Biomarker-guided q-RASAR Modeling of Antibiotics-Microplastics Mixtures: Towards Predictive Aquatic Toxicology and Resistance Risk Assessment

Presented

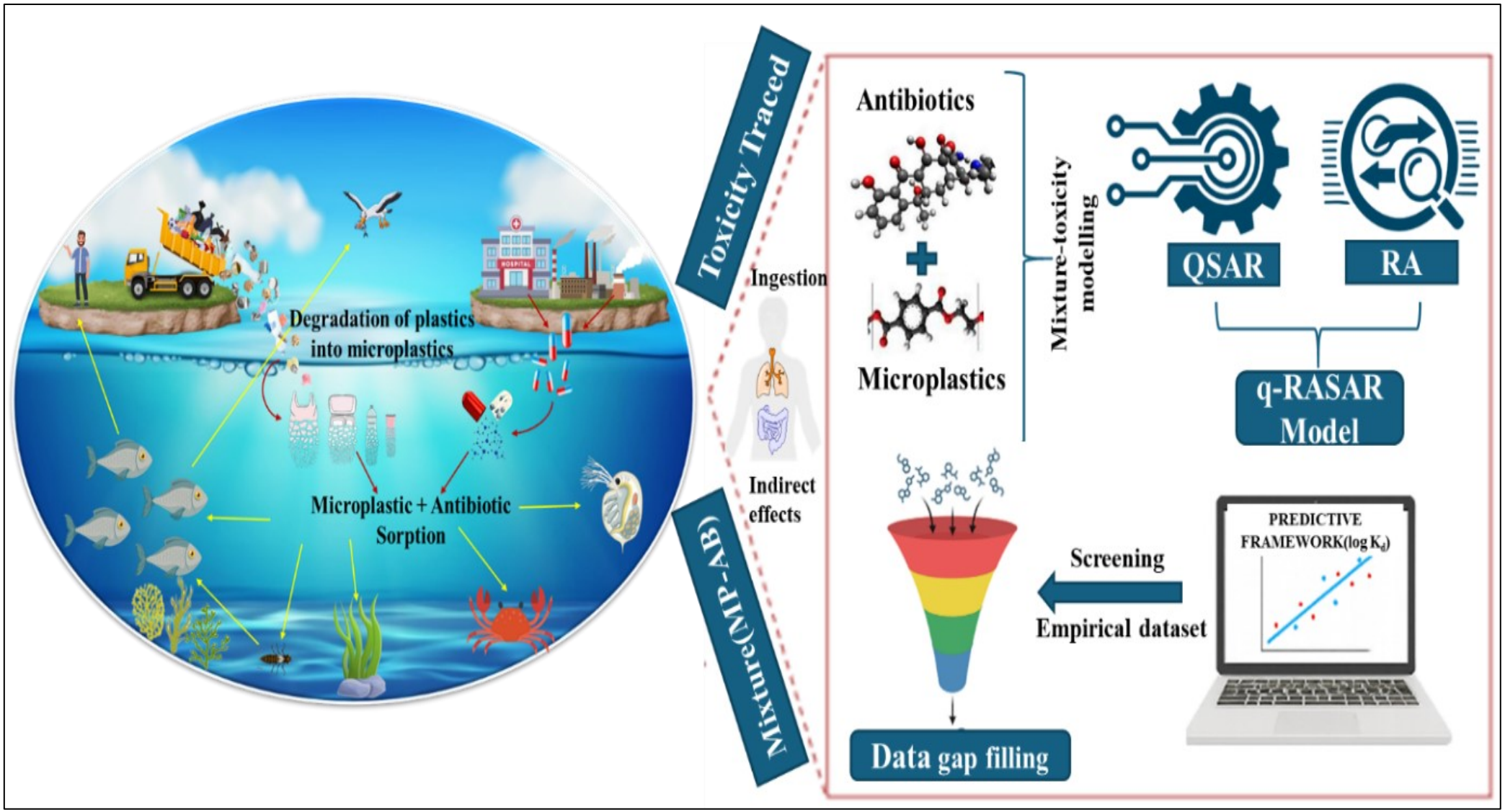
by

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Graphical Abstract



Introduction (why this study matters)

A prediction gap at the intersection of emerging contaminants and aquatic risk

Co-occurrence in aquatic systems

Antibiotics and microplastics can coexist; plastic particles may act as carriers for antibiotic residues.

Why sorption matters

Sorption influences where antibiotics partition, how long they persist, and how available they remain in water.

The research gap

Experimental mixture data are limited, while conventional single-chemical models may not represent mixture behaviour.

Study objective

Develop an interpretable PLS-based q-RASAR model to predict mixture log Kd and support data-gap filling.

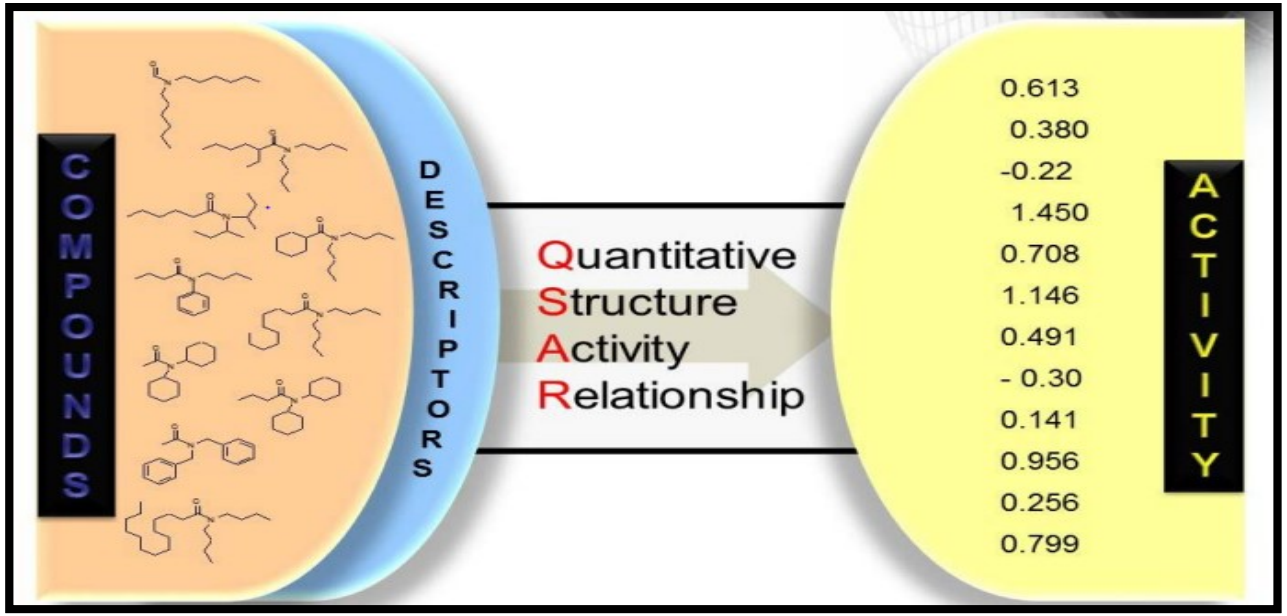
Endpoint: log K_d - a measure of partitioning between the aqueous and plastic phases; it is not a direct measurement of biological toxicity.

QSAR (Quantitative Structure-Activity Relationship)

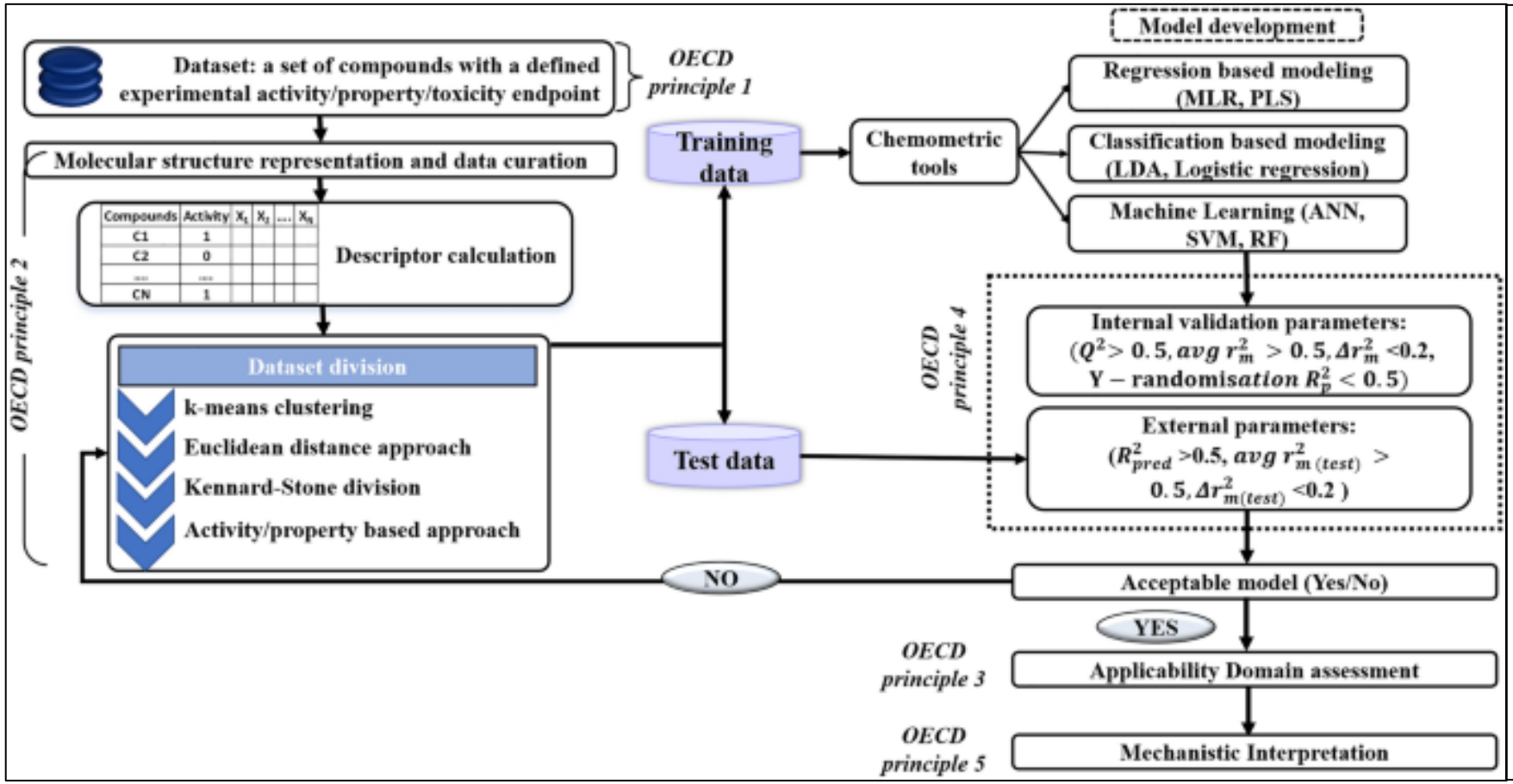
- QSAR is a mathematical relationship that can correlate chemistry with the properties (physicochemical/biological/toxicological) of molecules using various computationally or experimentally derived quantitative parameters.

- Descriptors are the numerical values that characterize specific information about a studied molecule.

Response (activity/property/toxicity)=*f*(Information in form of chemical structure or properties) =*f*(Descriptors)



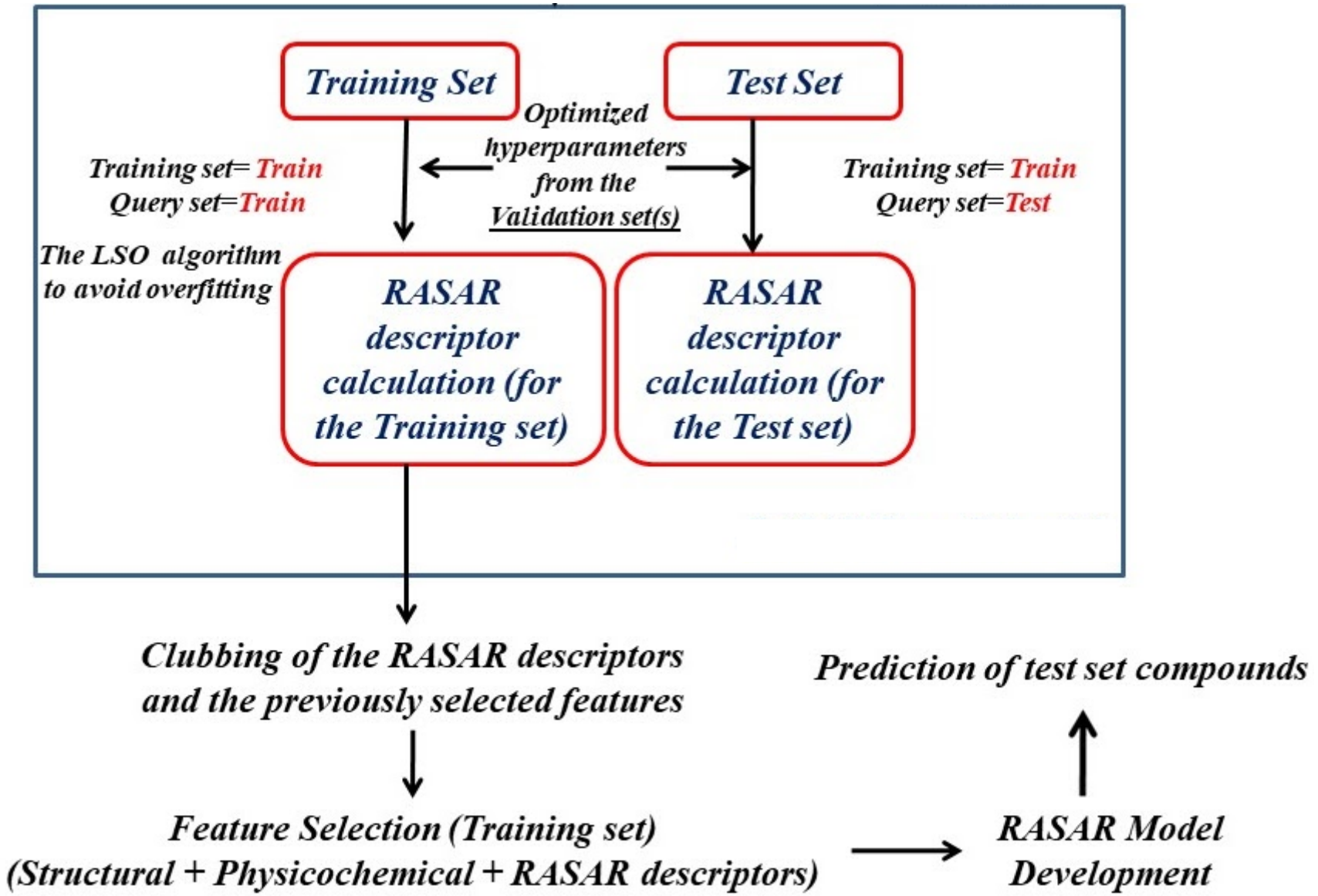
Standard algorithm of QSAR modeling: The OECD guideline



- ***OECD Principle 1***: A defined End point
- ***OECD Principle 2***: An unambiguous algorithm
- ***OECD Principle 3***: A defined domain of applicability
- ***OECD Principle 4***: Appropriate measure of goodness of fit, robustness, and predictivity
- ***OECD Principle 5***: A mechanistic interpretation, if possible

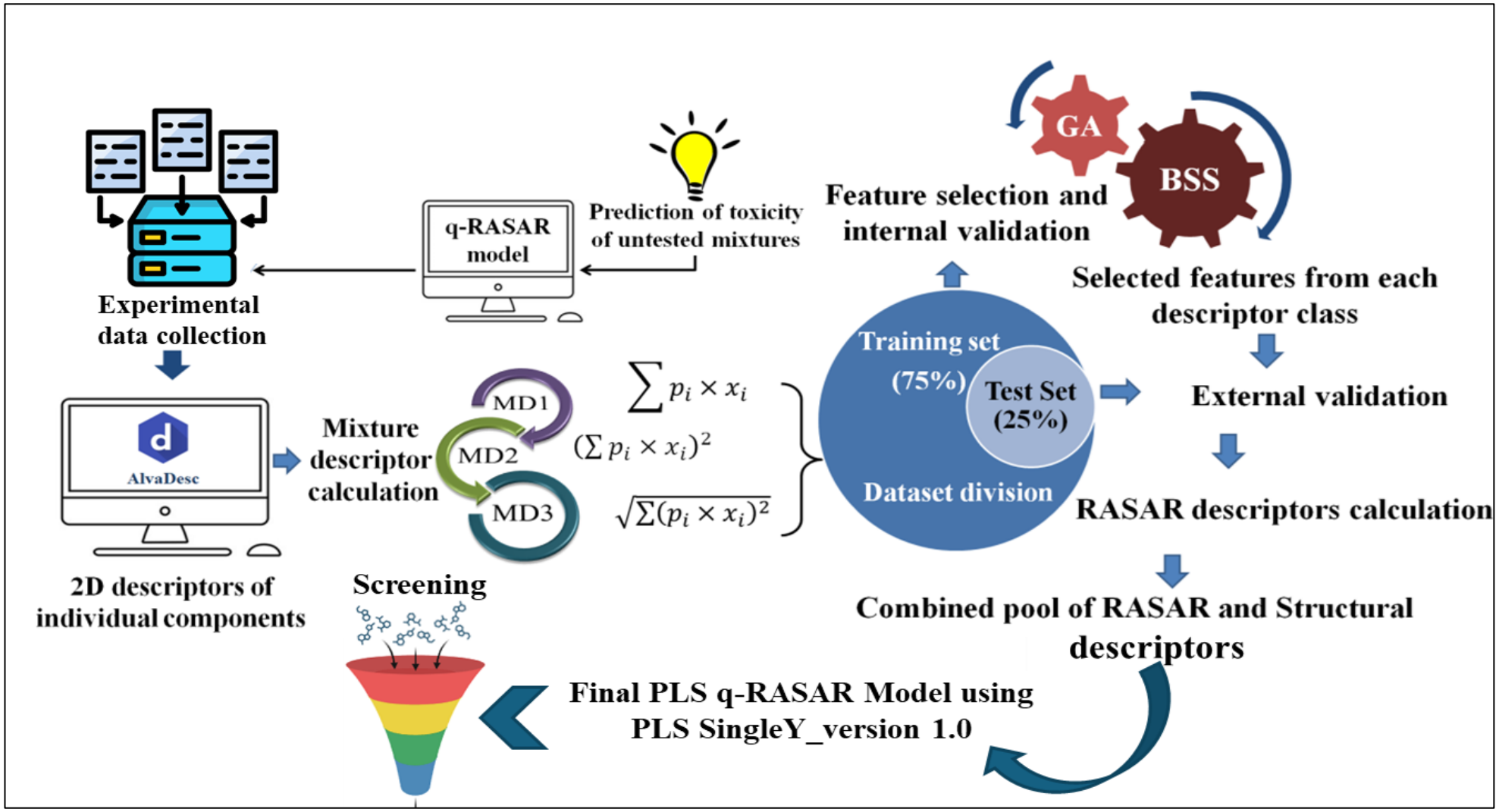
OECD, **2004**. Validation of (Q)SAR Models. URL https://www.oecd.org/chemicalsafety/risk-assessment/validationofqsarmodels.htm

q-RASAR (Quantitative Read Across Structure-Activity Relationship)



Available at: https://sites.google.com/jadavpuruniversity.in/dtc-lab-software

Methods and Materials (present work)



Results and discussion

QSAR model with validation metrics (Model 1)

$$log\ K_d = 1.18 - 0.93 \times (C - 027) + 2.93 \times (\text{Eta_D_epsiD}) + 0.61 \times (SaaO) + 0.88 \times (nR = Ct) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (\textit{Equation } \textbf{\textit{1}})$$

$R^2_{train} = 0.820$; $Q^2_{LOO(train)} = 0.761$; $MAE_{train} = 0.151$; $Q^2_{F1\ (test)} = 0.789$; $Q^2_{F2\ (test)} = 0.788$; $\overline{r^2_{m(test)}} = 0.719$; $\Delta r^2_m(test) = 0.083$; $MAE_{test} = 0.179$; $CCC = 0.883$

q-RASAR model with validation metric (Model 2)

$$log\ Kd = 1.21 - 0.82 \times (C - 027) + 2.97 \times (\text{Eta_D_epsiD}) + 0.60 \times (SaaO) + 0.95 \times (nR = Ct) - 0.17 \times (\text{Abs MaxPos} - \text{MaxNeg}) \ldots\ldots\ldots\ldots\ldots (\textit{Equation } \textbf{\textit{2}})$$

$R^2_{train} = 0.831$; $Q^2_{LOO(train)} = 0.761$; $Q^2_{F1\ (test)} = 0.832$; $Q^2_{F2\ (test)} = 0.831$; $MAE_{train} = 0.178$; $\overline{r^2_{m(test)}} = 0.801$; $\Delta r^2_m(test) = 0.005$; $MAE_{test} = 0.152$; $CCC = 0.907$

Predictive accuracy and robustness assessment

How was model reliability assessed?

Multiple checks were used rather than relying on a single performance statistic

Internal validation

Leave-one-out cross-validation gave $Q^2_{LOO} = 0.761$, supporting model robustness.

External test set

$Q^2_{F1} = 0.832$; $Q^2_{F2} = 0.831$; CCC = 0.907; $MAE_{test} = 0.152$.

Applicability domain

AD analysis identifies predictions that fall within the model's defined chemical space.

Y-randomization

Used to examine whether the observed model performance could arise from chance correlation.

Important: virtual-mixture screening is pseudo-external validation, not independent experimental validation.

Predictive accuracy and robustness assessment

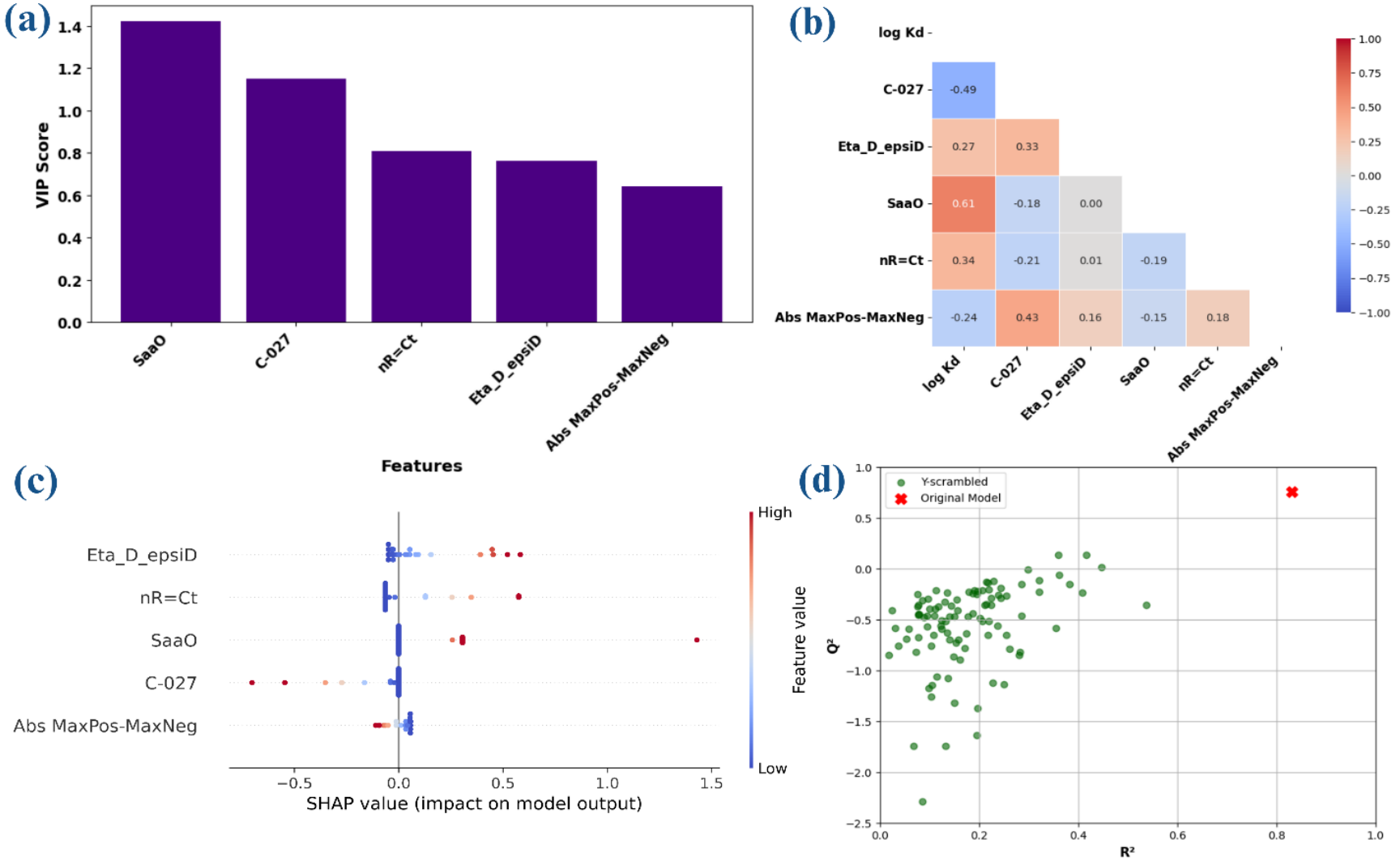
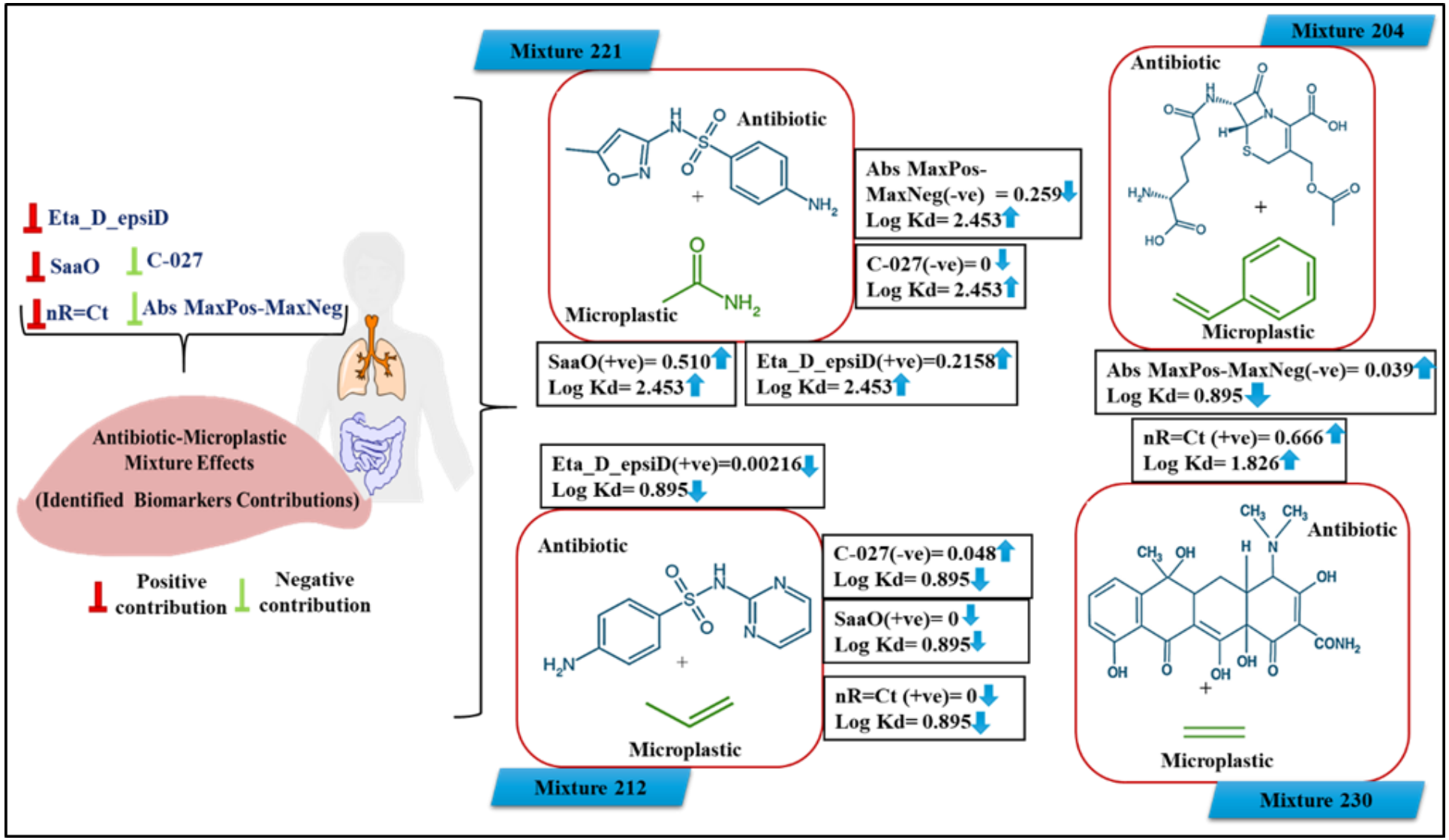


Figure 1. (a) The variable_importance (VIP) plot; **(b)** The correlation matrix plot; **(c)** SHAP plot; **(d)** Y-randomization plot of the q-RASAR model.

Mechanistic Interpretation



Virtual screening of hypothetical mixtures

A pseudo-external assessment to explore predictions beyond the 37 curated experimental mixtures

111
Hypothetical mixtures
Mixture IDs 501–611

3 ratios
Antibiotic : microplastic
25:75, 50:50, 75:25

PRI
Prediction reliability
Good / Moderate / Bad

What was observed?

Most virtual mixtures were within the applicability domain and received a “Good” PRI classification.

How should this be interpreted?

It supports exploratory use within the defined chemical space, but does not replace validation with new experimental data.

Conclusions

What this study contributes:

1. A mixture-focused predictive framework

A PLS-based q-RASAR model was developed to predict log K_d for antibiotic–microplastic mixtures.

2. Strong model performance

The final model achieved $Q^2_{LOO} = 0.761$, $Q^2_{F1} = 0.832$ and test MAE = 0.152.

3. Interpretable structural trends

Oxygen-rich/polar features, hydrogen-bond donor capacity and terminal unsaturation were associated with higher sorption; steric hindrance and charge asymmetry tended to reduce it.

4. Practical value-with a clear boundary

The model may support prioritization and data-gap filling, but it predicts sorption behaviour, not toxicity or antibiotic-resistance outcomes directly.

Limitations and future directions

A useful first framework that needs broader experimental testing

Current limitations

The 111 virtual mixtures are not independent experimental validation.

Environmental complexity

The current model does not explicitly capture all factors such as pH, ionic strength, microplastic ageing, or multi-component mixture effects.

Priority 1: new experiments

Test diverse antibiotic-microplastic combinations and use independent measurements for true external validation.

Priority 2: broader models

Incorporate environmental conditions and expand to more complex mixtures and contaminant classes.

Take-home message: q-RASAR can help prioritize what to test next not replace environmental experiments.


Thank
you