Supporting the SSbD approach with in silico methods

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QSAR Lab Ltd,
University of Gdansk, Poland

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QSAR in SSbD

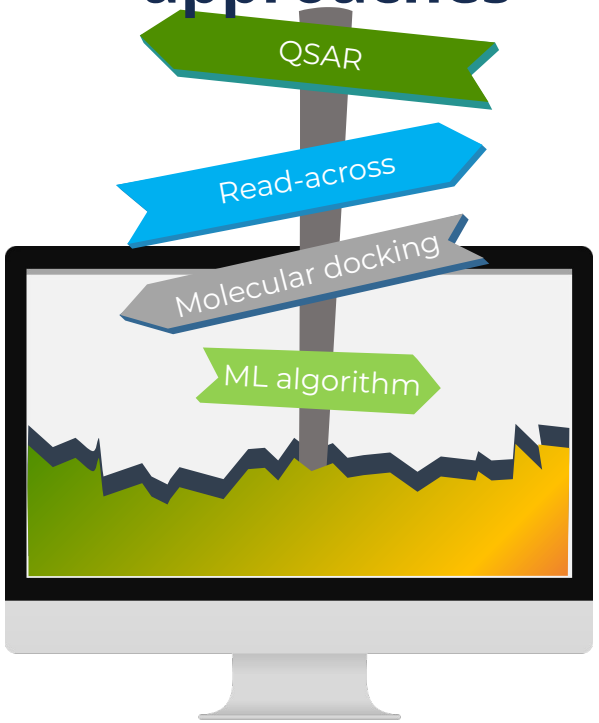
SSbD

Incorporating:

- Safety
- Environmental sustainability
- Functionality

Early in innovation and development of chemicals and materials

In silico approaches



Early prediction of hazardous properties and environmental fate of substances

Data-driven prioritization and screening of chemical candidates

Reducing the need for animal testing and resource

Together with regulatory frameworks (e.g., REACH, OECD guidelines) are integrated into **New Approach Methodologies (NAMs)** used for chemical risk assessment

Integration of in silico methods with SSbD frameworks

Enable to proactive identification and designing safer, more sustainable alternatives, optimize substance performance, and support life-cycle considerations

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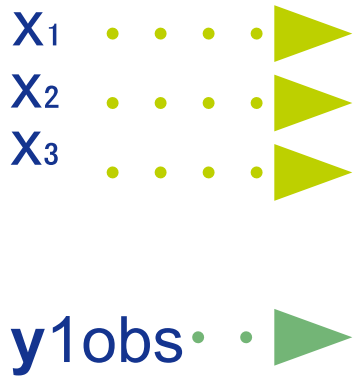
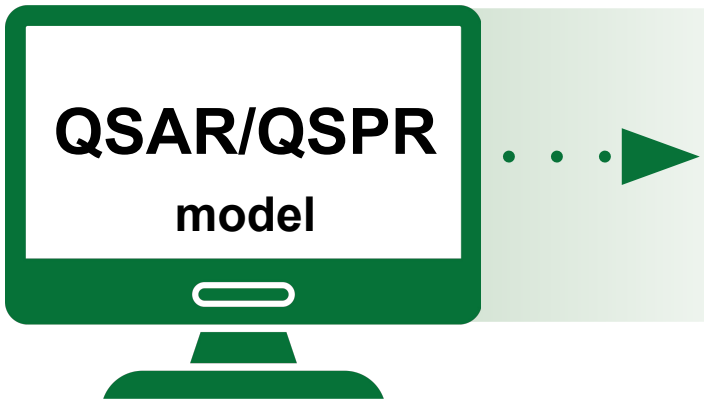
Introduction to QSAR/QSPR

INPUT

chemical structure (descriptors)

experimental values of activity / phys-chem property





OUTPUT

y = f(X)
(structure – activity / phys-chem property relationship)

QSAR – Quantitative Structure-Activity Relationships
QSPR – Quantitative Structure-Property Relationships

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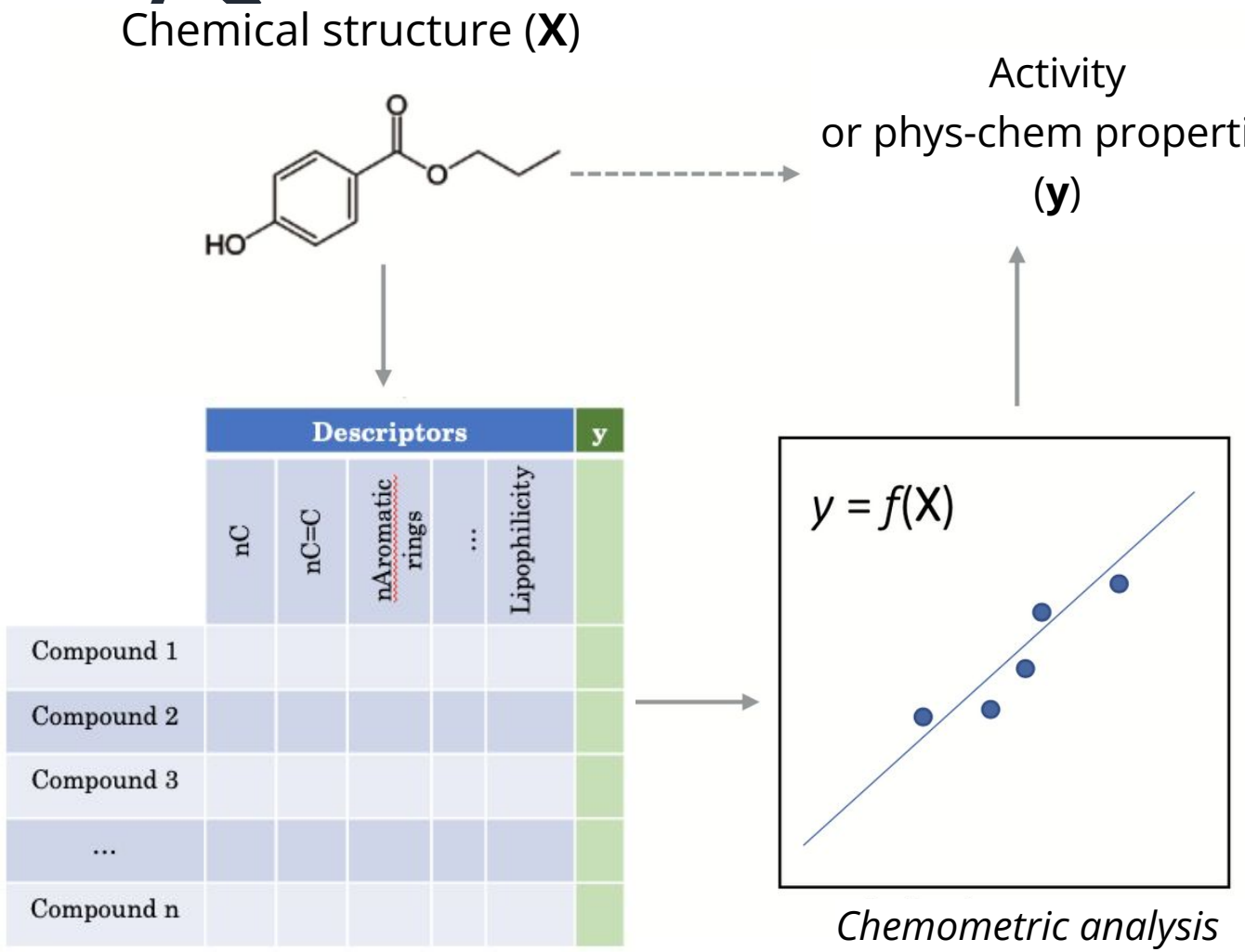
Introduction to QSAR/QSPR

For what purpose do we use QSAR/QSPR methods?

Predicting missing activity data and/or physicochemical properties of chemical compounds based on appropriate methods.

Searching for structural features affecting modelled activity or physicochemical property in a mechanistic context.



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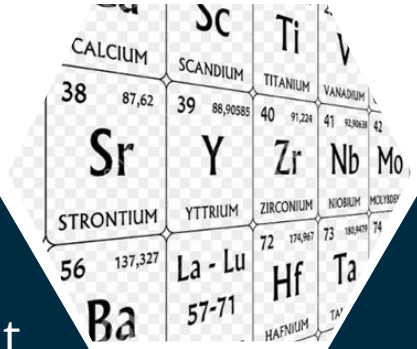
Applications of QSAR/QSPR modeling

Virtual screening of compounds

Assessing mobility and fate of compounds

Toxicity assessment of compounds



Assessing durability of chemicals

Designing safe cosmetics

Modeling of pharmacokinetic properties

Designing new materials

Green chemistry

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QSAR/QSPR modeling

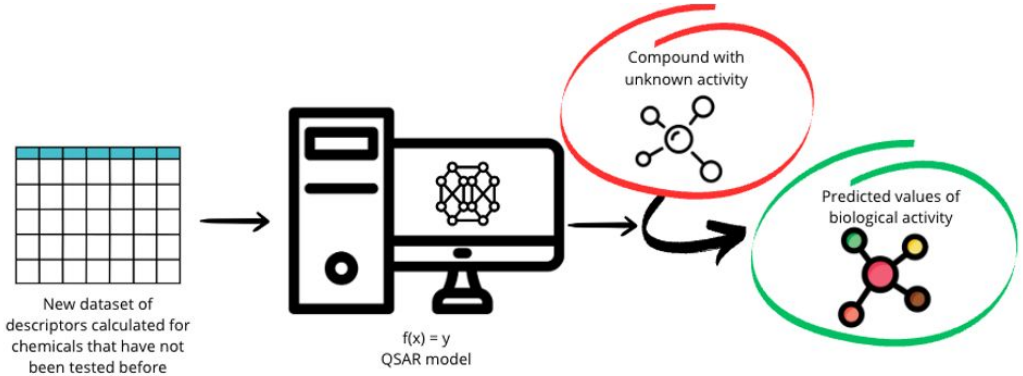
Development of new QSAR/QSPR model

Model calibration

Model validation

Model application

Application of existing QSAR/QSPR models



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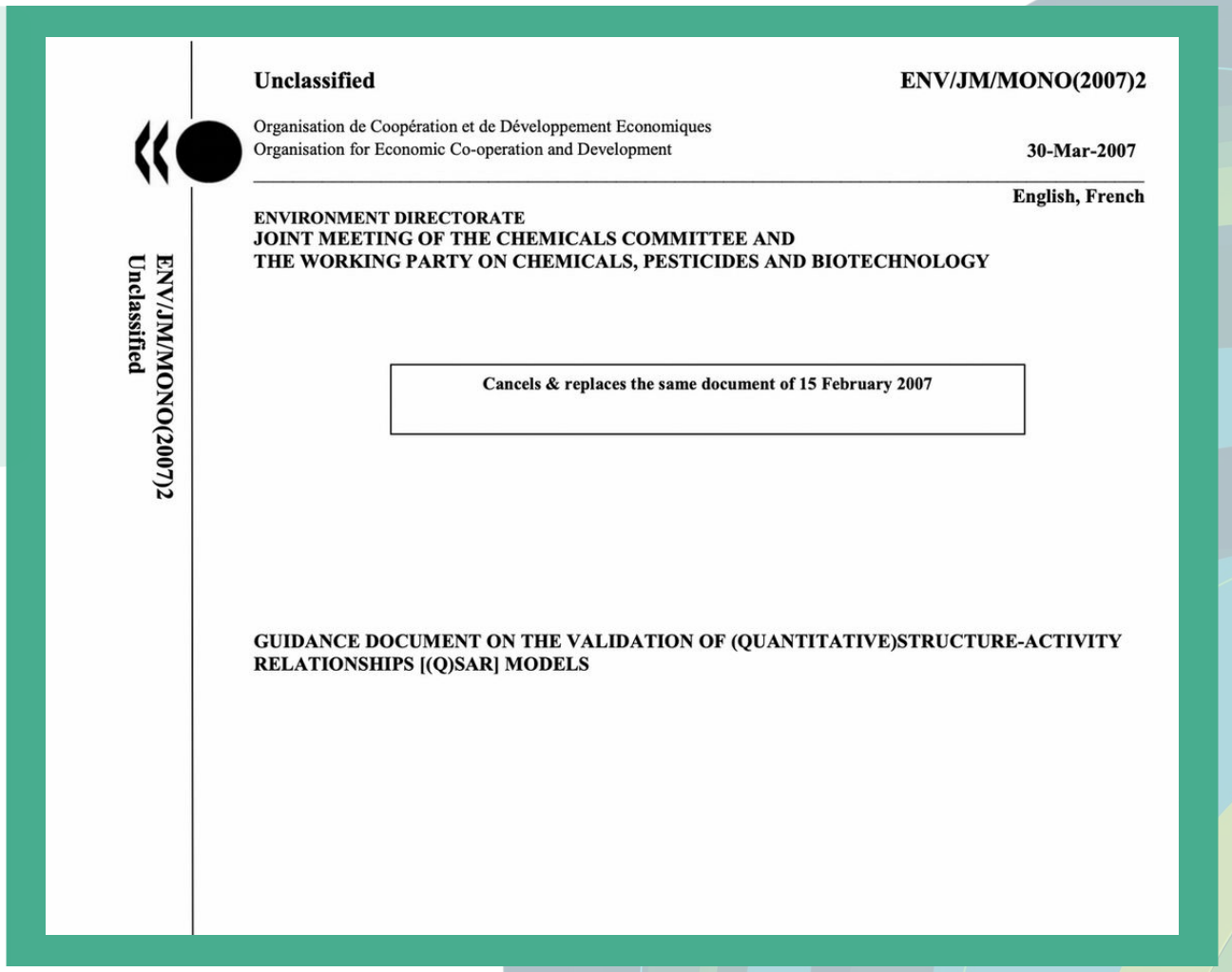
Development of QSAR/QSPR model

In 2004 OECD agreed principles for Validation, for Regulatory Purposes, of (Q)SAR models

"To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

- A defined endpoint;
- An unambiguous algorithm;
- A defined domain of applicability;
- Appropriate measures of goodness of-fit, robustness and predictivity;
- A mechanistic interpretation, if possible."



Unclassified ENV/JM/MONO(2007)2

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development 30-Mar-2007

English, French

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Cancels & replaces the same document of 15 February 2007

GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE)STRUCTURE-ACTIVITY RELATIONSHIPS [(Q)SAR] MODELS

ENV/JM/MONO(2007)2
Unclassified

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Development of QSAR/QSPR model

OECD principles for the assessment of (Q)SAR predictions and results based on multiple predictions and agreed on checklists to perform the assessment of models, predictions, and results from multiple predictions in practice.

21 November 2023

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QSAR in respect to FAIR

Findable

- QSAR models and datasets should have unique, persistent identifiers (e.g., DOIs).
- Metadata should be indexed in searchable repositories (e.g., OECD QSAR Toolbox, AMBIT, ChEMBL).

Accessible

- QSAR data and models should be openly available (where possible), with clear licensing.
- Use of standardized APIs and interfaces enables easy access to model predictions and training sets.

Interoperable

- QSAR benefits from data formatted using standardized vocabularies and ontologies.
- Interoperability enables integration with cheminformatics and bioinformatics tools.

Reusable

- Full documentation of model algorithms, applicability domains, and validation procedures enhances reusability.
- Reproducible workflows (e.g., KNIME, Jupyter notebooks) ensure that others can replicate and build upon results.

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Where can we find QSAR/QSPR models ?

Literature

Computational Toxicology 21 (2022) 100213

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.sciencedirect.com/journal/computational-toxicology

A review of *in silico* toxicology approaches to support the safety assessment of cosmetics-related materials

Mark T.D. Cronin [a,*], Steven J. Enoch [a], Judith C. Madden [a], James F. Rathman [b], Andrea-Nicole Richarz [a], Chihae Yang [b]

[a] School of Pharmacy and Biomolecula
[b] Molecular Networks GmbH – Compu

ARTICLE INFO

Keywords:
Cosmetics
Risk assessment
In silico
Computational
Read-across
Quantitative structure-activity relati

toxics

MDPI

Article

A Novel Machine Learning Model and a Web Portal for Predicting the Human Skin Sensitization Effects of Chemical Agents

Ricardo Scheufen Tieghi [1,2], José Teófilo Moreira-Filho [1], Holli-Joi Martin [2], James Wellnitz [2], Miguel Canamary Otoch [2], Marielle Rath [2], Alexander Tropsha [2,3,*], Eugene N. Muratov [2,*] and Nicole Kleinstreuer [1,*]

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ficant concern for chemical safety assessments. Traditional
man responses accurately, and ethical constraints limit the
ng a need for reliable in silico models of skin sensitization
SPred, an in silico tool based on the Human Predictive Patch
e the reliability of predicting human skin sensitization effects
egulatory assessment. We have curated an extensive HPPT
e analysis and grouping. Binary and multiclass QSAR models
parameter optimization. Model performance was evaluated
ormed model validation with reference data from the Defined
ASS) app. HuSSPred models demonstrated strong predictive
55 to 88%, sensitivity between 48 and 89%, and specificity
dictive value (PPV) ranged from 84 to 97%, versus negative
and coverage was between 75 and 93%. Our models exhibited
compared to existing tools, and the external validation showed
developed models. HuSSPred provides a reliable, open-access,
sting for skin sensitization. Its high accuracy and reasonable
r regulatory assessments, aligning with the 3Rs principles. The
offers a user-friendly interface for predicting skin sensitization

ational toxicology; QSAR; cheminformatics; NAMs

Environment International 185 (2024) 108568

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Environmental impact of PFAS: Filling data gaps using theoretical quantum chemistry and QSPR modeling

Michalina Mudlaff [a,1], Anita Sosnowska [a,c,1,*], Leonid Gorb [a,b], Natalia Bulawska [a,c], Karolina Jagiello [a,c], Tomasz Puzyn [a,c,*]

[a] QSAR Lab, Trzy Lipy 3, 80-172 Gdańsk, Poland
[b] Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, 150 Zabolotnogo str., 03680 Kyiv, Ukraine
[c] University of Gdansk, Faculty of Chemistry, Wita Stwosza 63, 80-308 Gdansk, Poland

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Per- and polyfluorinated alkyl substances (PFAS)
Theoretical chemistry

ABSTRACT

Per- and polyfluorinated alkyl substances (PFAS), known for their widespread environmental presence and slow degradation, pose significant concerns. Of the approximately 10,000 known PFAS, only a few have undergone comprehensive testing, resulting in limited experimental data. In this study, we employed a combination of physics-based methods and data-driven models to address gaps in PFAS bioaccumulation potential. Using the COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS) method, we predicted n-octanol/water

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Where can we find QSAR/QSPR models ?

Literature

- ✓ Evaluation of compliance with OECD principles (QMRF)
  - A defined endpoint;
  - An unambiguous algorithm;
  - A defined domain of applicability;
  - Appropriate measures of goodness-of-fit, robustness and predictivity;
  - A mechanistic interpretation, if possible.”
- ✓ Critical evaluation of endpoint and data used in the model
  - Reliable data?
  - Similar to target compound?

Actions

Descriptors calculation

↓

Recreation of the model

↓

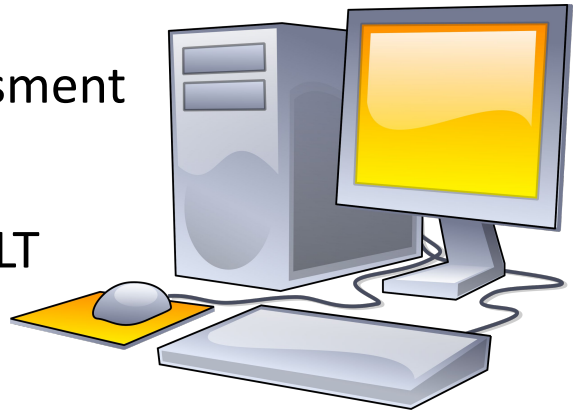
Prediction

↓

AD assessment

↓

RESULT



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Where can we find QSAR/QSPR models ?

Software/platforms

Open-source tools

EPI Suite™
Estimate chemical properties and environmental fate

VEGAHUB

QSAR TOOLBOX


Toxtree

Danish (Q)SAR Database

Actions

Proper model selection

↓

Input

↓

Prediction

↓

Critical expert assessment

↓

RESULT

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Where can we find QSAR/QSPR models ?

Software/platforms

Lhasa Limited

Derek Sarah Vitic

Mirabilis Zeneth

Skin Sensitisation Kaptis

instem Discover. Accelerate. Advance.

Leadscope Model Applier™

Comprehensive Metabolism Suite

N-Nitrosamine CPCA Module

ICH M7 Pharmaceutical Impurities Assessment

Advanced Skin Sensitization Models

Robust Acute Oral Toxicity Solution

Actions

Proper tool selection

↓

Input

↓

Prediction

↓

Critical expert assessment

↓

RESULT

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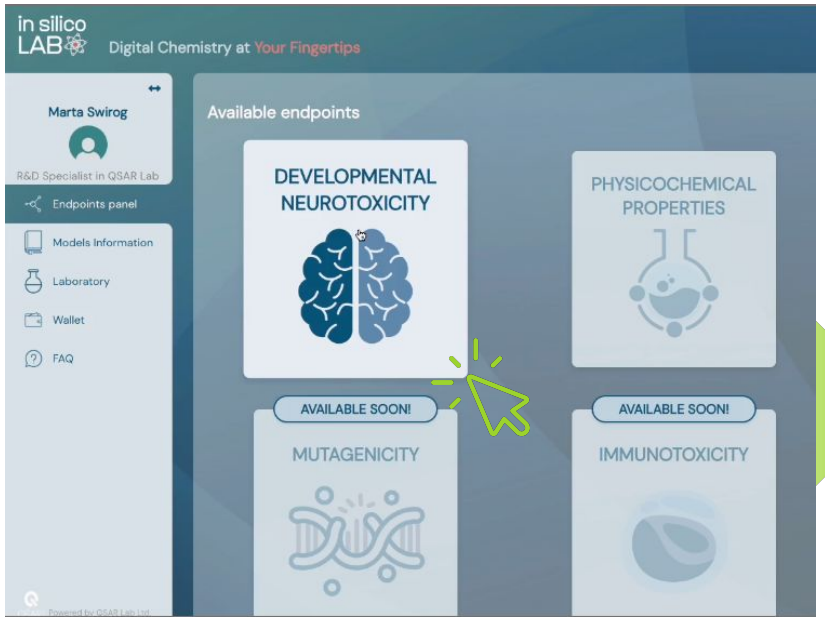
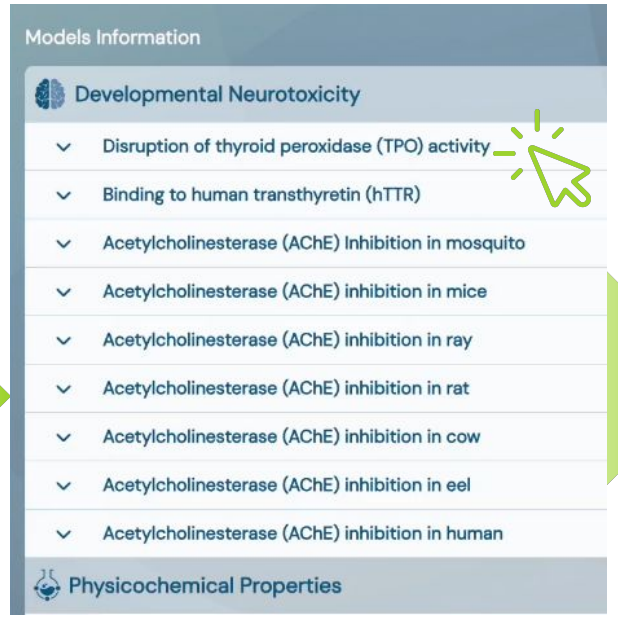
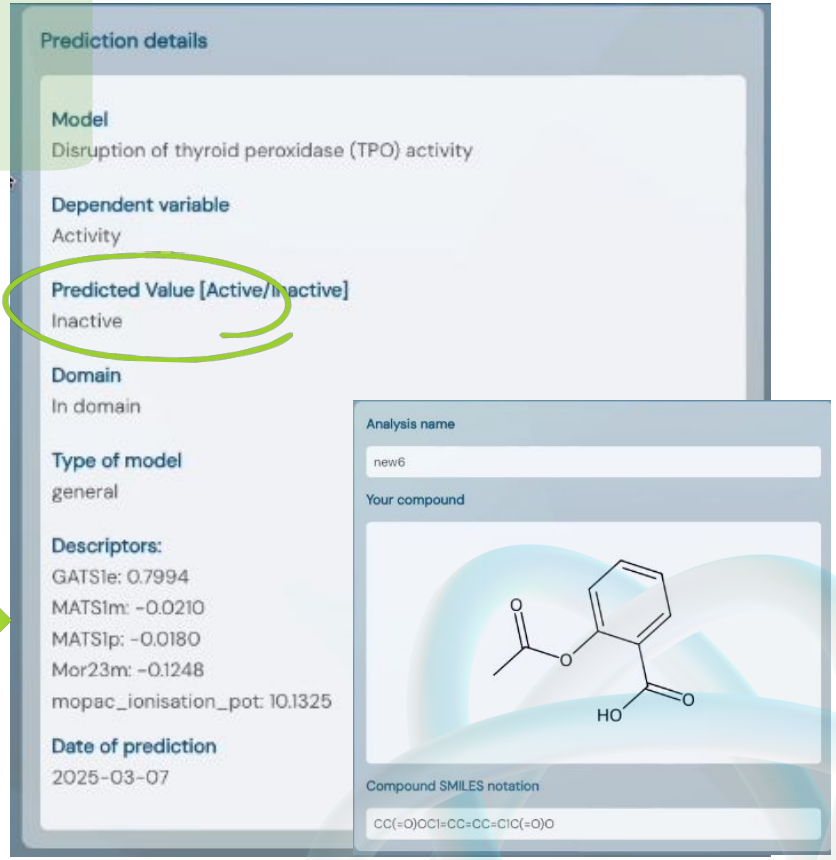
Where can we find QSAR/QSPR models ?

in silico LAB

Thanks to the already implemented QSAR models, e.g. for neurotoxicity, you can quickly and easily perform prediction for the entered structure. Prediction result with information about the domain, descriptor values, and the model statistics and its description are available at any time.







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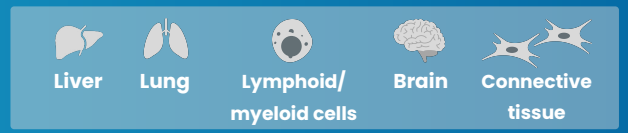
AI-powered Tools

Cellular models in nQTb.app:
16 for micronucleus test
23 for Comet assay



nQTb

Web-based tool, supported by machine learning algorithms for researchers, toxicologists and industry professionals for predicting genotoxicity and mutagenicity alerts of $nTiO_2$ & $nSiO_2$.

- Relevant endpoints & tests
- Pay less, test more
- Simple & intuitive use

https://nqtb.app/

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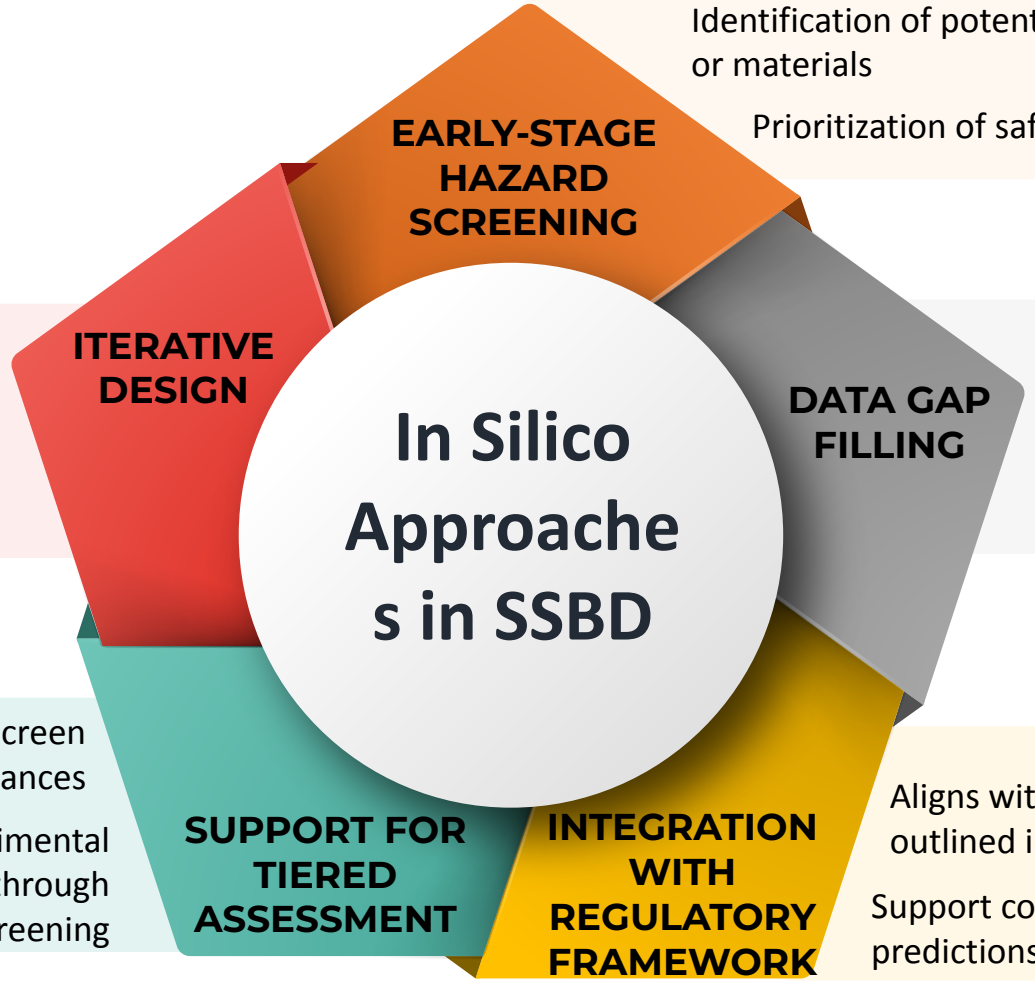
In Silico Approaches in the SSbD Framework



Identification of potential hazards associated with new chemicals or materials

Prioritization of safer alternatives during the (re)design phase

Provide predictive insights to fill these gaps, ensuring a more comprehensive assessment

Valuable in early development stages, where data scarcity is common.

Aligns with regulatory requirements, such as those outlined in REACH and CLP regulations

Support compliance by providing scientifically justified predictions for hazard identification and risk assessment

In silico methods are employed in initial tiers to screen and prioritize substances

Eficient allocation of resources by focusing experimental efforts on high-priority substances identified through computational screening

Providing continuous feedback on hazard and sustainability profiles as new data become available or as designs evolve

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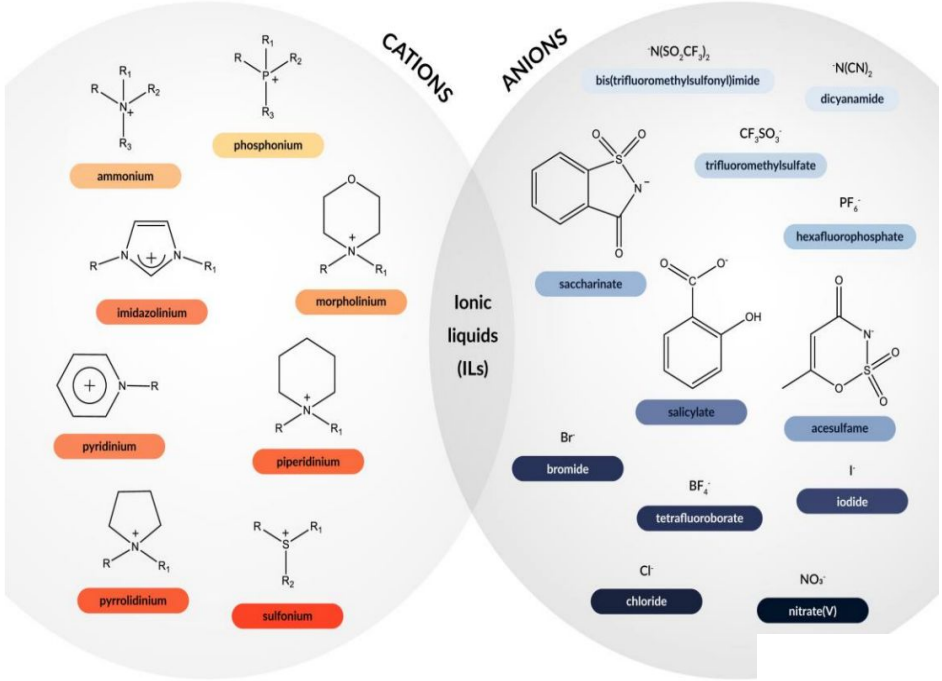
Case Study 1

Searching for chemical compounds with the desired type of activity.



Wyrzykowska E., Green Chemistry 2019, 21, 1965–1973

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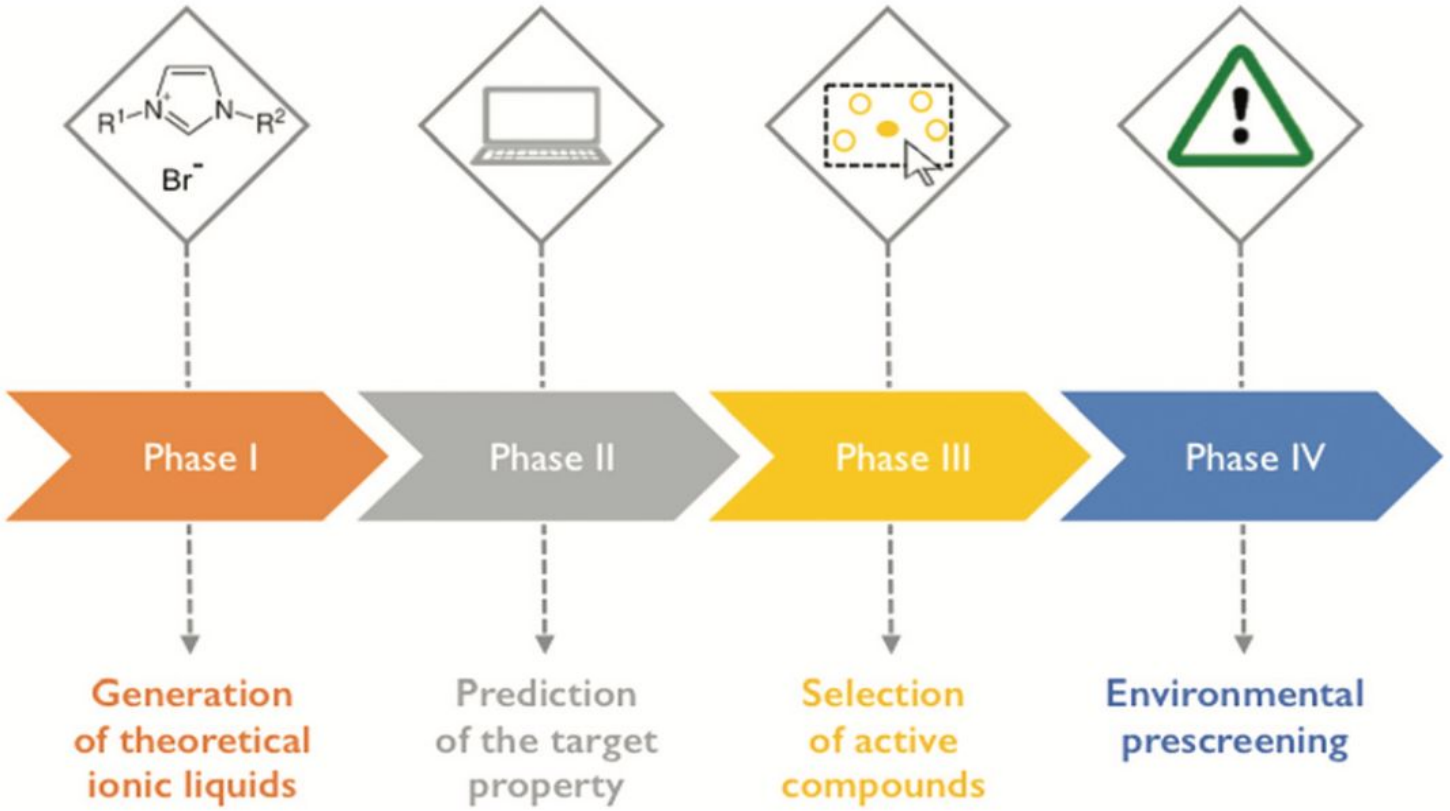
Design of ionic liquids used as bactericide



Four-step strategy for virtual screening in the design of safer products based on ionic liquids.

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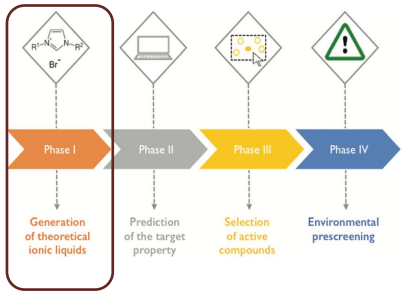


Design of ionic liquids used as bacteri

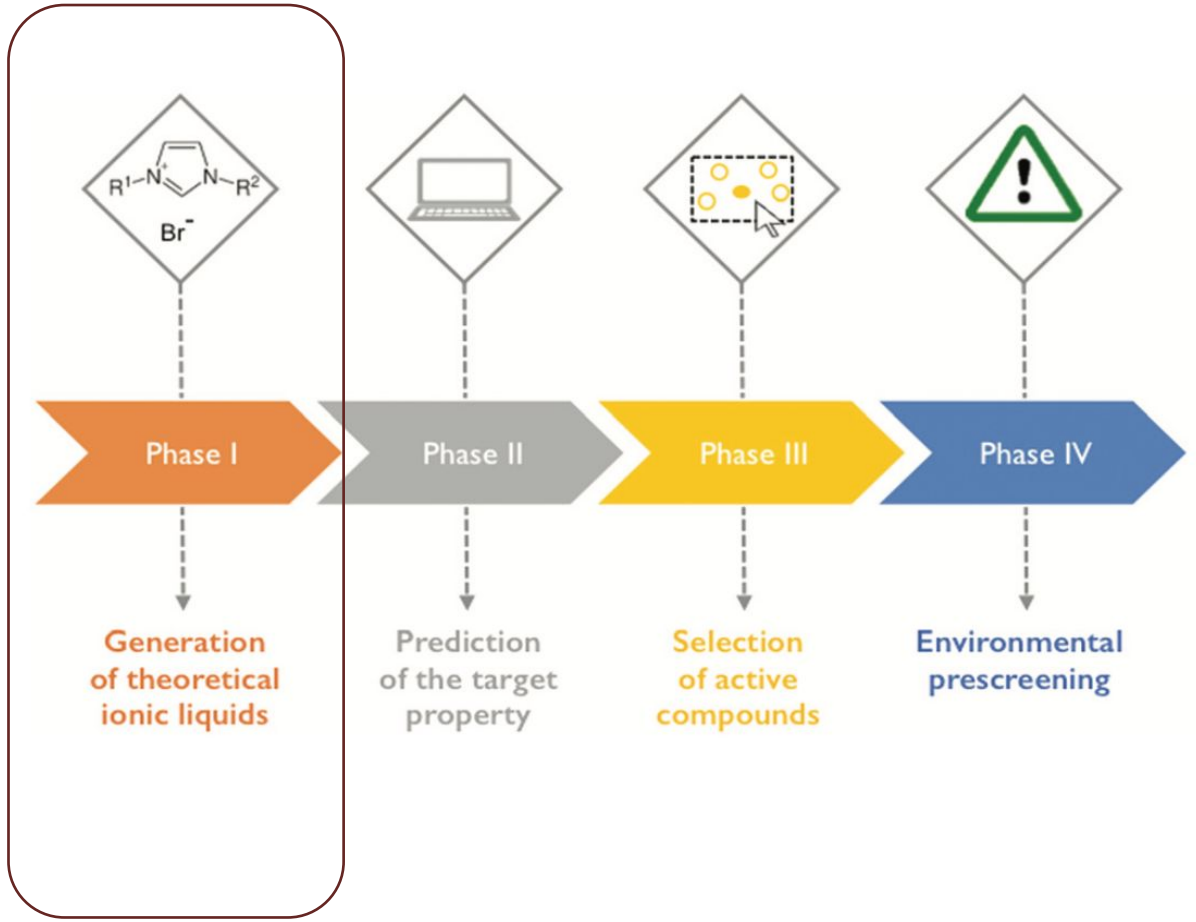
Phase I

735 structures of the cations

82 structures of anions

735 x 82 = 60

270 ILs



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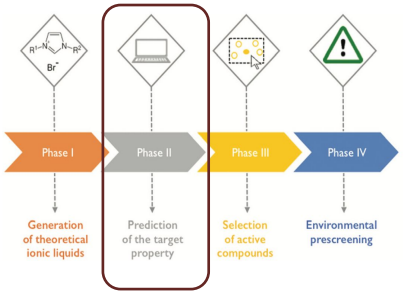


Classification model

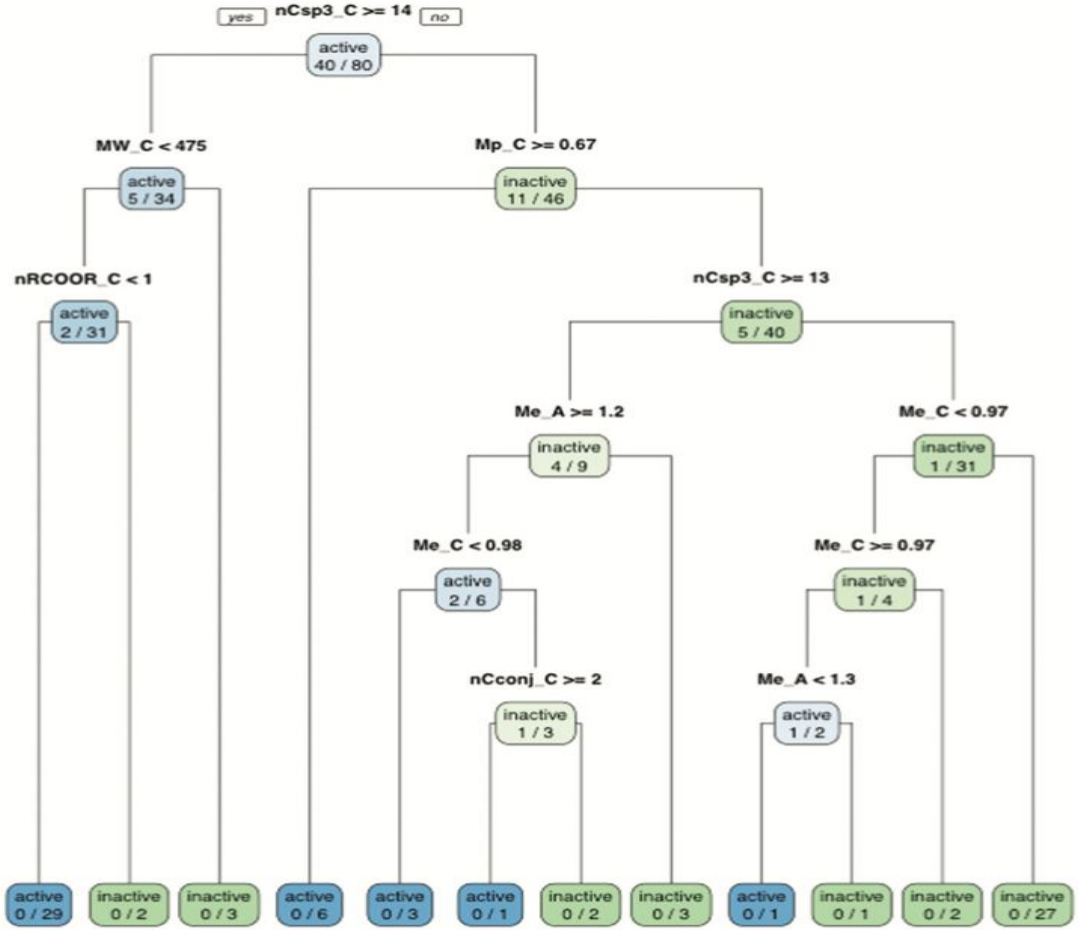
Prediction of the target prop

Endpoint: toxicity towards Staphylococcus aureus

120 data points (24 h incubation at 37 °C)

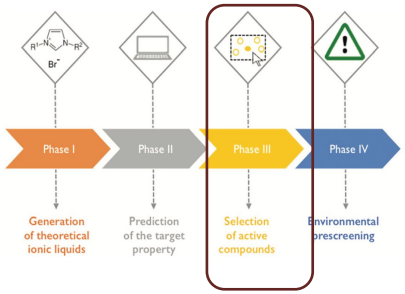
Qualitative data: active/inactive

Method: classification tree



Decision tree scheme for the classification of Ils according to their toxicity towards *Staphylococcus aureus*.

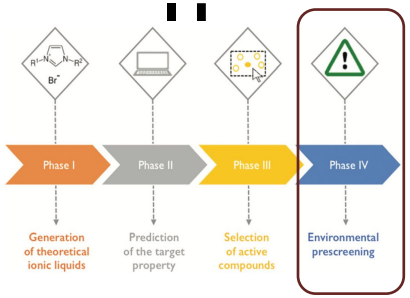
Funded by the European Union



Selection of active compounds – classification mo

60 270 → 25 214 ILs

ACTIVE



Environmental mobility – 5 QSPR models

25 214 ILs → 1026 ILs

ACTIVE

Wyrzykowska E., Green Chemistry 2019, 21, 1965–1973

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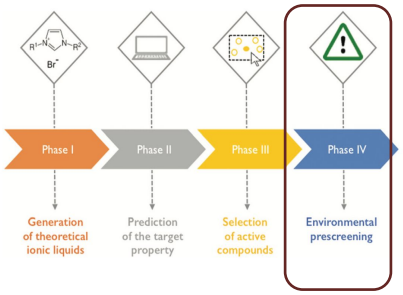

Environmental sustainability - biodegradati

1026 ILs

73 readily biodegradable ILs

953 ILs **not** readily biodegradable

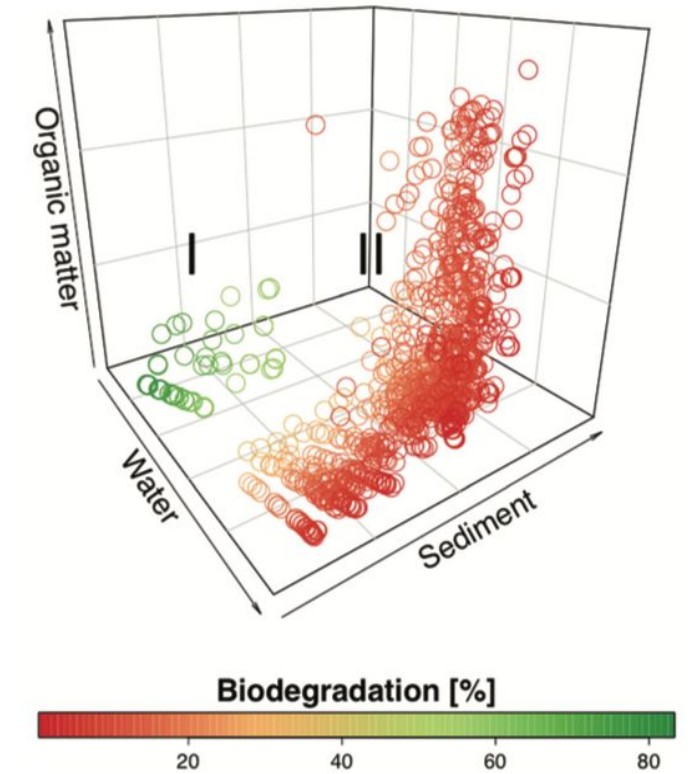

Fig. 5 Estimated distribution of the analyzed ILs after release into the environment: I – readily biodegradable ILs; II – not readily biodegradable ILs.

Wyrzykowska E., Green Chemistry 2019, 21, 1965–1973

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Design of ionic liquids used as bacteric - conclusion in numbers -

60 270 ILs

classification model

25 214 ILs

5 QSPR models

ACTIVE 1026 ILs

biodegradation potential

73 ILs

- reduction more than **60k** theoretically generated ILs to **25k ILs** predicted as active
- selection of **1026 ILs** with desired environmental mobility
- finally, only **73 ILs** selected to further experimental studies

Wyrzykowska E., Green Chemistry 2019, 21, 1965–1973

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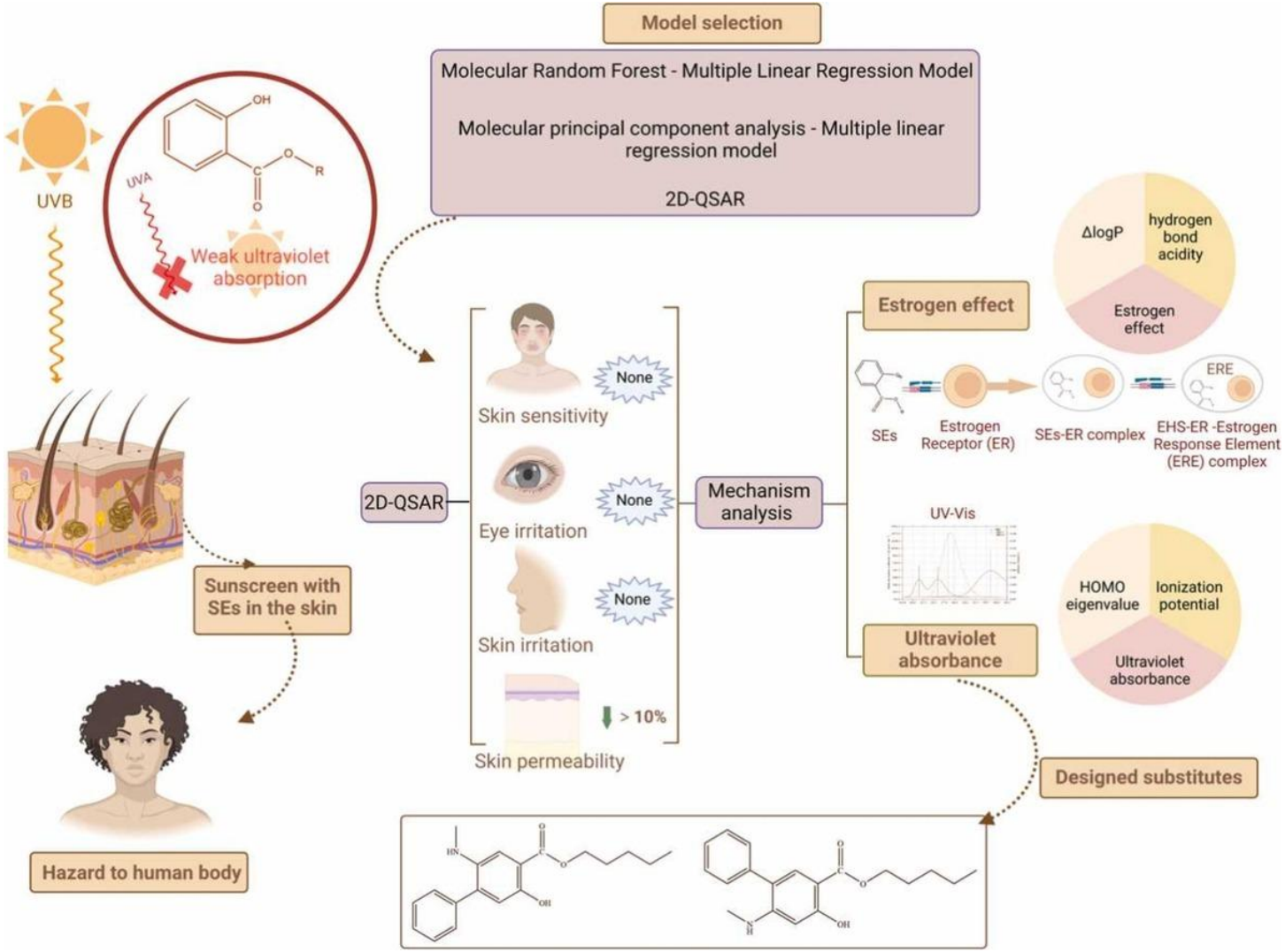
Reduced estrogenic risks of a sunscreen ad

Case Study 2

Theoretical design and evaluation of functionally improved salicylates



https://doi.org/10.1016/j.jhazmat.2024.135371

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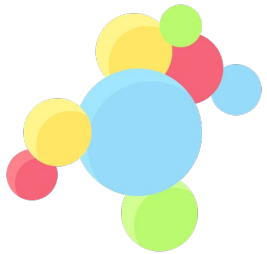
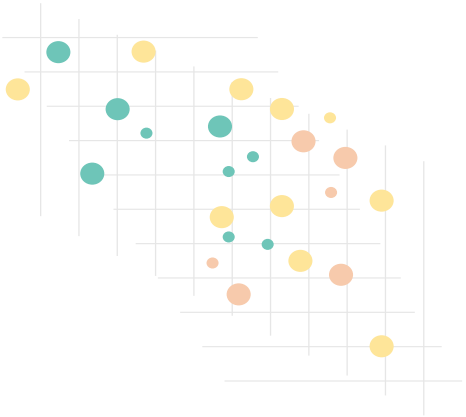
Design of the study - methods



molecular docking



2D-QSAR
3D-QSAR

The estrogenic effect of chemicals can be characterized by them docking scores with receptors

Construction of a machine learning model for UV absorbance and estrogenic effects of SEs

Screening most reliable model of UV absorbance and estrogenic effects of SEs

Screening of SE substitutes with high UV absorbance using the 3D-QSAR model

https://doi.org/10.1016/j.jhazmat.2024.135371

Funded by the European Union

Key factors for effects

Estrogenic Effect Model:

CaPV: Represents the covalent hydrogen bond (H-bond) acidity of steroid estrogens (SEs).

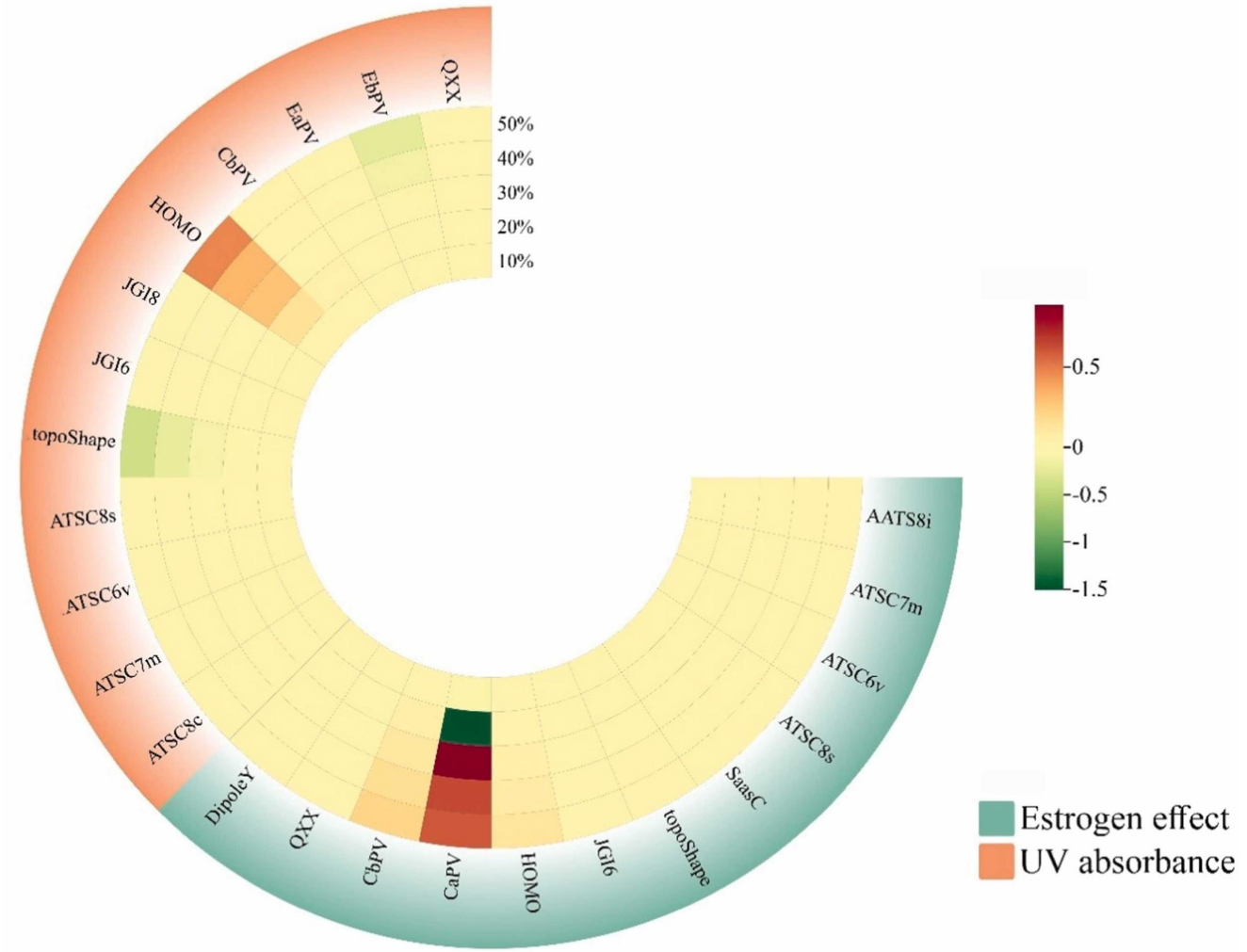
CbPV: Reflects the covalent hydrogen bond (H-bond) basicity of SEs.

Both descriptors are calculated using a semiempirical molecular orbital method.

UV Absorbance Model:

HOMO Eigenvalue: The main descriptor for UV absorbance.

HOMO (Highest Occupied Molecular Orbital) refers to the highest energy molecular orbital that contains electrons.



Screening of key factors affecting the estrogenic effect and UV absorbance of SEs.

https://doi.org/10.1016/j.jhazmat.2024.135371

Funded by the European Union

Main outputs

SE UV absorbers were improved to enhance UV absorbance while reducing their estrogenic effect.

EHS-5 and EHS-15 were identified as promising candidates for new SE-based products, due to their high UV absorbance, low skin permeability and estrogenic activity, and lack of skin sensitization or eye irritation potential.

The strong UV absorbance of SEs is mainly due to how their electrons move between energy levels. Key factors include electron migration between orbitals, vibronic strength, and the specific orbitals involved in the transition.

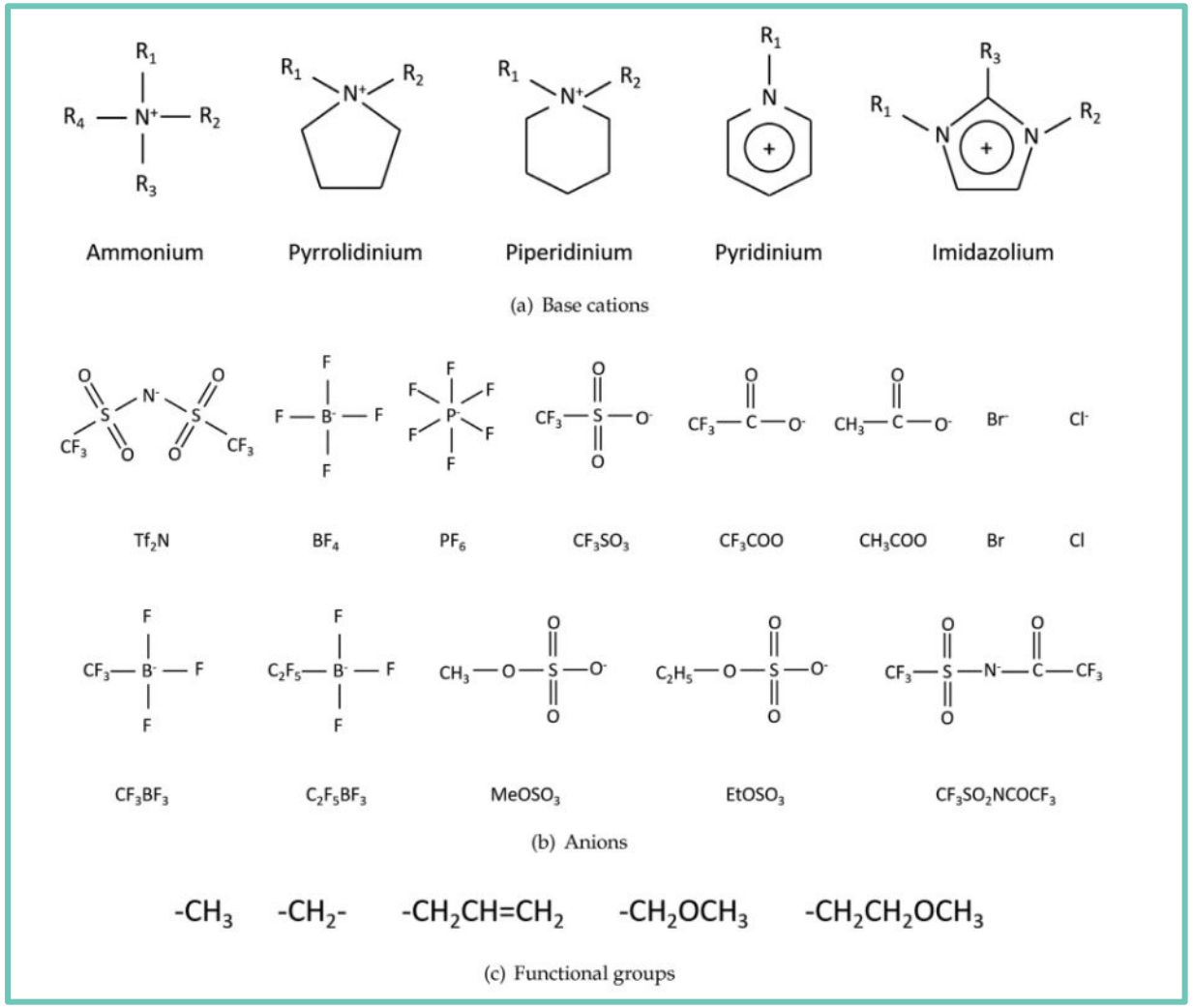
Enhanced UV absorbance of SEs is driven by efficient electron migration between orbitals and strong vibronic interactions.

https://doi.org/10.1016/j.jhazmat.2024.135371

Funded by the European Union

Case Study 3

Computer aided molecular design coupled with molecular dynamics as a novel approach to design **new lubricants**



https://doi.org/10.1016/j.compchemeng.2021.107523

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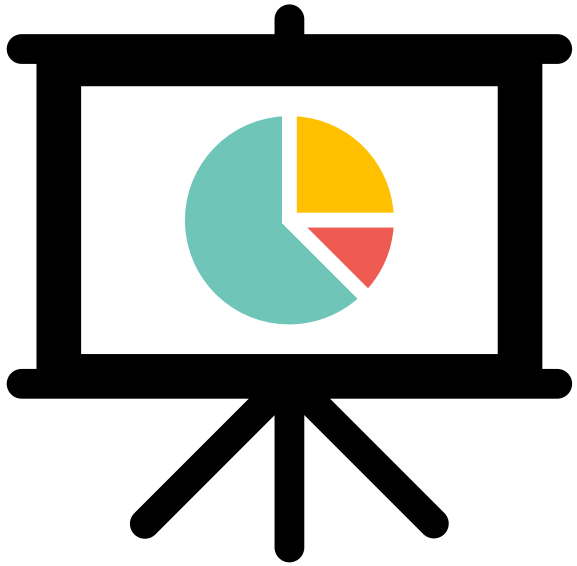
In silico methods application



CAMD Results:

- Three different ionic liquid designs were developed for automotive lubricants.

Candidate Screening:

- **QSPR models** provided fast and satisfactory property predictions, reducing the number of candidates for testing.

Chemical Feasibility:

- Addressed using **molecular dynamics (MD)** simulations for the design with the **lowest kinematic viscosity.**

Property Validation:

- **MD simulations** were used to validate critical lubricant properties before synthesis.

https://doi.org/10.1016/j.compchemeng.2021.107523

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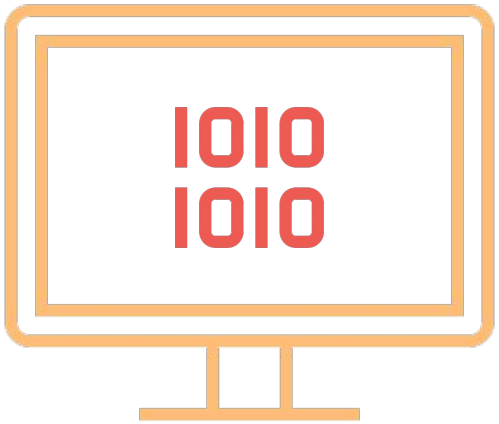
In silico methods application



Laboratory Testing:

- Molecules should be tested for chemical feasibility after synthesis to assess lab-scale manufacturability

Thermodynamic Feasibility:

- Evaluated using the Grand Canonical Monte Carlo algorithm to estimate Gibbs free energy

Efficiency of Combined Approach:

- **CAMD combined with MD simulations effectively narrows down candidate molecules before experiments.**

Limitations:

- Current work is limited to pure compounds; however, the methodology can be extended to mixtures.

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Thank you for your attention!

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