Unilever & EPA
CRADA
(Cooperative Research & Development Agreements)

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*The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

23rd August 2021

Background

- Cooperative Research & Development Agreement
- CRADA are a mechanism for US Federal Agencies and Industry to work together:
  - Share expertise to solve common problems and develop *(in this case, new non-animal)* approaches together
  - Build confidence in New Approach Methods (NAMs) and apply them in Next Generation Risk Assessment (NGRA) decisions
- Original Unilever-EPA CRADA implemented in 2015 until 2018
  - Two amendments until 2021

Where We Started (in 2015)

SHARED EXPERIENCE AND EXPERTISE

CASE STUDY CHEMICALS		METHOD DEVELOPMENT	
Exposure scenarios	Selected ToxCast assays	Cell type & biological coverage	High throughput transcriptomics
In vitro inputs for exposure modelling	In silico characterisation & read across	High throughput *in vitro* metabolism	No Observed Transcriptional Effect Level (NOTEL)
True dose predication & measurement	Other *in vitro* assays	Point of Departure (PoD) determination	

DECISION MAKING

Reverse dosimetry - In vitro to in vivo extrapolation (IVIVE) - Uncertainty characterisation

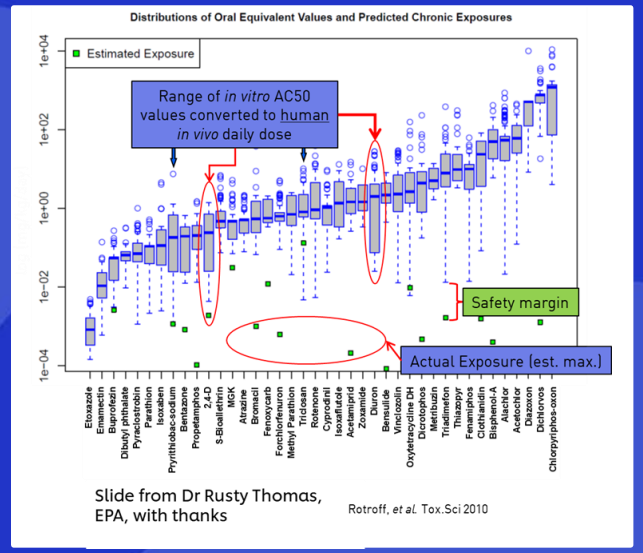
Ways of Working

- Split into activities - appointed Activity Leads with scientist to scientist interactions
- Monthly telecons between Unilever and EPA colleagues
- Visits to/from EPA (CCTE) and Unilever (SEAC)
- Annual overviews and deep technical discussions
- Secondments
- Developing and maintaining a close relationship to foster the same goals & mindset*

Goals & Mindset*

Safety without animal testing – New Approach Methodologies (NAMs) for Next Generation Risk Assessment (NGRA)

- NGRA: an exposure-led, hypothesis-driven risk assessment approach that integrates NAMs to assure safety without the use of animal testing
- The hypothesis underpinning these NGRA: if there is no bioactivity observed at consumer/worker/environmental-relevant concentrations, adverse health effects are highly unlikely to occur



At the Heart of this:
In Vitro Bioactivity Can be Used to Determine (Conservative) Margins of Safety

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

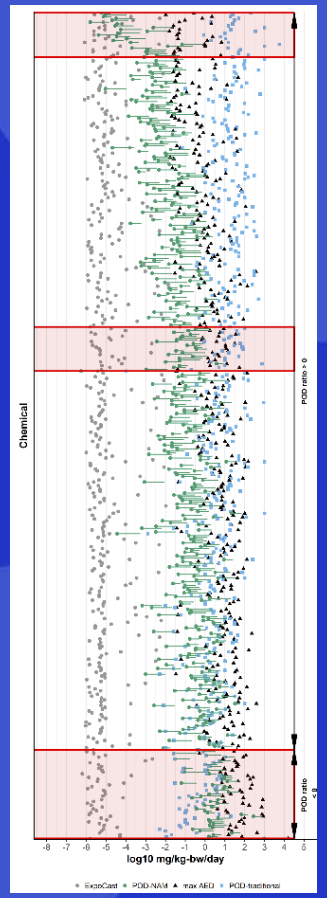
EPA, NTP, HC, A*STAR, ECHA, EFSA, JRC, RIVM…

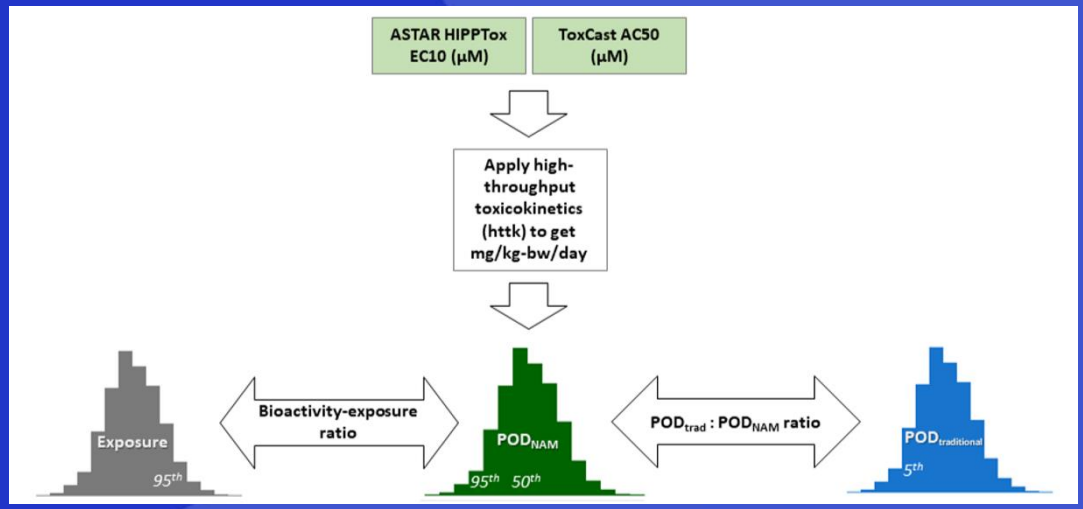
OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman ,*,1 Matthew Gagne,† Lit-Hsin Loo,‡ Panagiotis Karamertzanis,§ Tatiana Netzeva,§ Tomasz Sobanski,§ Jill A. Franzosa,¶ Ann M. Richard,* Ryan R. Lougee,*,|| Andrea Gissi,§ Jia-Ying Joey Lee,‡ Michelle Angrish,|| Jean Lou Dorne,|| Stiven Foster,# Kathleen Raffaele,# Tina Bahadori,|| Maureen R. Gwinn,* Jason Lambert,* Maurice Whelan,** Mike Rasenberg,§ Tara Barton-Maclaren,† and Russell S. Thomas *





"The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals". APCRA, 2020

The NEW Gold Standard

Was:

- Rodents
- Pathology
- High-dose apical endpoints
- No adverse effect level
- Uncertainty factors

Is Now:

- Broad-based NAMs
- Implementing new NAMs
- Exposure led (PBK)
- **Bioactivity not pathology**
- **Protection not prediction**

Press Release 19 August 2021

EPA and Unilever Announce Major Research Collaboration to Advance Non-animal Approaches for Chemical Risk Assessment

August 19, 2021

Contact Information
EPA Press Office (press@epa.gov)

WASHINGTON – Today, the U.S. Environmental Protection Agency (EPA) and Unilever announced a collaborative agreement to explore better ways to assess chemical risks associated with consumer products. This agreement builds on prior cooperation between EPA and Unilever regarding New Approach Methods (NAMs), which are a promising alternative to conventional toxicity testing that are intended to reduce reliance on the use of animals.

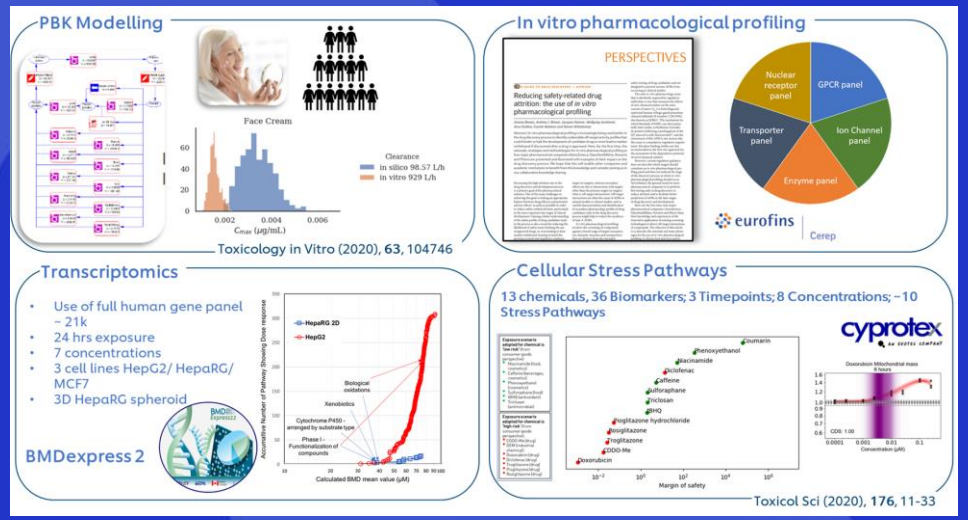
EPA and Unilever have been jointly evaluating and using NAMs since 2015. This collaboration is helping EPA implement its New Approach Methods Work Plan and is the foundation for new efforts to demonstrate that these novel approaches can help decision makers better protect consumers, workers and the environment.

"EPA is a pioneer in developing and applying NAMs to identify and quantify risks to human health, while reducing the use of animals in chemical toxicity testing," said **H. Christopher Frey, Deputy Assistant Administrator for Science Policy in EPA's Office of Research and Development**. "We are excited to continue the collaboration with Unilever, which enhances the robustness of our mutual research to demonstrate the use of NAMs."

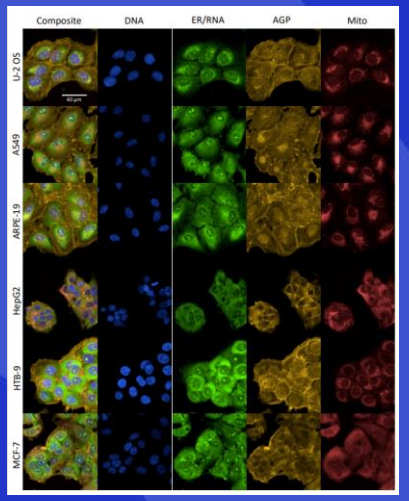
The new collaborative effort aims to establish a framework for the Next Generation of Risk Assessments based on NAMs. Such assessments are intended to quantify health risks to humans with sufficient scientific rigor to replace conventional animal-based methods and to support EPA's mission to protect human health and the environment.

This collaboration will bring together more than $2 million in both monetary and in-kind contributions, including scientific expertise and equipment, to develop a comprehensive NAMs dataset for a minimum of 40 chemicals. The chemicals will be selected and grouped such

New CRADA Key Outputs



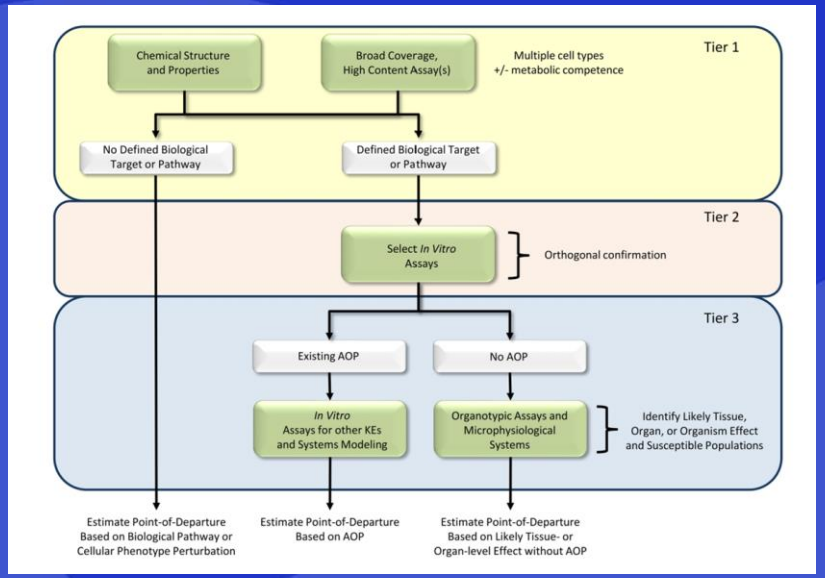
- Develop a comprehensive NAMs data set across our labs on a minimum of 40 chemicals
  - To evaluate and cement the utility of the EPA CompTox Blueprint and the Unilever NGRA Toolbox
- Show how the EPA Blueprint using HTTr and HTPP, in combination with computational methods, can be complemented by other broad coverage tools such as the Unilever Cell Stress Panel (CSP) and In Vitro Pharmacological Profiling (IPP)
  - To make an NGRA decision or to direct higher-tier targeted NAMs testing towards an NGRA decision
- Use this data set to develop prototype risk assessment dossiers to present externally at conferences and across the scientific community
  - Evaluating utility for regulatory application; i.e. develop and publish a set of recommendations for a NAM battery for evaluating the safety of new chemicals
- Explore the potential use of Human safety data to inform on Environmental risk assessment
  - Through application of cross species extrapolation computational tools



Come see the output of all this at:

SOT 61ST ANNUAL MEETING & TOXEXPO SAN DIEGO MAR 27-31 2022

Some Details



UNILEVER	EPA
HTTr in HepG2, MCF7 and HepaRG	HTTr in 10 human cell types + 2 fish lines
Cell Stress Panel (CSP) in HepG2 and additional cell types	HTPP in 10 human cell types + 2 fish lines
Safety Screen Panel (IPP)	Adding metabolic capacity to one or more HTTr or HTPP cell system
In silico (QSAR and MIE Atlas) battery	Assays for HTTK (fraction unbound, intrinsic hepatic clearance, absorption blood:plasma ratio)
Cytotoxicity Panel	*In vitro* disposition (i.e. true *in vitro* dose over time)
Metabolite determination in relevant cases	Metabolite determination in relevant cases
Additional Unilever-Partner panels e.g. Toxys Reprotracker, Stemina quickPredict	Additional EPA devtox, neurotox and cardiotox panels
Unilever SEAC Genes to Pathways (G2P) tool	EPA SeqAPASS analysis

Continuing to take on the difficult questions

- Temporal aspects of short-term assays versus lifetime exposures
- Paucity of metabolic activation or detoxification in *in vitro* systems
- Uncertainties in PBK predictions of tissues/plasma
- Adequate margins and uncertainty factors
- Sufficient biological coverage

Many thanks for listening! Any Questions?