Predicting developmental toxicity of pyrethroid insecticides *in vitro* using human induced pluripotent stem cells

ASCCT-ESTIV webinar, 24th March, 2023

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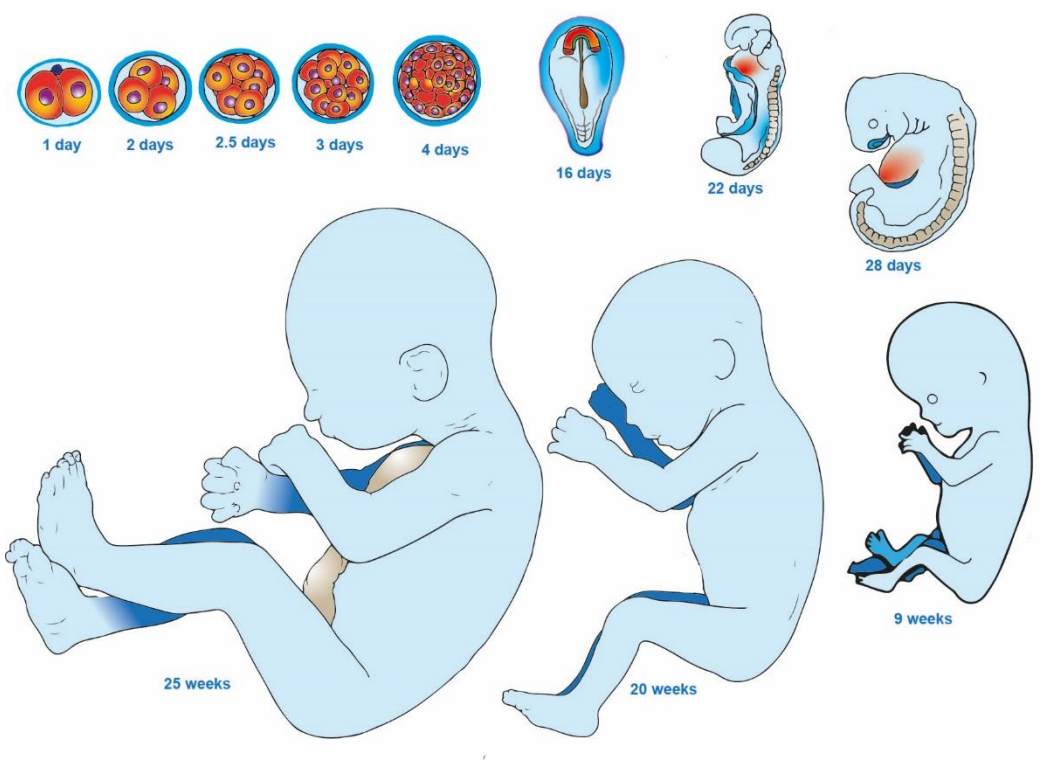
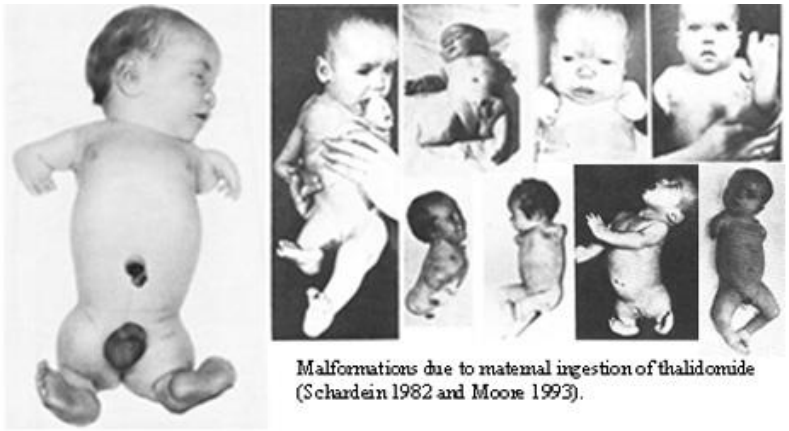
Developmental toxicity

Human prenatal development:

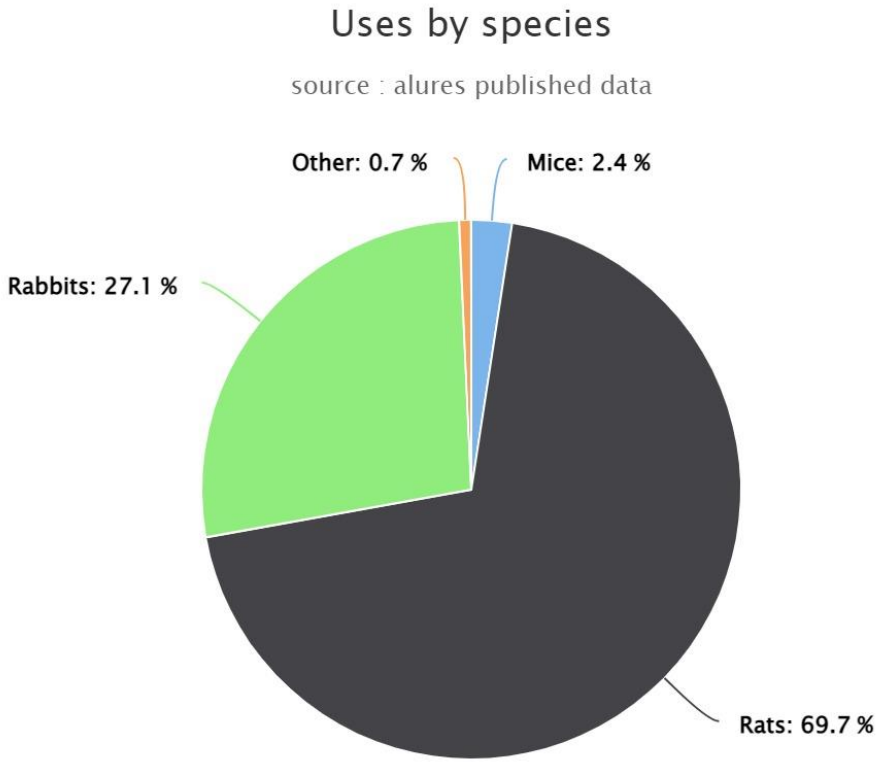


Agent orange, herbicide contains TCDD



Thalidomide, 1960s

Animals used in the EU in 2019 for developmental toxicity testing

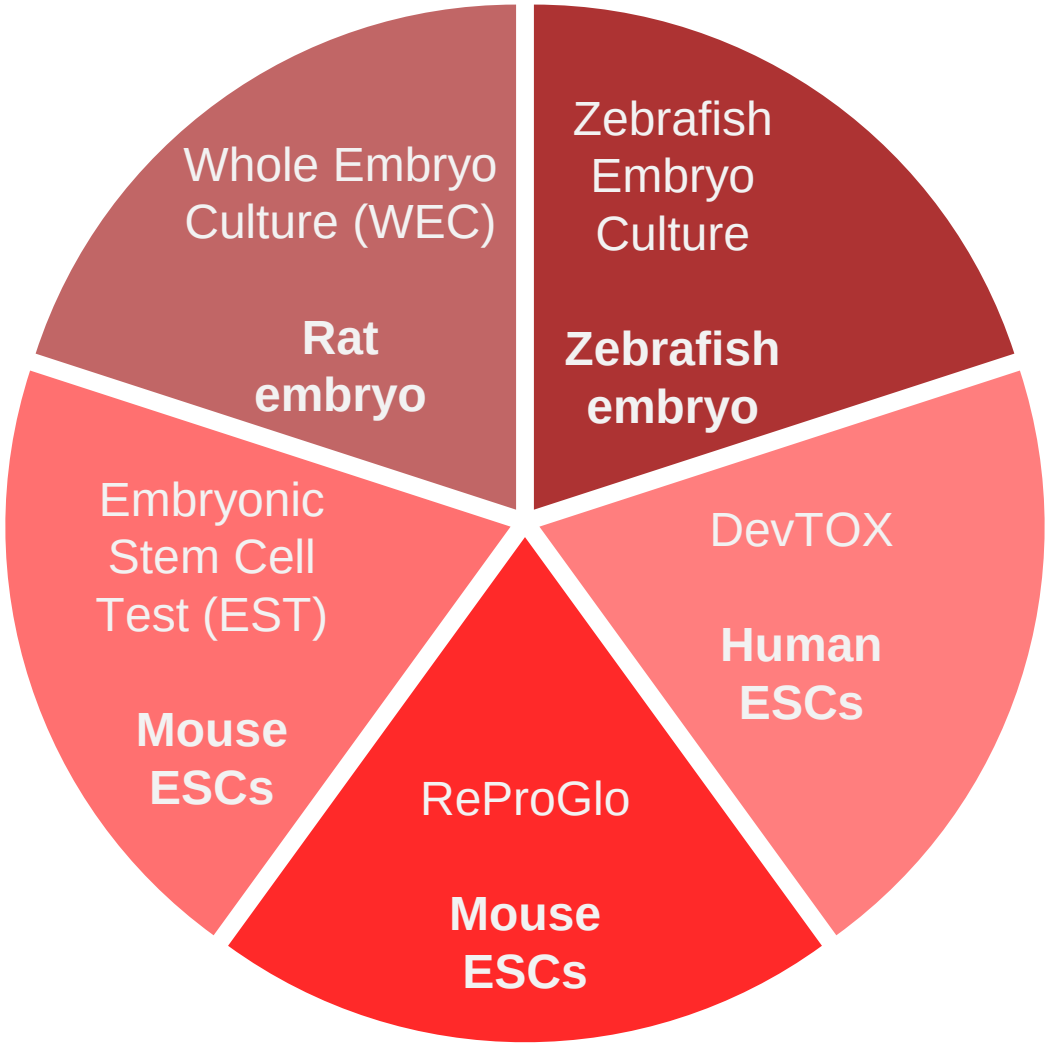


Species	Number of uses	Percentage
Mice	2039	2.43%
Rats	58529	69.75%
Rabbits	22754	27.12%
Dogs	12	0.01%
Cynomolgus monkey	260	0.31%
Other fish	320	0.38%
Total	**83914**	**100,00%**

Source: ALURES Statistical EU Database on the use of animals for scientific purposes

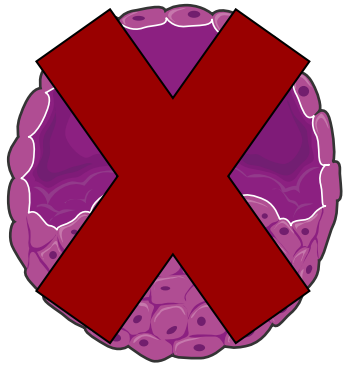
Developmental toxicity

***In vitro* and *ex vivo* approaches**

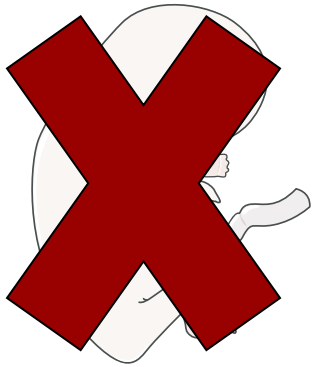


Human-induced Pluripotent Stem Cells (hiPSC)

A model for embryonic development



Blastocyst

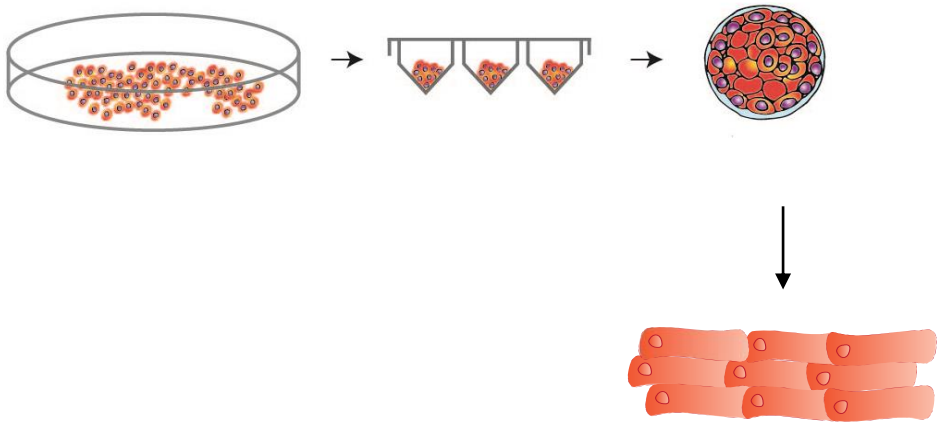


Fetus

Somatic cells from human adult

Embryoid Bodies (EBs):

Embryoid bodies are aggregates of hIPSC that mimic the blastocyst

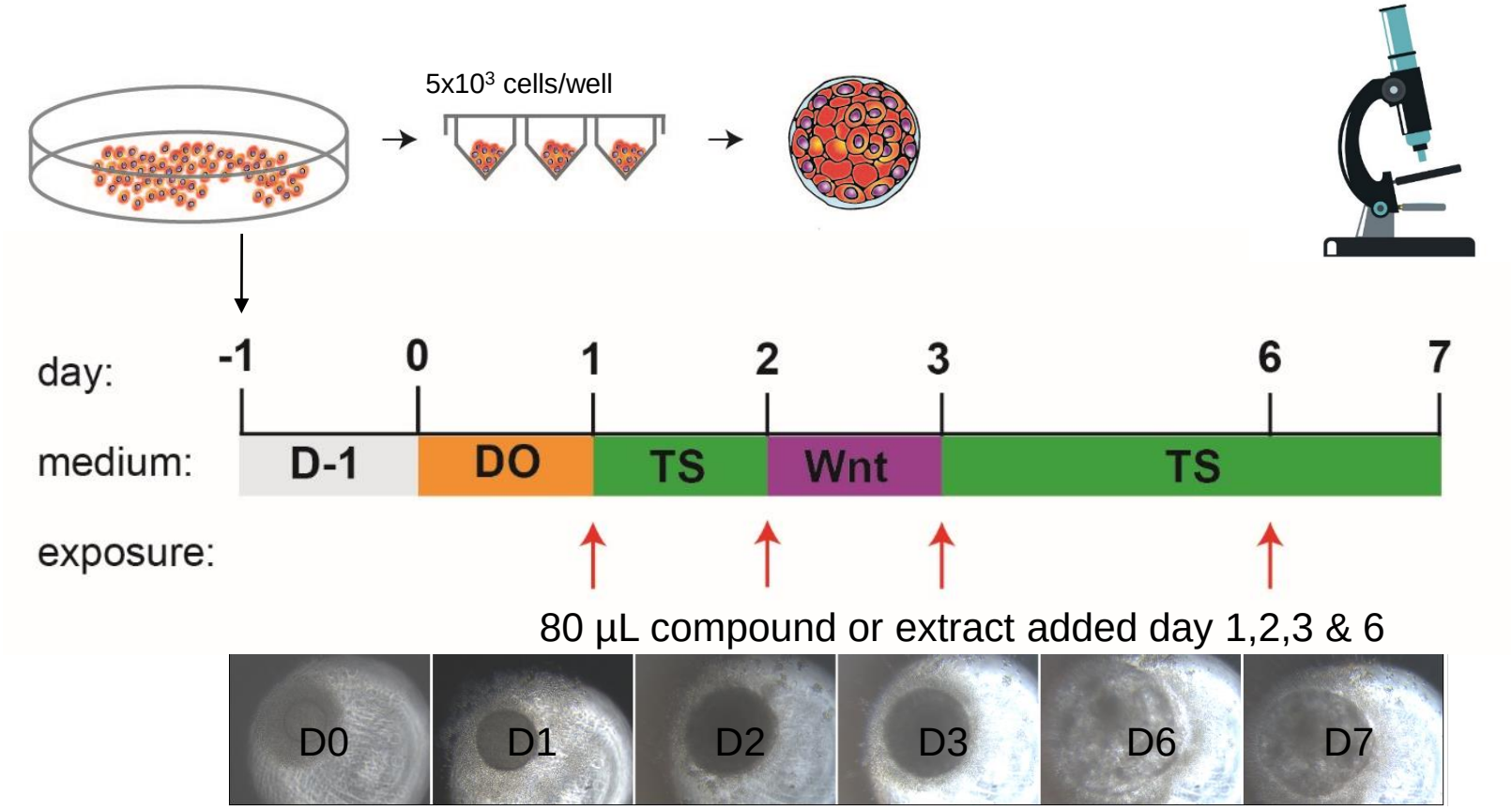


- EBs can differentiate into most cell types of the body including cardiomycytes

Methods

Development of the PluriBeat and PluriLum assays based on 3D embryoid bodies made from hIPSC

hiPSC line: BIONi010-C



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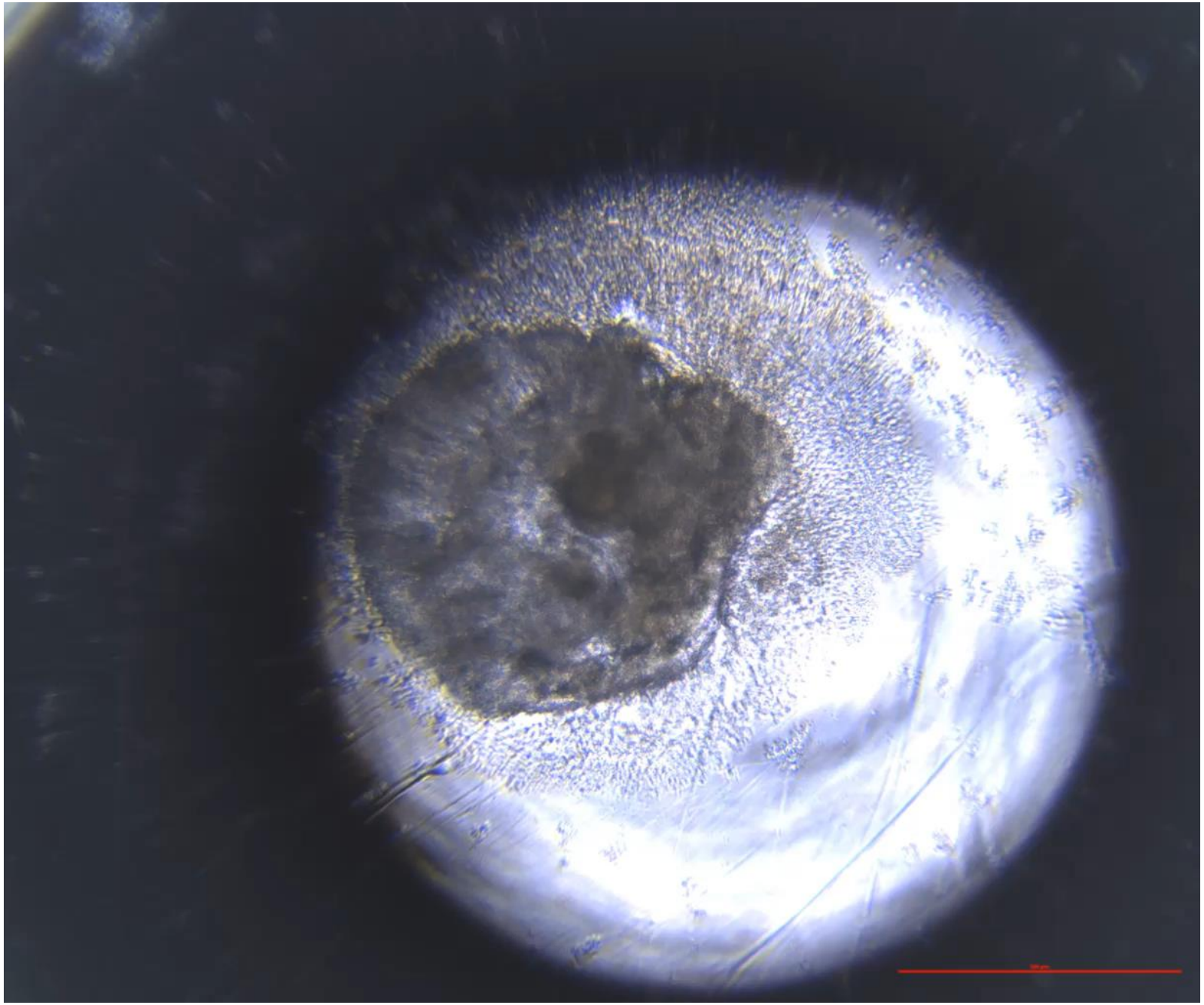
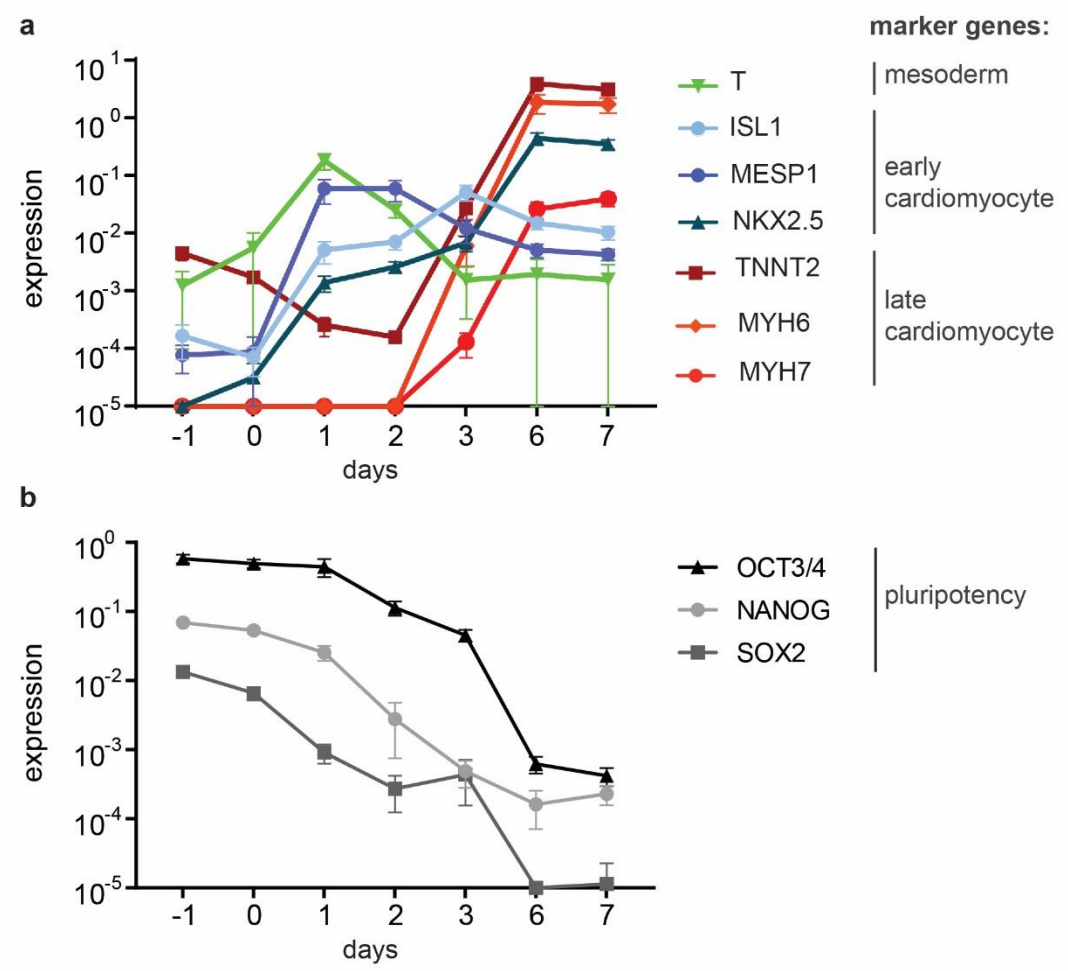
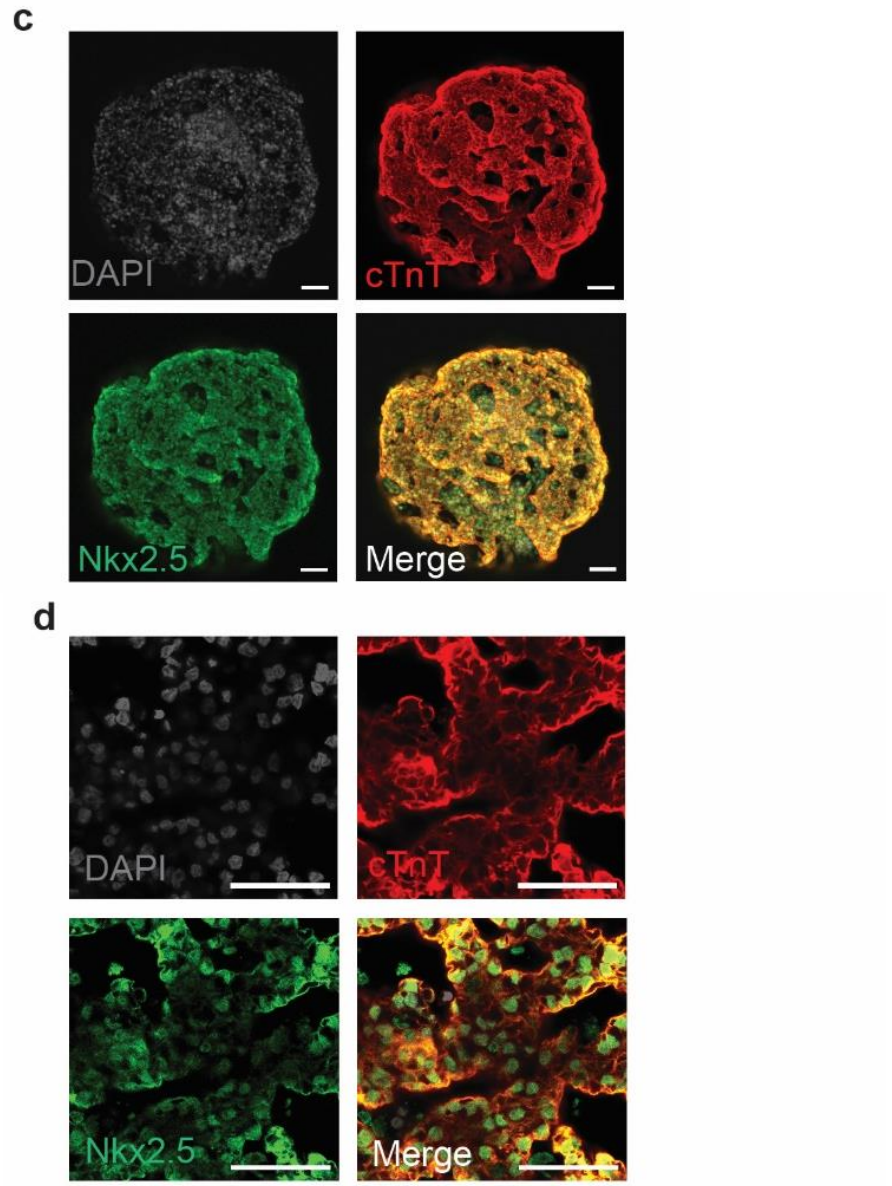


Methods

Characterizing the PluriBeat assay





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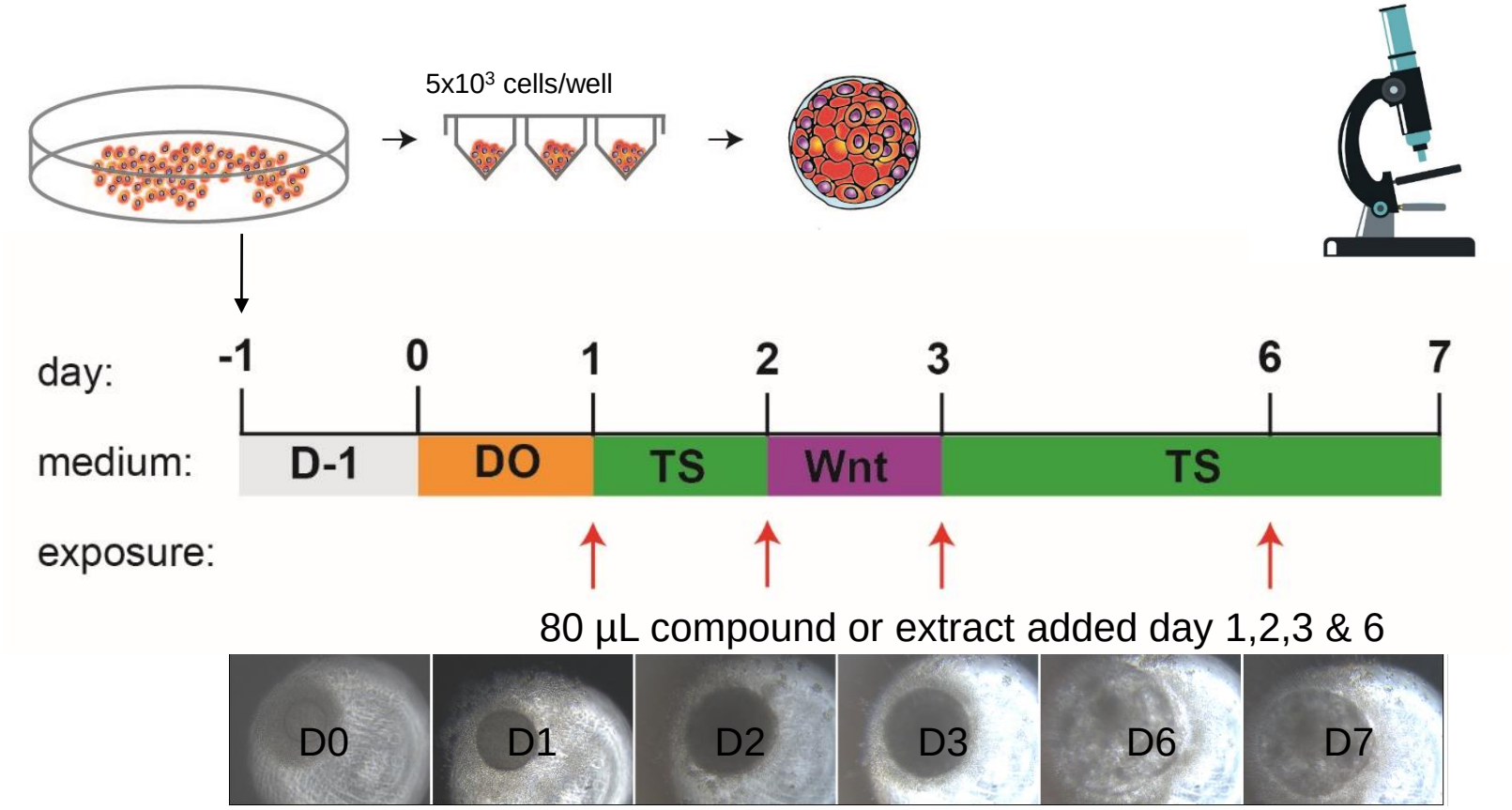

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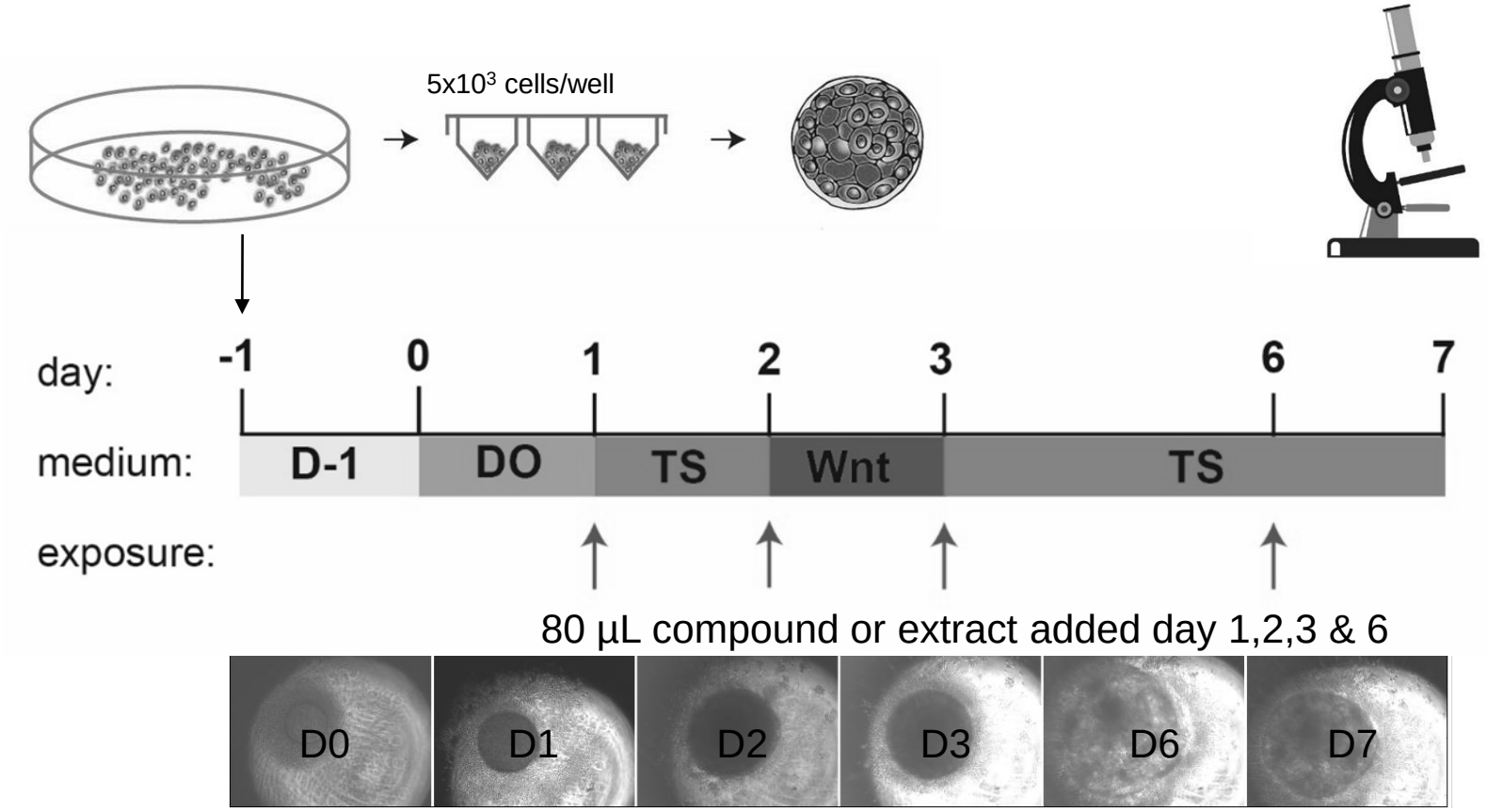

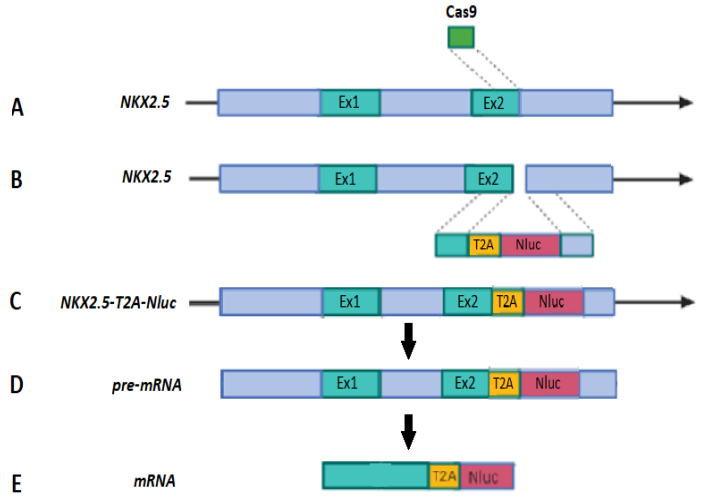

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Project aim

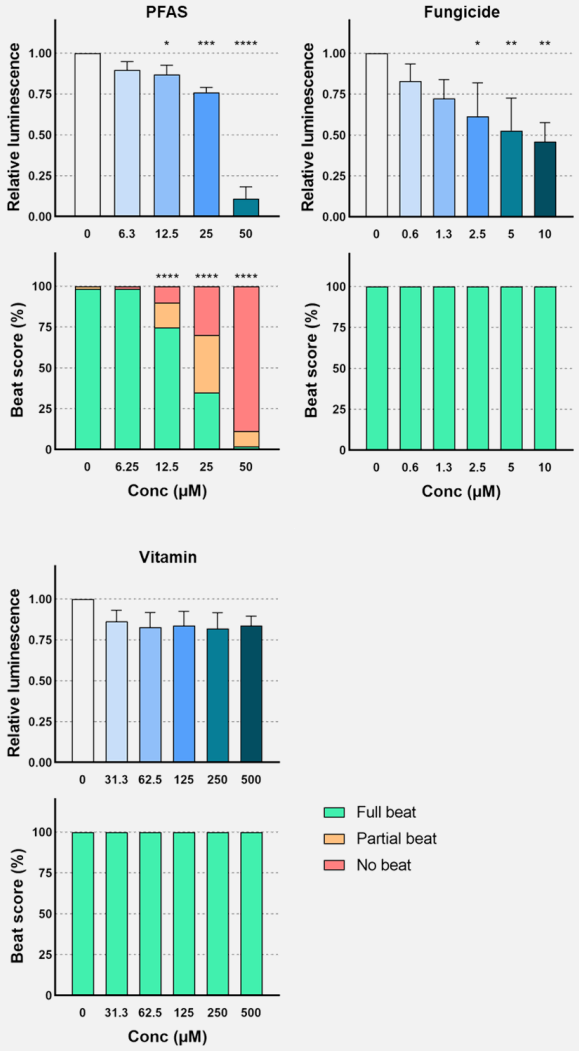
- Three of the **most often detected pyrethroids** in Danish foods and **the common metabolite** were selected

- Pyrethroids are known neurotoxicants, acting primarily by interfering with **voltage-gated sodium channels**

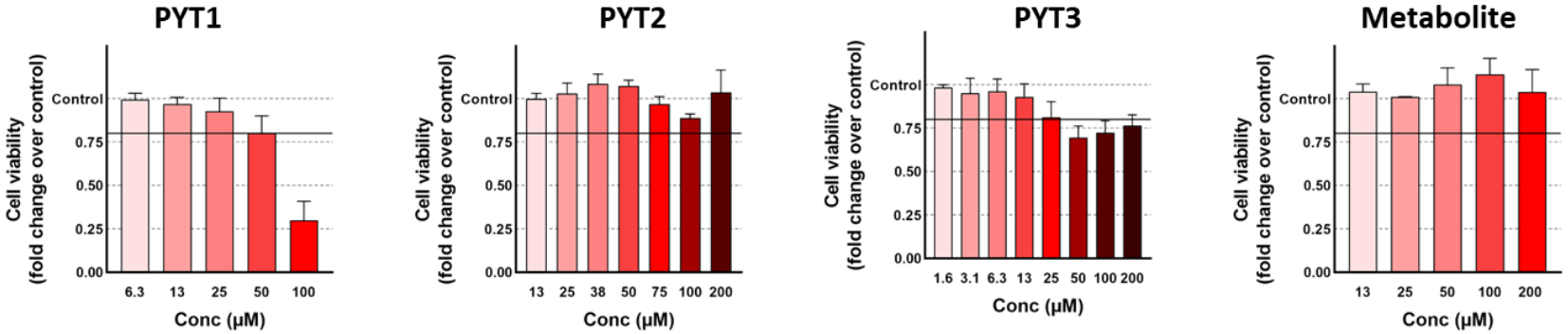
- Evaluate the potential **developmental toxicity** of pyrethroids and the common metabolite using a stem cell based assay

Results

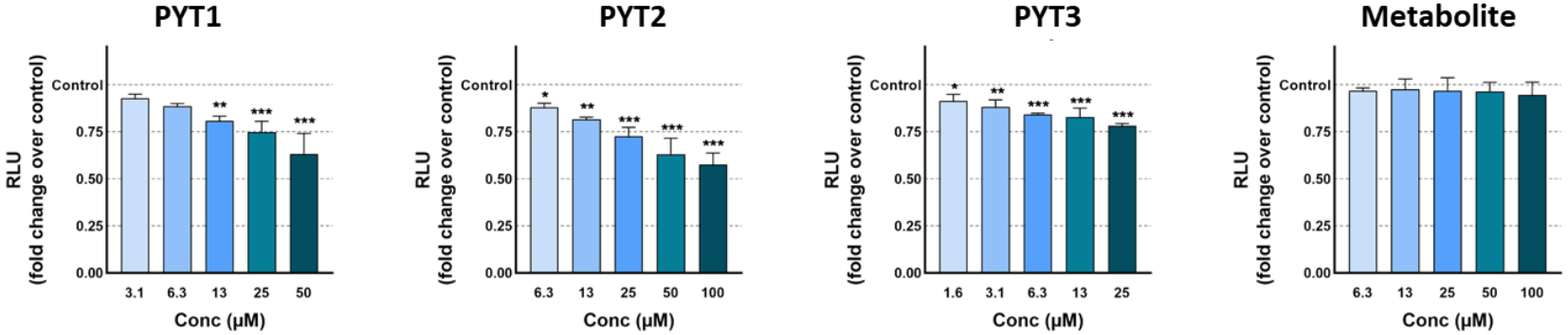
Reference compounds



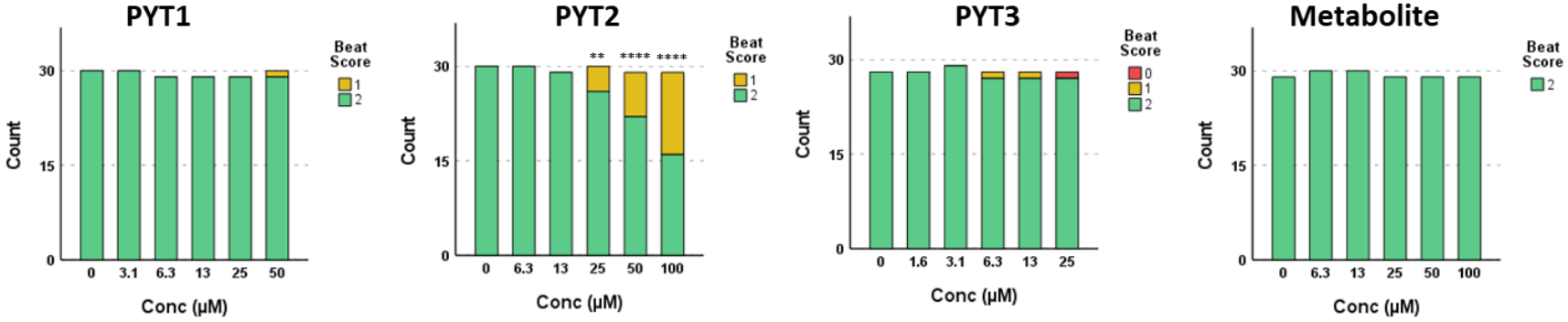
Cytotoxicity



Luminescence (*PluriLum*)



Beat Score (*PluriBeat*)



Take home messages and future perspectives

Pyrethroids negatively affected cardiomyocyte differentiation in the PluriLum assay, but not the metabolite

PluriLum is more **sensitive** compared to the **PluriBeat** assay for the pyrethroids

We need to expand our database and test more chemicals

Human exposure levels are predicted to be **much lower** than the tested range

- Mixture effect?

Acknowledgements

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