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QSAR assisted predictive toxicology and animal experimentation replacement

A Transdisciplinary Conference on Alternative technologies and models (NAMs) to Reduce the use of laboratory animals in Industry – June 6th & 7th, 2023

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Outline

- The 3Rs principle and computational methods – e.g. QSAR – for the alternative to animal testing

- Examples of QSAR method in early toxicity profiling
  - Case Study : Selecting most promising molecule(s) with less *in vivo* testing

- Conclusions and advantages of QSAR methods

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The 3Rs Principle

COMPUTATIONAL METHODS –
e.g. QSAR FOR THE ALTERNATIVE TO ANIMAL TESTING

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The 3Rs Principle

GENERAL CONTEXT:

- The 3Rs are principles of responsible science designed by scientists to improve animal welfare and scientific accuracy.

DEFINITIONS:

- **Refinement** – Finding ways of making animals' lives better in labs, this can include toys for animals or better training for technicians

- **Reduction** – Using as few animals as possible to get reliable results

- **Replacement** – Using non-animal alternatives wherever they exist

→ In that context, computational methods like QSAR are suitable

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Alternative methods

- Researchers **must,** by law, use these techniques if they would be as effective as using animals.

Computer models

Cells and tissue cultures

Alternative organisms
- Lower vertebrates
- Invertebrates
- Microorganism

→
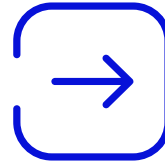
QSAR METHOD
FOR
EARLY TOXICITY
PROFILING

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QSAR MODELS

FOR EARLY TOXICITY PROFILING

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Case study

CONTEXT :

Client R&D program aims at synthesizing compounds devoid of neurotoxic effect.

OBJECTIVE :

Select the most promising molecule(s) without neurotoxicity from a large dataset of synthesized compounds.
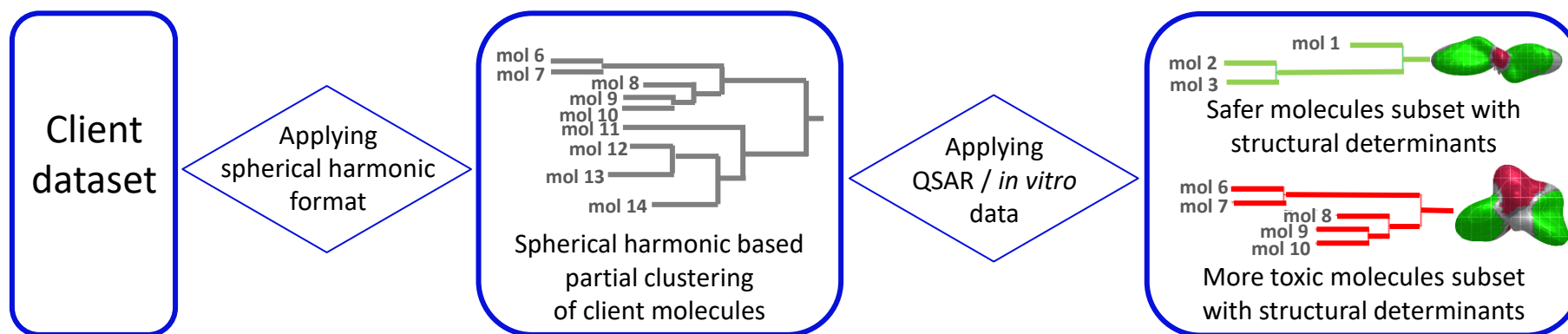
SOLUTION :

Combining clustering, QSAR and *in vitro* assessment to significantly reduce/replace animal testing.

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Case study : NAM to replace animal testing

- Clustering, QSAR predictions and *in vitro* assays as three pillars of a New Approach Method (NAM) to ultimately replace/reduce animal studies.

Clustering of the molecule dataset
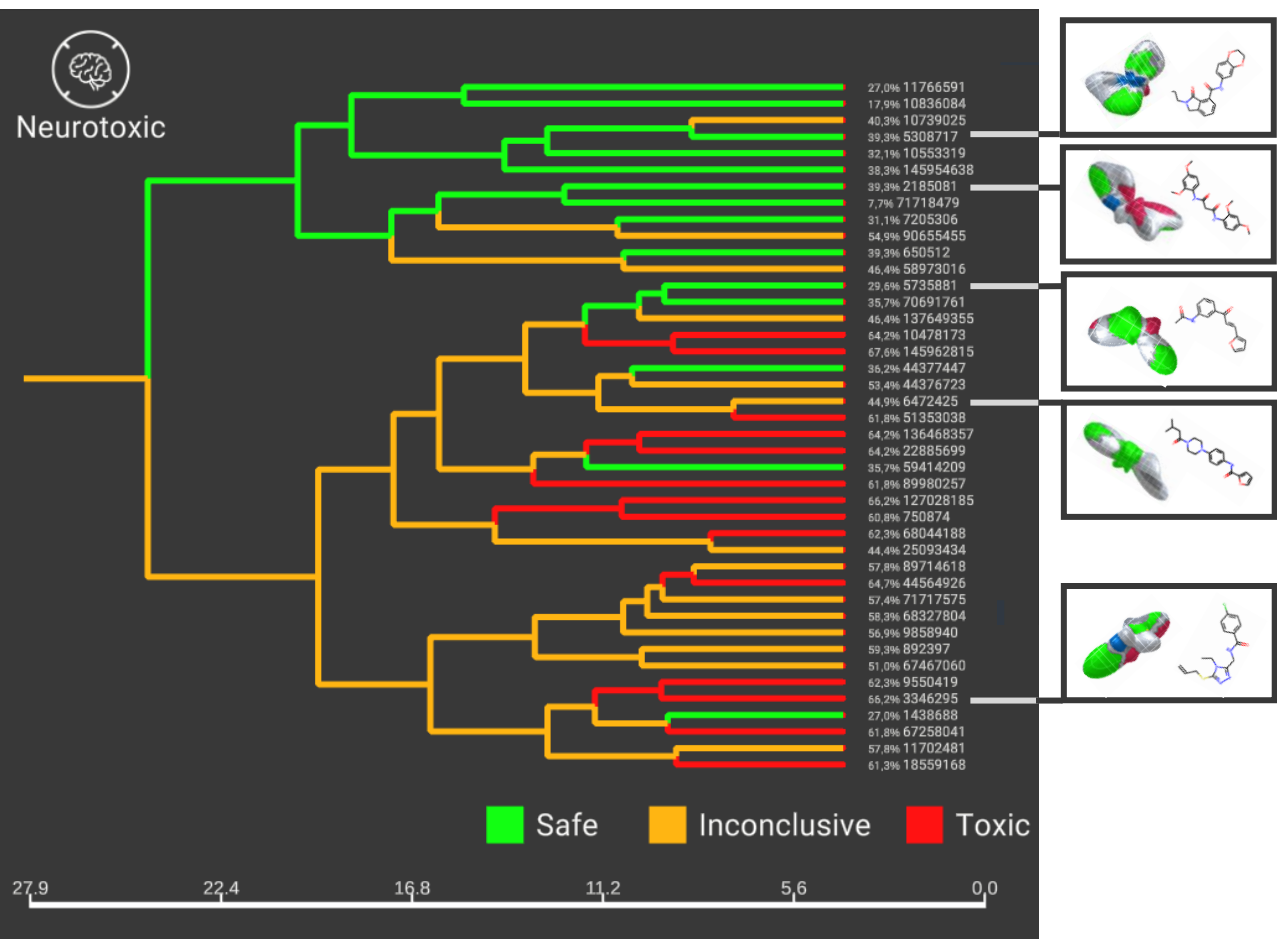
- 42 molecules were clusterized based on their structural similarity using spherical harmonic descriptors

- 4 clusters of molecules are identified

- Neurotoxicity results using QSAR are mapped onto the clustering

  - Green (predictive as safe)

  - Orange (inconclusive)

  - Red (predicted as toxic)

- It comes out that cluster 1 containing 15/42 molecules represents the safest molecules to focus on

QSAR prediction versus *in vitro* assay

	QSAR VS IN VITRO RELIABILTY				
	Correct Prediction	False Prediction	Inconclusive	Tested In vitro	Concordance rate (%)
cluster 1	9	4	2	15/15	73%
cluster 2	6	2	-	8/9	75%
cluster 3	2	-	-	2/3	100%
cluster 4	7	5	3	15/15	66%
			GLOBAL	40/42	73%

- Neurotoxicity is assessed *in vitro* through the inhibitory capacity of compounds onto acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) biological activity

- Overall, 73 % of concordance between QSAR prediction versus *in vitro* result.

- 73% of compounds comprising cluster 1 are correctly assigned by QSAR with regards to *in vitro* assays

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In vitro assay versus *in vivo* experiments

	IN VITRO VS IN VIVO RELIABILTY				
	Correct	False	Inconclusive	Tested In vivo	Concordance rate (%)
cluster 1	7	0	0	7/15	100%
cluster 2	2	1	-	3/9	67%
cluster 3	-	-	-	0/3	-
cluster 4	5	0	3	8/15	63%
			GLOBAL	18/42	78%

- Asexual planarians of the species *Dugesia japonica* were used for *in vivo* studies which is an effective bridge between *in vitro* and whole animal/ mammalian testing methods

- Overall, 78 % of concordance between *in vitro* and *in vivo* results.

- 100% of compounds comprising cluster 1 are correctly assigned by *in vitro* assays with regards to *in vivo* experiments

- Reliability of *in vitro* assays with regards to *in vivo* experiments is assessed with a reduced number of compounds : 18 out of 42.

→ 47% of animal experiments were skipped

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Conclusion

- We assessed neurotoxicity of 42 compounds using clustering, QSAR predictions, and *in vitro* assays combined into a NAM.
  - 47 % of animal experiments were avoided

- This NAM helped to point out that compounds from cluster 1 represent the safest molecules to focus on.
  - 100% concordance of In vivo/In vitro
  - 73% concordance of In vitro/In silico

- As a consequence, any novel chemicals similar to molecules making up cluster 1 are expected to be synthesized without the need to go for *in vivo* experiments.

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Conclusion

- QSAR models are one of the alternative methods recognized by regulatory agencies for replacing animal testing when possible.

- Combining clustering approaches, QSAR models and *in vitro* data constitute a powerful NAM

- That NAM enables to reduce significantly animal testing by focusing on the most promising molecules.

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Advantages of QSAR and clustering methods

Alternative to animal testing

Guide you towards experimental assessments

Accelerate market access with cost-effectiveness

Consolidate compliance with regulatory requirements

Profile simultaneously on multiple endpoints

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