TOWARDS THE EVALUATION OF TOXIC COMPOUNDS IN *IN VITRO* BLOOD-BRAIN BARRIER MODELS FOR SAFETY AND SUSTAINABILITY ASSESSMENTS WITHIN THE CHIASMA PROJECT

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3) Experimental design

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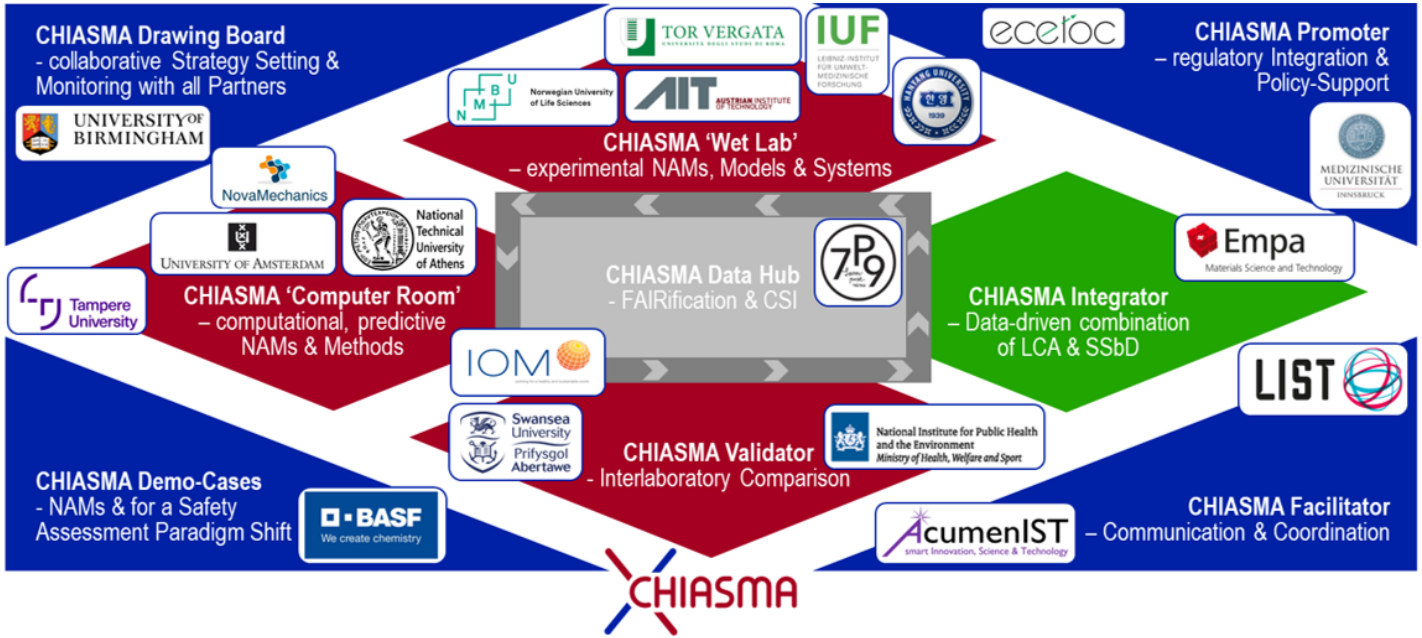
THE CHIASMA PROJECT

CHIASMA: **A**ccessible **I**nnovative **M**ethods for the **S**afety & Sustainability **A**ssessment of **Ch**emicals & Materials



NAMs = New Approach Methodologies

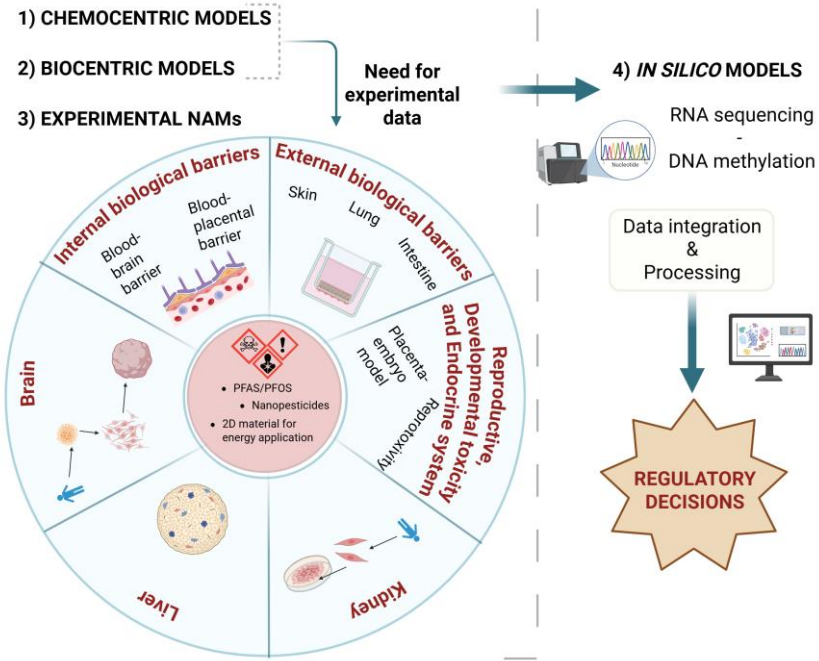
CSI = Chemical Safety Interface

FAIR = Findable, Accessible, Interoperable, Reusable

LCA = Life Cycle Assessment

SSbD = Safe and Sustainable by Design

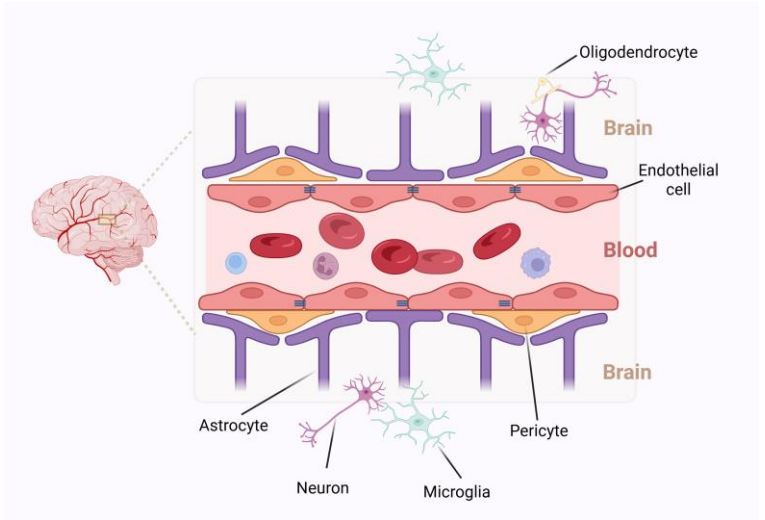
THE CHIASMA PROJECT



Addressing Gaps in *In Vitro* Neurotoxicity Testing:

RELEVANCE OF BBB FOR NEUROTOX

- Classical *in vitro* neurotoxicity tests lack a functional blood-brain barrier (BBB).



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TOWARDS IDEAL TISSUE MODELS

- ✓ Robust & Repeatable
- ✓ Easy for transfer
- ✓ Applicable to a broad compound range
- ✓ Physiologically relevant

TO ACHIEVE THIS:

1) Model optimization:

- Stable barrier integrity
- Neuronal differentiation in co-culture

→

2) Treatment Pipeline Development:

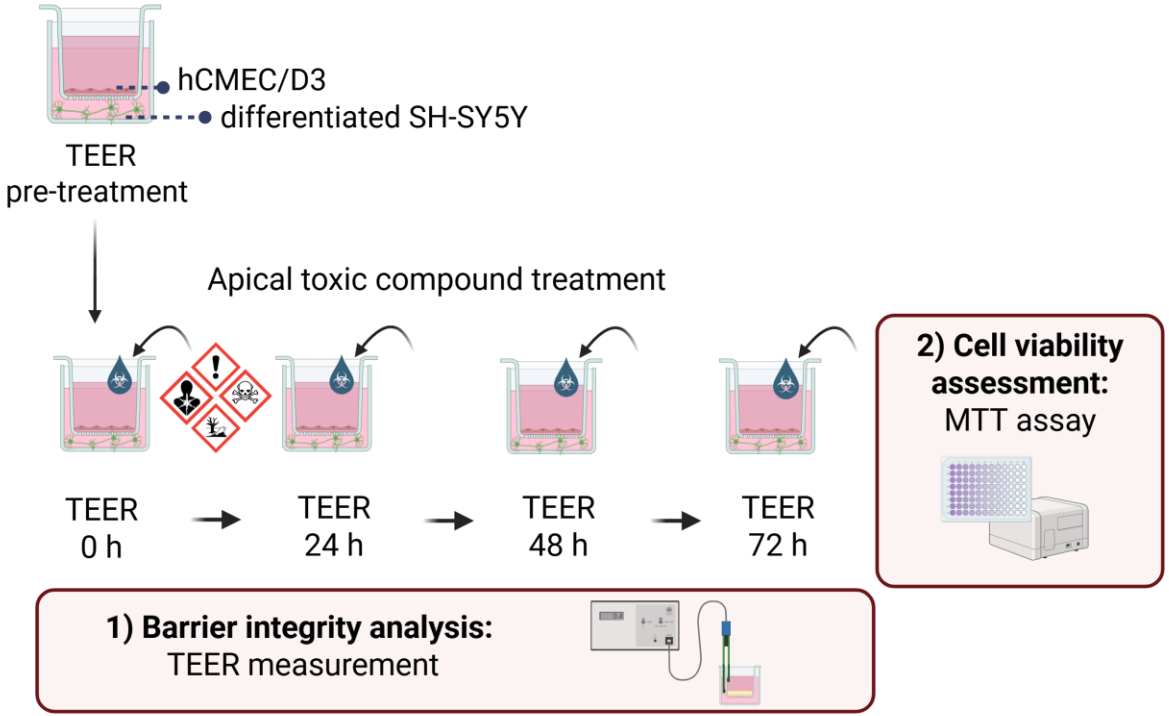
- Defining appropriate vehicles
- Testing compound solubility, (e.g. effect of BSA for PFAS)
- Testing compounds in 96-well plate assays prior to co-culture
- Volatile compounds → Sealing plates

→

3) Validation of the BBB model for toxicity:

- Phase 1 chemicals: genotoxic, reprotoxic, respiratory toxicant and cytotoxic agents
- IC_{50} or IC_{10} value calculation

EXPERIMENTAL DESIGN



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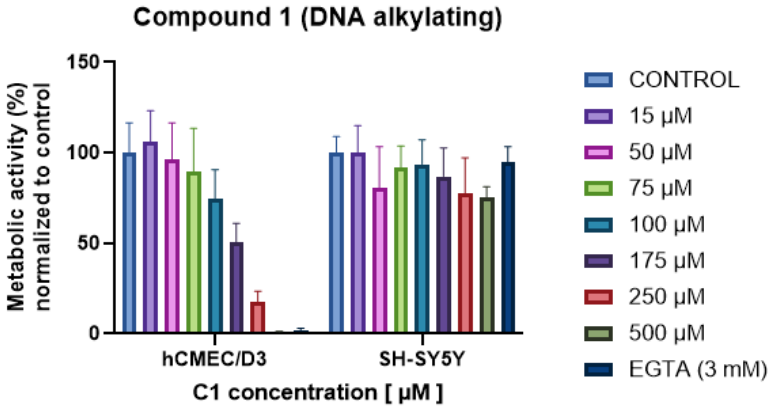
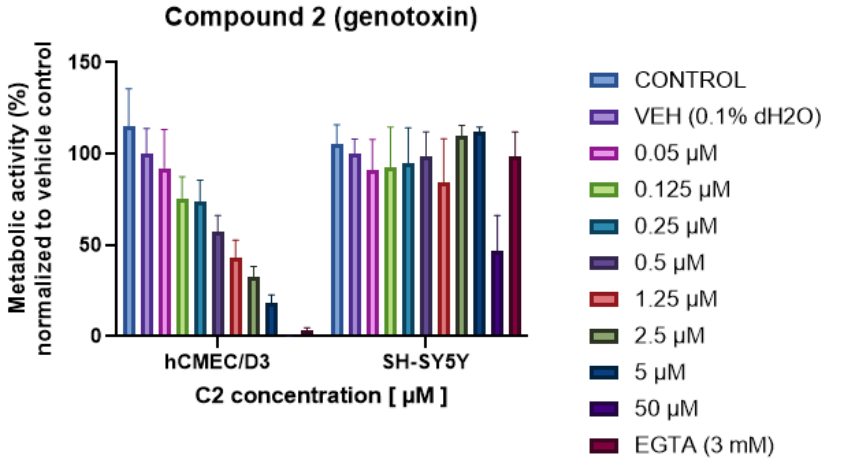
PRELIMINARY RESULTS

DOSE-RESPONSE CURVES



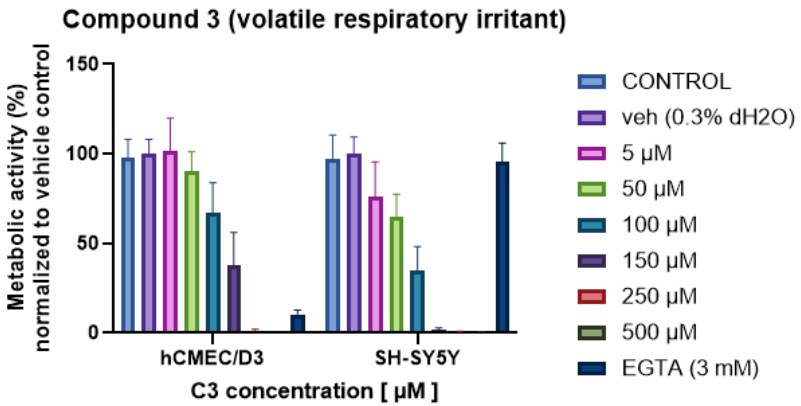


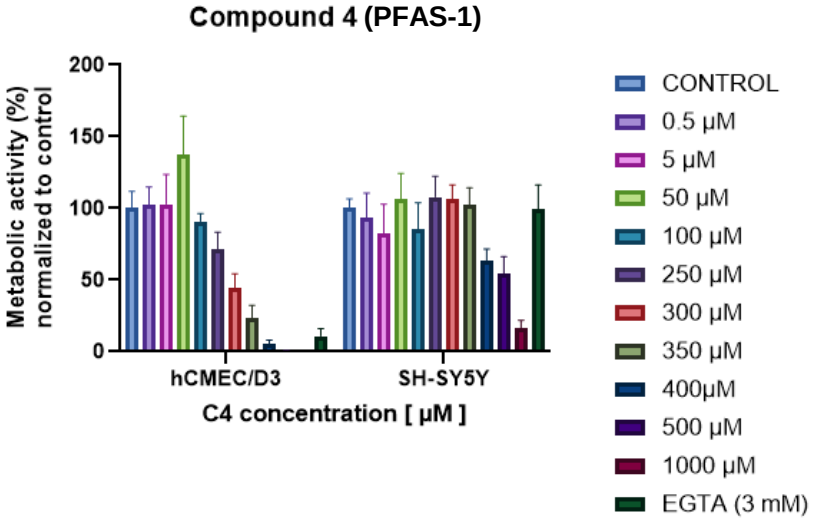
	hCMEC/D3	SH-SY5Y
	IC50 values (µM)	IC50 values (µM)
C1	158	4524

	hCMEC/D3	SH-SY5Y
	IC50 values (µM)	IC50 values (µM)
C2	0.8	49

PRELIMINARY RESULTS

DOSE-RESPONSE CURVES





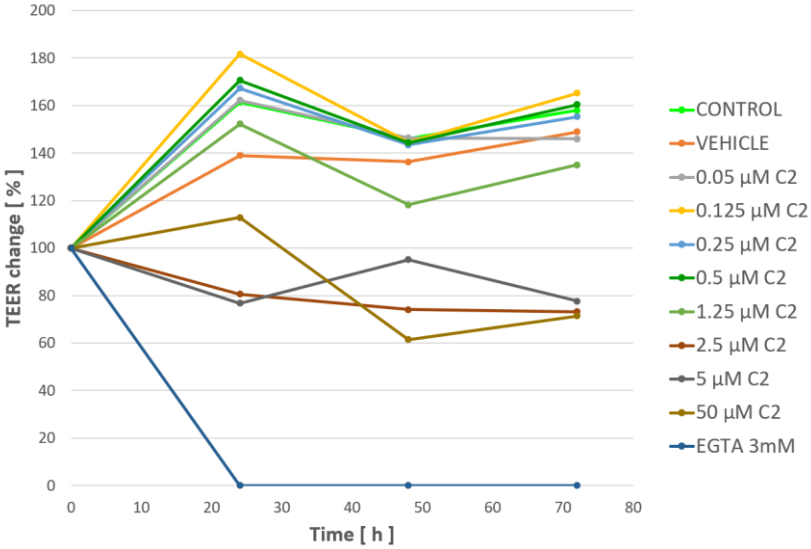
	hCMEC/D3	SH-SY5Y
	IC50 values (µM)	IC50 values (µM)
C3	123	67

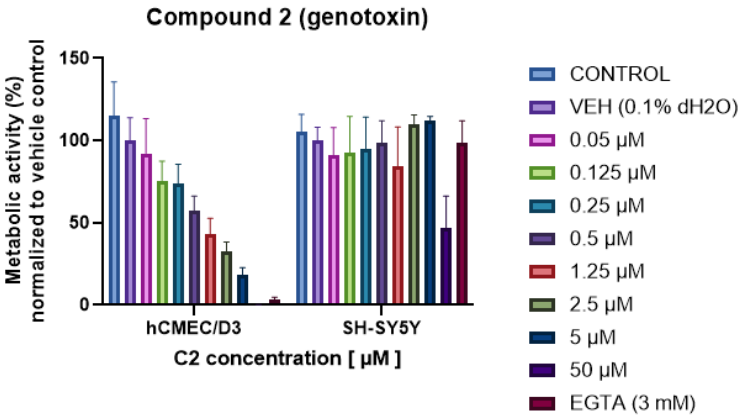
	hCMEC/D3	SH-SY5Y
	IC50 values (µM)	IC50 values (µM)
C4	289	509

PRELIMINARY RESULTS

TRANSENDOTHELIAL ELECTRICAL RESISTANCE (TEER) MONITORING

Transendothelial Electrical Resistance (TEER) was used as a non-invasive approach to monitor barrier integrity of the brain endothelial cells at 24-, 48-, and 72-hour exposure to toxic compounds.





SUMMARY AND NEXT STEPS

Co-culture model was established. → The sensitivity of the model for known toxins (phase 1 chemicals) was validated.

Testing phase 2 chemicals

Transferability of the generated NAMs will be tested to ensure reproducibility across different laboratories.

Monitor toxins in the system:
- extent of toxic compound permeation
- adherence to the plastics & membrane

In silico analysis of molecular data (RNAseq, DNA methylation) to identify toxin specific biomarkers & develop assays for toxicological assessment and regulatory applications (later description of AOPs)

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