


Are Cell Painting and High Through Transcriptomic Robust for Next Generation Risk Assessment ?
Emerging Collaborative HESI Project on Hepatotoxicity

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With the support of Connie Mitchell and Saddef Haq from HESI

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Agenda

- // Introduction on the evolution of regulatory context for chemicals
- // Research proposal concept
- // Few words about HESI
- // Call for contributions !!

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Next Generation Risk Assessment

Animal Testing will not be the gold standard anymore for industrial and agro chemicals

SCIENCE AND POLICY

U.S. EPA to eliminate all mammal testing by 2035

Move makes Environmental Protection Agency the first federal agency to put a deadline on reducing animal use



13 SEP 2019 • BY DAVID GRIMM

ANIMAL RESEARCH

EPA plan to end animal testing splits scientists

Some see nonanimal models as the future, but others worry about health impacts

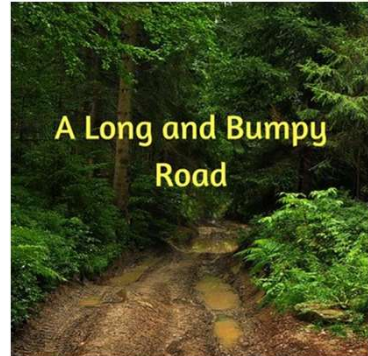
[Science, 2019, 365, 6459, p. 1231](#)



The EU is also committed to reduce animal testing, and strongly promoting safety evaluation by alternative methods (New Approach Methodologies or NAMs)

MEP voting in 2021-09 -> [LINK](#)

EFSA are developing a NAMs roadmap leading to the "majority of safety data being generated using NAMs by 2027" -> [LINK](#) and [LINK](#) (2021, SPIDO update)



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To learn how to ride on this bumpy road



Conceptual learnings on in vitro to in vivo translation



Fully validated suite of NAMs applied for regulatory decision based on NGRA

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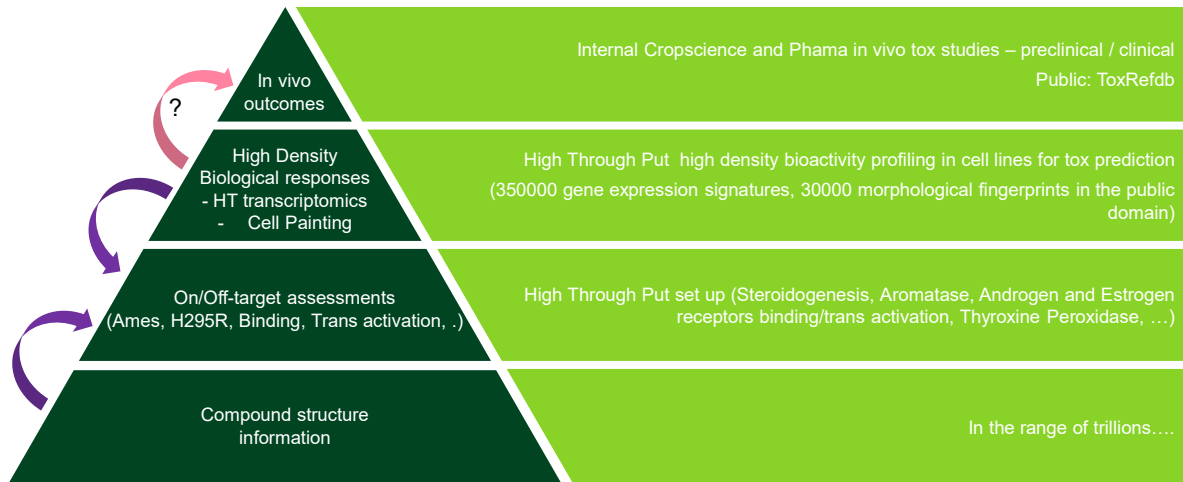
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Data available or to be generated for toxicity predictions

And the elephant in the room ... internal exposure data



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Objective of the proposal

// The idea is to make use of **non genotoxic compounds that were stopped in the R&D processes in AgChem and Pharma** but with known in vivo tox profiles. Those compounds will be used to benchmark several dimensions of tox prediction using in vitro transcriptomic and cell painting



// ***The objective of this proposal is to generate in vitro cell painting and transcriptomic data for compounds with existing high-quality in vivo animal data to validate and establish these techniques as robust and useful NAMs using hepatotoxicity as usecase***

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Overall project outline

Rat cell culture(s)

POD x qIVIVE

POD x qIVIVE

Human cell culture(s)

POD x qIVIVE

POD x qIVIVE

?

Set of compounds with diverse hepatotoxicity profiles in the rat :

LOEL

- Tissue damage
 - // Necrosis
 - // Degeneration
- Inflammatory changes
 - // Inflammation
 - // Infiltration
 - // Proliferation
- Structural alterations
 - // Hyperplasia
 - // Hypertrophy
- Accumulative lesions
 - // Steatosis
 - // Vacuolation

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Anticipated outcomes and learnings

Quantitatives aspects :

- // in vitro rat POD vs in vivo rat LOEL
- // in vitro rat POD vs in vitro human POD ?

Qualitative/mechanistic aspects:

- // in vitro rat cells vs in vivo rat finding
- // in vitro rat cells vs in vitro human cells
- // in vitro human cells vs in vivo human findings

The dataset generated could also be used for

- // MIE prediction
- // Read across
- // And possibly in the future for AI guided de novo chemical design.

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Health and Environmental Sciences Institute (HESI)



OUR MISSION

Engage scientists from academia, government, industry, and other scientific organizations to identify and resolve global health and environmental issues.



Decision frameworks



Data sharing & collective analysis



Novel experimental studies



Manuscripts



Tool / assay development



Scientific meetings & trainings



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Emerging Systems Toxicology for the Assessment of Risk (eSTAR)

Committee Mission and Objectives

- ▶ Develop and deliver innovative systems toxicology approaches for risk assessment
- ▶ Catalyze adoption of new translational and predictive tools that guide decision-making based on mechanistic understanding of toxicological response
- ▶ Support identification of biofluid and tissue-based genomic biomarkers for toxicology

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Mission of eSTAR Cell Painting/Transcriptomic Working Group

Mission: Predicting the results of *in vivo* studies with Cell Painting and/or transcriptomics for toxicological assessment.

- ▶ Working group is comprised of stakeholders from industry (ag chem, pharma, CROs), academia, and government agencies
- ▶ We are currently in the process of designing experimental studies and finding funding and in-kind contributions
- ▶ Meetings are held between stakeholders once a month for 1-2 hours; eSTAR annual meeting (Nov 3 & 4) will dedicate a ½ day session to this project

Join us!

For more information about HESI and this project please contact Saddef Haq (shaq@hesiglobal.org), Connie Mitchell (cmitchell@hesiglobal.org), or David Rouquié (david.rouquie@bayer.com)



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Outreach

- ▶ Proposal for a Symposium Session was accepted for SOT 2023!!

Session Title: High Content Imaging: Cell Painting Basics and Emerging Applications to Toxicological Research

Chairs:

David Rouquie – Bayer AG

Alison Harrill – US EPA

Speakers:

Anne Carpenter – Broad Institute

Joshua Harrill – US EPA

Jessica LaRocca - Corteva

Deidre Dalmas - GSK

Fabrice Camilleri – Bayer AG



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Thank you!

David Rouquié

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@DavidRouquie
#GlobalCooperationNeeded

