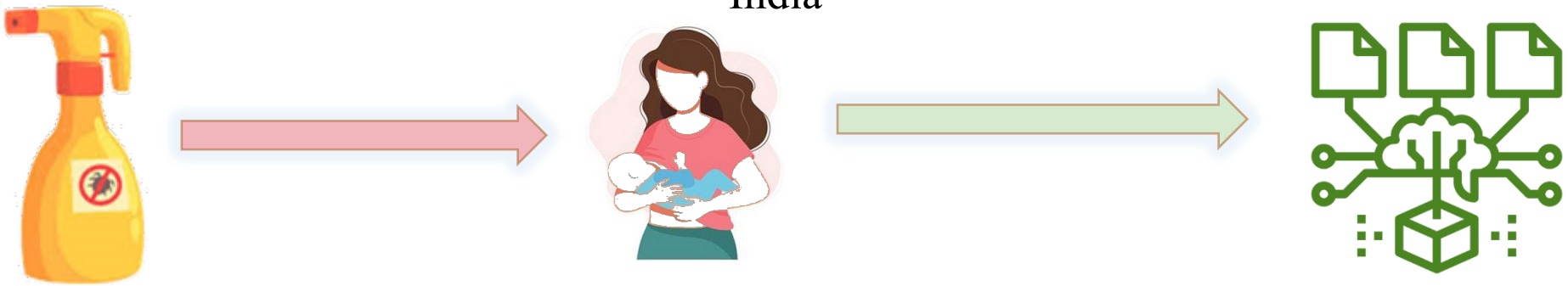
ESTIMATION OF RETENTION TIME OF ORGANIC PESTICIDES IN HUMAN MILK USING QSPR AND READ-ACROSS METHODS: AN ALTERNATIVE APPROACH TO EXPERIMENTAL HAZARDS ASSESSMENT

Presented by

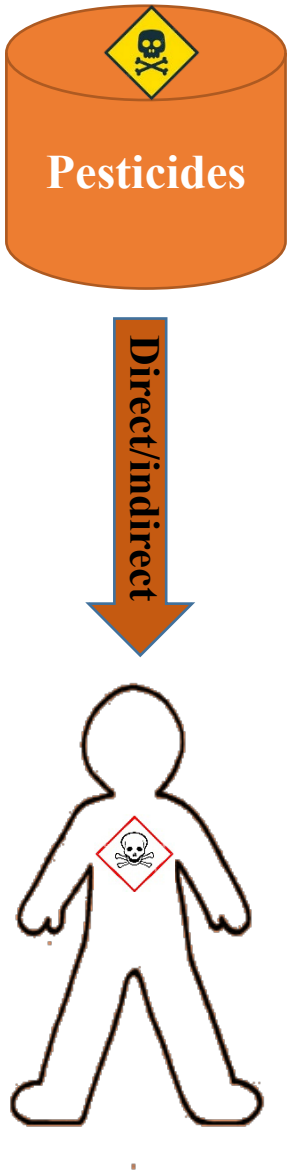
Ankur Kumar

Ph.D. Research Scholar
Dept. Of Pharm. Tech
Jadavpur University, Kolkata-700032
India



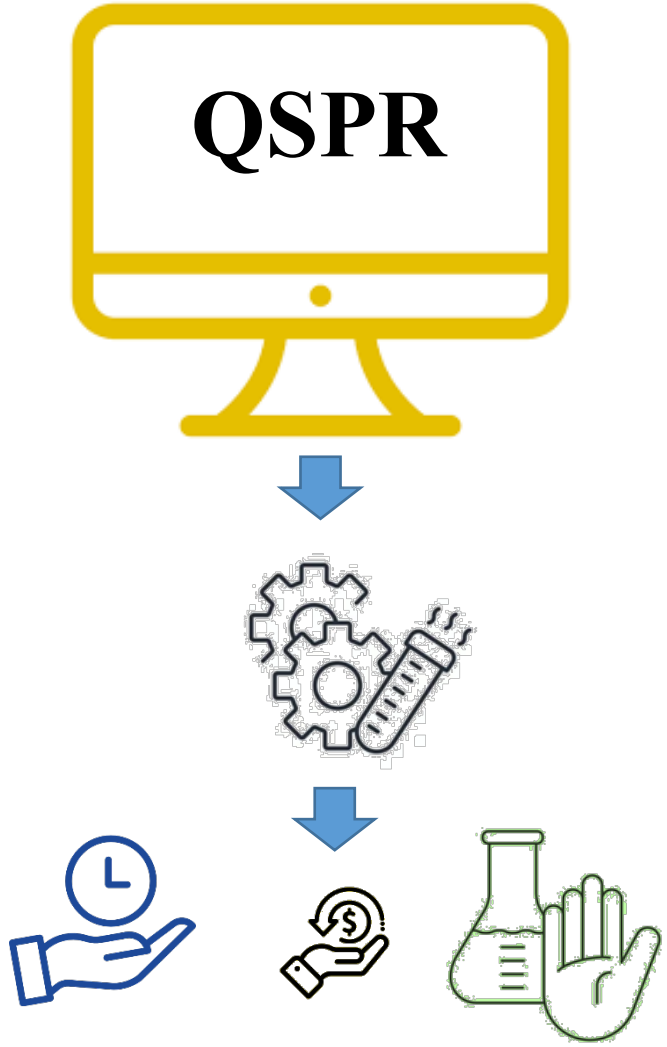
Introduction

- Uncontrolled and excessive utilization of pesticides results in serious health effects in humans due to their accumulation in breast milk, blood, etc.
- Health effects associated with direct or indirect (via food, water, air, etc.) consumption of excessive pesticides include neural effects, carcinogenic effects, liver and kidney disease, abnormal behavior, genotoxicity, infertility, Parkinson's, obesity, bronchitis, infertility, birth defects, dull behavior in new-born babies, autism spectrum disorders, etc.
- Some of the most toxic and harmful pesticides include organochlorines, organophosphates, phenoxyacetic acids, and triazine compounds which are mainly responsible for different diseases.



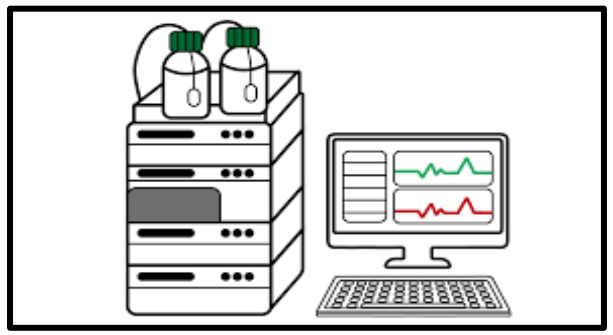
❖ **Kumar, A., Ojha, P.K. and Roy, K., 2024. The first report on the assessment of maximum acceptable daily intake (MADI) of pesticides for humans using intelligent consensus predictions. Environmental Science: Processes & Impacts, 26(5), pp.870-881. DOI: 10.1039/D4EM00059E**

- So, it is necessary to identify the pesticides, harmful and carcinogenic food hazards, and related compounds (the higher the RT, the more will be toxicity) in human milk. Retention time (RT) prediction is one of the analytical techniques to identify the chemical hazards in milk, it requires complex processes, sophisticated equipment, and highly skilled labor, but it requires complex processes, sophisticated equipment, highly skilled labor, high cost, etc.
- In this work, we have developed a QSPR univariate model and read-across method using RT of 29 pesticides in human milk (Ultrahigh Performance Liquid Chromatography Coupled to Tandem Mass Spectrometry) for the estimation of the retention time of pesticides in human milk to overcome the analytical problems and experimental costs.
- The QSARs/QSPRs/QSTRs are computational tools that are used to predict various endpoints using 2D/3D descriptors, by establishing a relationship between activity/property/toxicity with structural properties.



- **Kumar, A., Ojha, P.K. and Roy, K., 2024. The first report on the assessment of maximum acceptable daily intake (MADI) of pesticides for humans using intelligent consensus predictions. Environmental Science: Processes & Impacts, 26(5), pp.870-881. DOI: 10.1039/D4EM00059E**
- **J. Agric. Food Chem. 2021, 69, 23, 6676–6689. https://doi.org/10.1021/acs.jafc.0c05950**

Graphical abstract

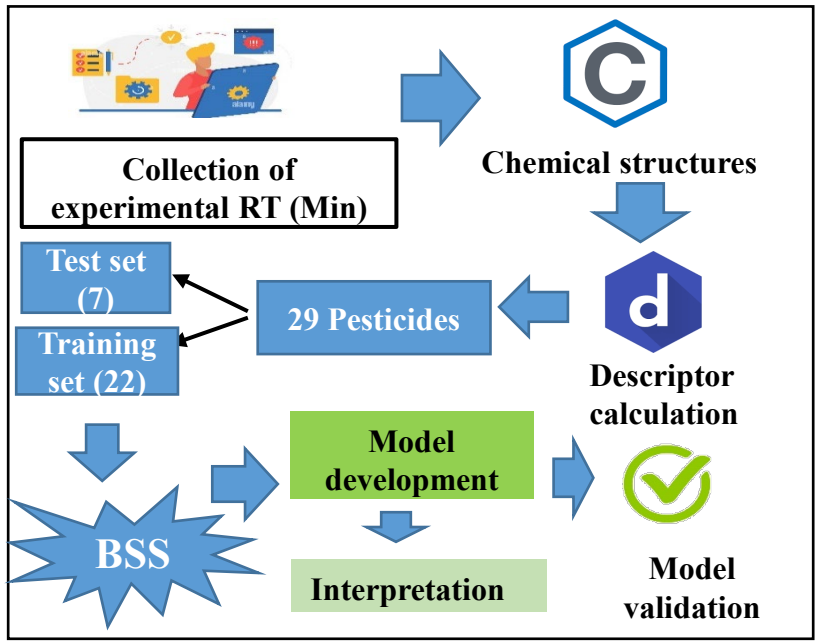


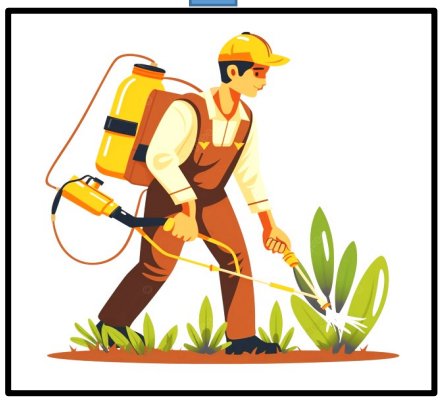
Retention time (RT) of 29 pesticides in human milk

QSPR

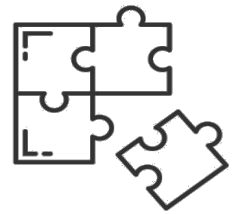
logRT(MIN) = 0.29585+0.08498××LOGPcons

Read-across





PPDB DATABASE SCREENING



RT DATA GAP FILLING

HEALTHIER ECO-SYSTEM

Method and material

Fig. Schematic representation of QSPR model development

- J. Agric. Food Chem. 2021, 69, 23, 6676–6689. https://doi.org/10.1021/acs.jafc.0c05950
- Roy, K., Kar, S. and Das, R.N., 2015. Understanding the basics of QSAR for applications in pharmaceutical sciences and risk assessment. Academic press.

Result and discussion

Univariate model for Retention time as an endpoint:

Model 1 (Log(RT/min)):

$$\boldsymbol{Log}\left(\frac{\boldsymbol{RT}}{\boldsymbol{min}}\right) = 0.29585(+/-0.0199) \ + 0.08498(+/-0.006)\boldsymbol{X}(LOGPcons)$$

Where $LOGPcons$ indicates the Octanol-water partition coefficient (logP) (consensus), RT shows the retention time of pesticides in human milk in minutes.

- The statistical results of the developed model show that models are highly validated, robust, accurate, predictive, and easily interpretable.

- **Properties responsible for Retention time:** Lipophilicity ($LOGPcons$)

- Roy, K., Das, R.N., Ambure, P. and Aher, R.B., 2016. Be aware of error measures. Further studies on validation of predictive QSAR models. Chemometrics and Intelligent Laboratory Systems, 152, pp.18-33.

Applicability domain assessment and Y-randomization test

- In the present study, we have performed the applicability domain using standardization approach with the help of the "MLRPlusValidation1.3" tools and it was seen that all compounds are within the domain of applicability.

- We have also checked the y-randomization of the developed model to ensure whether the model is not come by any chance using the "MLRPlusValidation1.3" tool and it was observed that (cRp^2>0.5) it was not a random model.

- **Roy, K., Das, R.N., Ambure, P. and Aher, R.B., 2016. Be aware of error measures. Further studies on validation of predictive QSAR models. Chemometrics and Intelligent Laboratory Systems, 152, pp.18-33.**
- **Roy, K., Kar, S. and Das, R.N., 2015. Understanding the basics of QSAR for applications in pharmaceutical sciences and risk assessment. Academic press.**

Table 1 : Statistical results of the QSPR model (Model 1)

Validation Metrics	QSPR model's statistical quality	Read-across results
R^2(train)	0.909	-
Q^2_{LOO} (train)	0.891	-
$Q^2_{F1\ (test)}$	0.945	0.960
$Q^2_{F2\ (test)}$	0.942	0.960
$Q^2_{F3\ (test)}$	0.692	-
MAE_{test} and prediction quality	0.026 and GOOD	0.020
$\overline{r^2_{m(LOO)}}$	0.852	-
Δr^2_m(LOO)	0.055	-
$\overline{r^2_{m(test)}}$	0.917	-
Δr^2_m(test)	0.037	-

R^2: Coefficient of determination, $Q^2_{(LOO)}$:Cross-validated correlation coefficient (leave one out), Q^2_{F1}:Predictive R^2

- Roy, K., Kar, S. and Das, R.N., 2015. Understanding the basics of QSAR for applications in pharmaceutical sciences and risk assessment. Academic press.
- Ojha, P.K., Mitra, I., Das, R.N. and Roy, K., 2011. Further exploring rm2 metrics for validation of QSPR models. Chemometrics and Intelligent Laboratory Systems, 107(1), pp.194-205. https://doi.org/10.1016/j.chemolab.2011.03.011

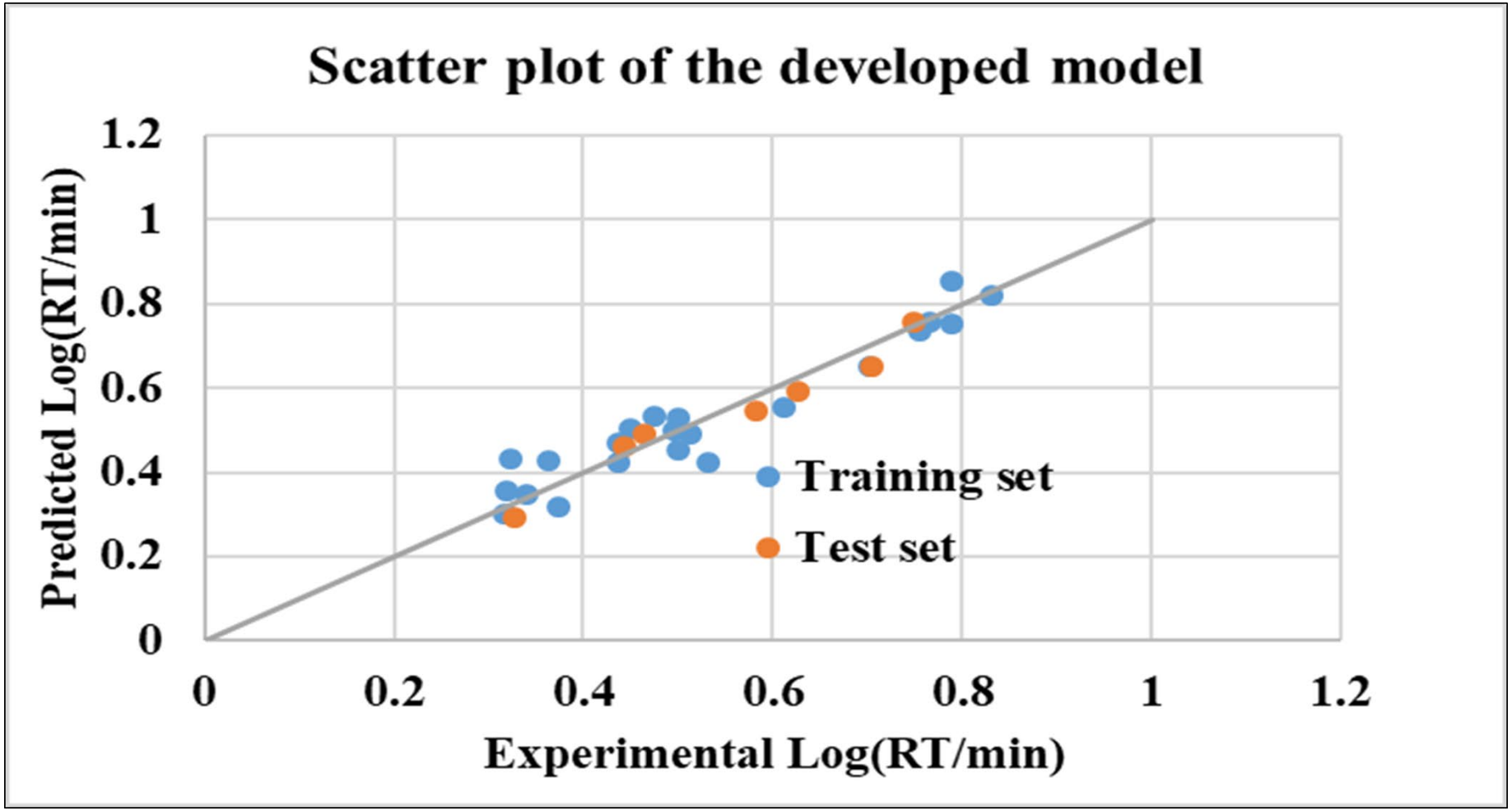


Fig. Scatter plot of the developed QSPR model

The scatter plot show that the developed model perform well both for the internal (training) and external (test) sets.

List of top 20 pesticides with high retention time (in minutes) in human milk as predicted by our developed model

S.no.	Pesticides	S.no.	Pesticides
1	Cyproflanilide	11	Brodifacoum
2	Decafentin	12	Cholecalciferol
3	Difethialone	13	Calciferol
4	Butyl stearate	14	Triarathene
5	Diclobutrazol	15	Halfenprox
6	Protrifenbute	16	Silafluofen
7	Broflanilide	17	Difenacoum
8	Flocoumafen	18	Brofluthrinate
9	2,4-DEP	19	Cycloprate
10	Chlorphonium	20	Fluvalinate

Conclusion

- The statistical results of the developed model show that models are highly **validated, robust, accurate, predictive, and easily interpretable**.
- From the study, it was inferred that **lipophilicity (LOGPcons descriptor)** is responsible for the retention time, which will be helpful in the **design of pesticides and chemicals** with desired RT.
- **The PPDB database** screening shows the model's real-world application.
- This study will be useful for **data-gap filling** (prediction of RT of untested and new compounds in milk, identification of food hazards in human milk, and overcoming the analytical problems and experimental costs, which will maintain healthier ecosystems and serve as a **vital application for food informatics**.

My sincere thanks to:

Dr. Kunal Roy

Dr. Probir Kumar Ojha

DDD LAB


thank
you