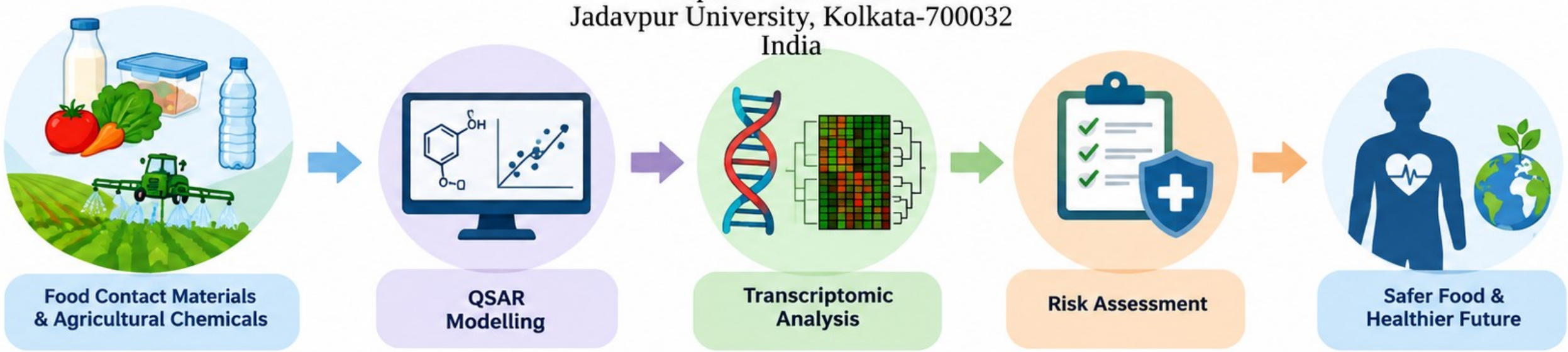
# Integrated QSAR Risk Assessment and Transcriptomic Evaluation of Chemical Safety: Applications to Food Contact Substances and Chronic Ultra-Low-Dose Roundup Exposure


Presented by

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# Study overview

A combined framework is presented for screening chemical safety by linking molecular structure, endpoint-specific QSAR models, and transcriptomic interpretation.

### Chemical safety

Food-contact substances and chemicals used in agricultural or food-related settings.

### Predictive modelling

QSAR models for human exposure, carcinogenic potency, and N/LOAEL.

### Biological context

Transcriptomic evidence discussed in relation to chronic ultra-low-dose Roundup exposure.

# Background: why chemical risk assessment matters

- Chemicals may enter food systems through food-contact materials, agricultural products, and production processes.
- Exposure may occur directly or indirectly through food, water, air, and other environmental pathways.
- Prolonged exposure can raise concerns about adverse biological effects.
- Conventional toxicity testing may involve extensive experimental work, specialist expertise, time, cost, and animal studies.
- Structure-based methods can help screen and prioritize substances for further evaluation.

# Study objective and endpoints

The study links chemical descriptors with three reported toxicological endpoints and discusses how transcriptomic findings may add mechanistic context.

### Human exposure

Endpoint reported in mg/day. Modelled to explore structure-associated exposure patterns.

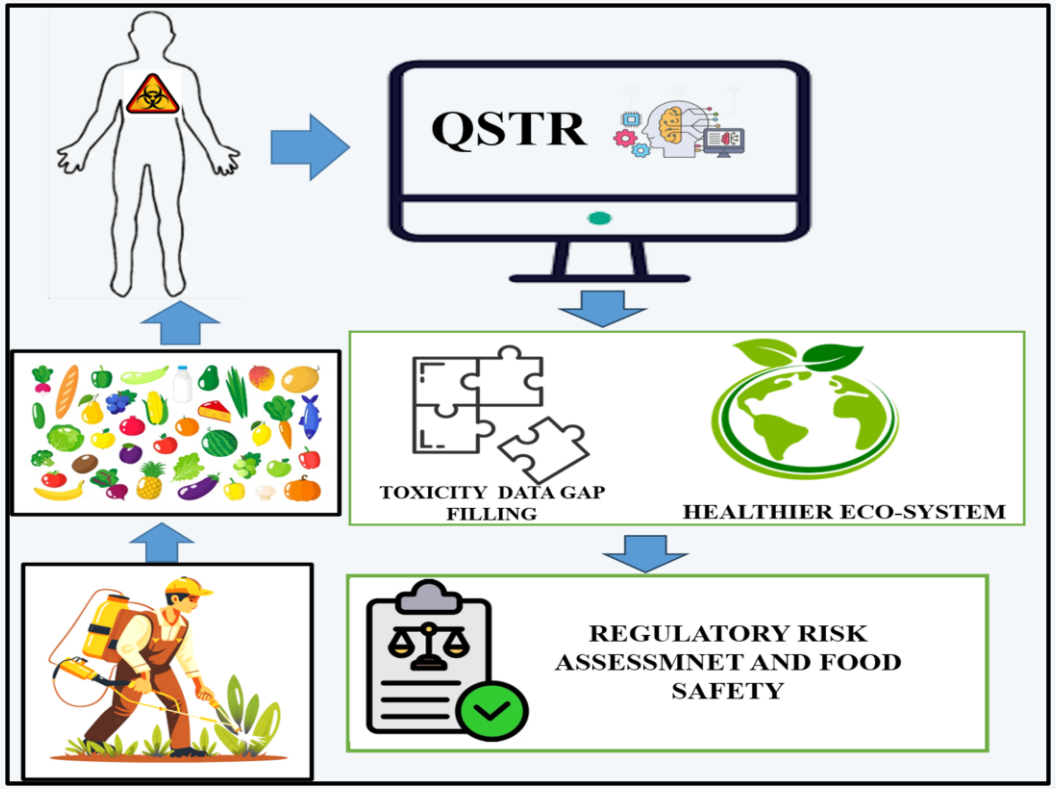
### Carcinogenic potency

$TD_{50}$, reported in mg/kg/day, used as the carcinogenic-potency endpoint.

### Adverse-effect level

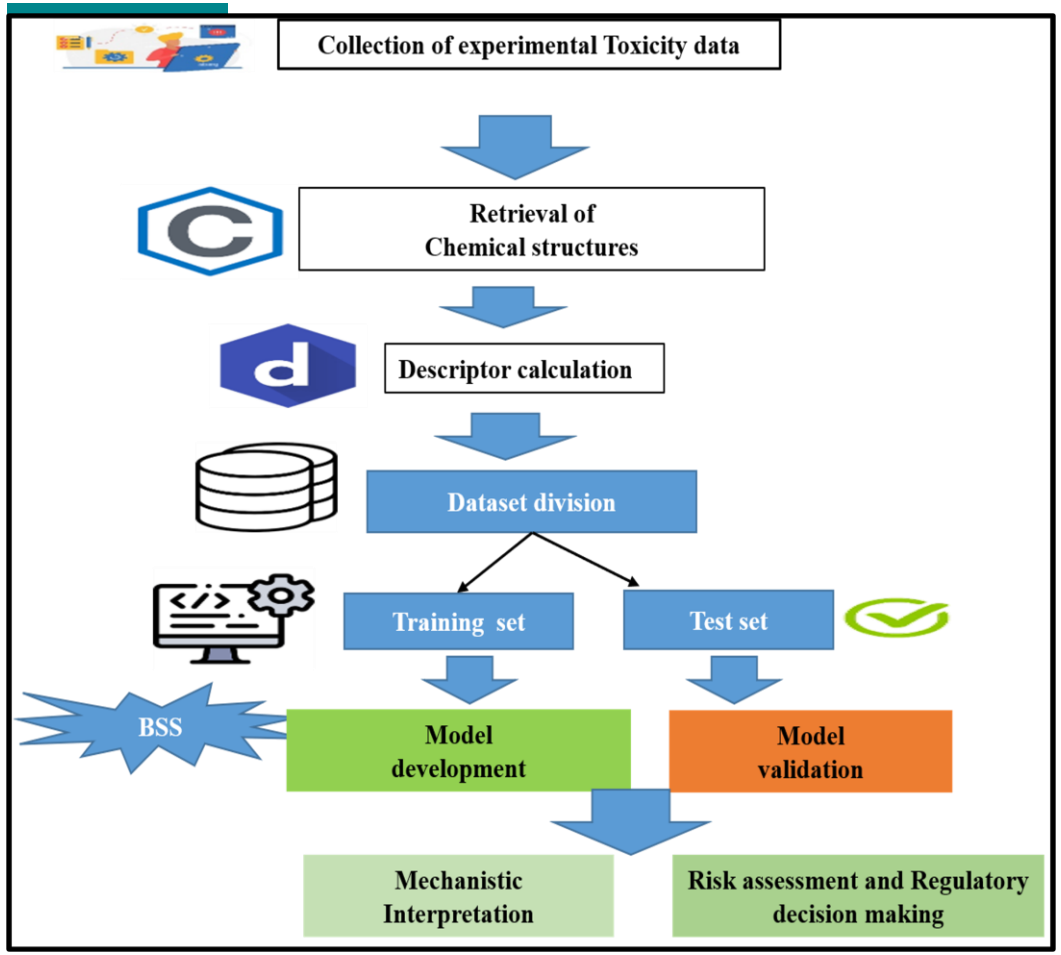
N/LOAEL: no/lowest observed adverse-effect level as labelled in the poster.

# Graphical abstract: from exposure to food-safety decisions




- The graphical abstract connects potential exposure and chemical-safety concerns with QSTR prediction.
- It highlights data gaps, a healthier ecosystem, and regulatory risk assessment as part of the broader context.

# QSPR model-development workflow




- Collect experimental toxicity data.
- Retrieve chemical structures and calculate descriptors.
- Divide the dataset into training and test sets.
- Develop models and validate their predictive performance.
- Interpret mechanisms and inform risk-assessment decisions.


**European Food Safety Authority (EFSA). (2016). Recent developments in the risk assessment of chemicals in food and their potential impact on the safety assessment of substances used in food contact materials. EFSA Journal, 14(1), 4357. https://doi.org/10.2903/j.efsa.2016.4357**

**Ames BN, Magaw R, Gold LS. Ranking possible carcinogenic hazards. Science. 1987;236(4799):271–280. doi:10.1126/science.3563506**

# Methods: descriptor-based model construction

### 1. Data collection

Experimental toxicity / endpoint data form the starting point.

### 2. Structure processing

Chemical structures are retrieved and converted into descriptors.

### 3. Dataset division

Training and test subsets support model development and evaluation.

### 4. Model development

Descriptor combinations are used to fit endpoint-specific models.

### 5. Validation and use

Predictive metrics and mechanistic interpretation inform prioritization.

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# Reported QSTR model statistics

| Endpoint | $R^2$ Train | $Q^2$(LOO) Train | $Q^2F1$ Test | $Q^2F2$ Test | MAE95 Test |
|---|---|---|---|---|---|
| Human exposure\n(mg/day) | 0.835 | 0.705 | 0.847 | 0.735 | 0.525 |
| $TD_{50}$\n(mg/kg/day) | 0.827 | 0.715 | 0.883 | 0.825 | 0.456 |
| N/LOAEL | 0.686 | 0.557 | 0.628 | 0.597 | 0.330 |

# Mechanistic interpretation: structural alerts

### Chlorinated fragments

May relate to chemical persistence and resistance to metabolic degradation.

### Nitrogen-containing groups

May alter polarity, hydrogen-bonding capacity, and protein-binding affinity.

### Unsaturated regions

Identified among structural patterns associated with higher predicted toxicity.

## Physicochemical properties related to present studies

- Greater lipophilicity may increase membrane permeability and tissue accumulation.
- Halogenated substituents may contribute to environmental persistence.

# Transcriptomic evidence: biological context

## Oxidative stress

Present study highlights biomarkers related to reactive oxygen species generation as potentially relevant to toxicity.

## Mitochondrial dysfunction

Transcriptomic signals associated with impaired energy metabolism are described as prominent.

# Integrating QSAR and transcriptomic evidence

### Chemical structure

Descriptors encode molecular patterns.

→

### QSAR outputs

Models estimate endpoint-specific outcomes.

→

### Biological response

Transcriptomic signals suggest possible pathways.

→

### Risk prioritization

Combined evidence helps target follow-up review.

# Conclusions

- Structural interpretation of the models revealed that chemicals possessing **chlorinated molecular fragments, nitrogen-containing functional groups,** and **unsaturated structural regions** were more frequently associated with elevated toxicity.
- These features are known to influence c**hemical persistence, electrophilic reactivity**, metabolic activation, and interactions with biological macromolecules.
- Several physicochemical properties appeared to contribute to the observed toxicological behavior. Increased **lipophilicity** and **hydrophobicity** may enhance membrane permeability, tissue accumulation, and bioavailability, while the **presence of halogenated substituents, particularly chlorine atoms**, can increase environmental persistence and resistance to metabolic degradation.
- Biomarkers related to **oxidative stress and mitochondrial dysfunction** were particularly prominent, indicating that reactive oxygen species generation and impaired energy metabolism may represent key mechanisms of toxicity.
- Nitrogen-containing moieties may alter **molecular polarity, hydrogen-bonding capacity**, and **protein-binding affinity**, thereby affecting biological activity and toxic potential.
- The integration of QSAR-derived structural alerts with transcriptomic biomarkers provides a comprehensive framework for chemical risk assessment.
- This combined approach strengthens the mechanistic interpretation of toxicity and supports the **prioritization of potentially hazardous chemicals** used in food-related applications and environmental exposure settings.

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thank
you