Perspectives on current status and short- to long-term opportunities **Repeat Dose Toxicity**

New approach methodologies workshop

Towards an animal free regulatory system for industrial chemicals

Helsinki, 31 May 2023

Mounir Bouhifd
Computational Assessment and Alternative Methods Unit
European Chemicals Agency

→ Current status of REACH database + newly registered substances

→ A discussion "***Towards an animal testing-free regulatory system for industrial chemicals***"

- ECHA's activities to promote NAMs
- towards a full replacement of animal testing

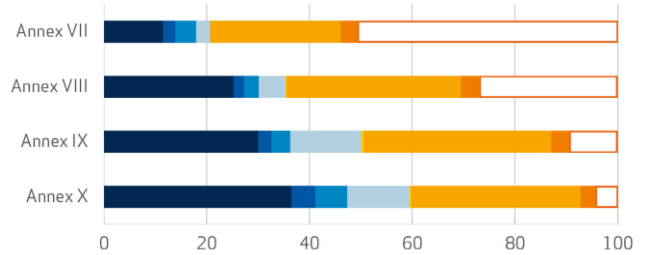


FIGURE 2: Options used to fulfil the information requirements (breakdown per REACH Annex)

Regulatory information requirements under REACH
Repeated dose toxicity

Standard information requirements

→ Annex VIII 8.6.1. Short-term repeated dose toxicity study (28 days)

→ Annex IX 8.6.2. Sub-chronic toxicity study (90-day)

Additional information requirements

→ Annex X 8.6.3. Long-term repeated dose toxicity study (≥ 12 months)

→ Annex VIII/IX 8.6.2. and X – 8.6.4. Further studies

Refer to internationally validated methods

→ Standardised

→ Reliable

Repeated dose toxicity (RDT) studies

Indicate **health hazards (adverse effects)** likely to arise from **repeated exposure** over a prolonged period of time

Basis for **risk characterisation and C&L** (for repeated dose toxicity)

Adverse effects & target organs?

Dose response relationship and **threshold**

Possible **MoA** and mechanism data

Potential **cumulative** effects?

Repeated dose toxicity (RDT) studies

Indicate **health hazards (adverse effects)** likely to arise from **repeated exposure** over a prolonged period of time

Basis for **risk characterisation and C&L** (for repeated dose toxicity)

Risk characterisation

- **threshold** of the critical effect(s)
- NOAEL, LOAEL, BMD

C&L

- **strength and severity** of adverse effects
- **dose levels** at which they occur

Additional concerns (triggers)

- **Specific target organs / systems**
- **Cumulative effects**

Repeated dose toxicity (RDT) studies

Indicate **health hazards (adverse effects)** likely to arise from **repeated exposure** over a prolonged period of time

Basis for **risk characterisation and C&L** (for repeated dose toxicity)

More than 200 parameters

- Body weight, body weight gain, feed consumption
- Clinical observations, behaviour, reflexes, etc
- Clinical chemistry, haematology, (urinalysis)
- Absolute and relative organ weights
- Necropsy & Histopathology including oestrous cycle
- Hormone measurements (thyroid, others if included)

Repeated dose toxicity (RDT) studies

What “comparable with RDT” means for NAMs?

To demonstrate that an outcome is comparable with RDT 90d in the context of hazard characterisation and risk management, NAM testing has to:

→ Provide estimate of NOAEL and LOAEL:

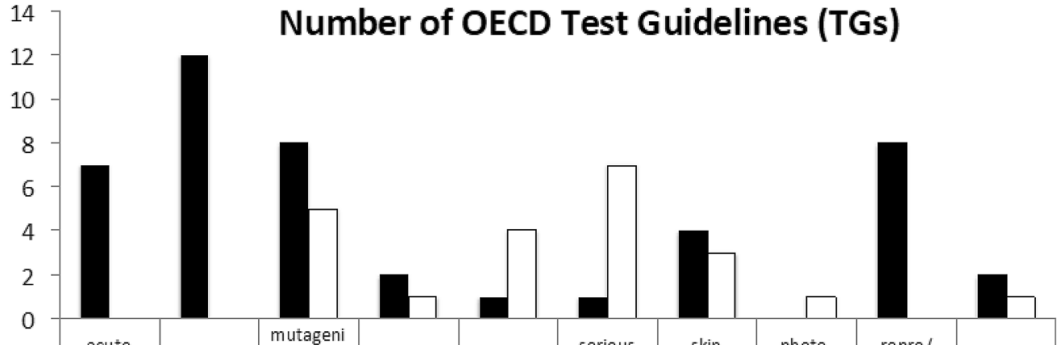
- NOAEL as potential source for systemic DNEL (Risk Characterisation)
- LOAEL for STOT RE classification (C&L)

→ Provide indications/triggers for:

- Toxicity to reproduction
- Immunotoxicity
- Neurotoxicity
- Carcinogenicity
- ED related effects

Repeated dose toxicity (RDT) studies

Status of OECD TGs in current regulatory testing paradigm



	acute systemic tox	repeated dose tox	mutagenicity/ genotoxicity	carcinogenicity	skin corr/ irrit	serious eye dam/ irrit	skin sensitisation	photo-induced tox	repro/ develop m tox	ADME/TK
■ in vivo TGs	7	12	8	2	1	1	4	0	8	2
□ In vitro/in chemico TGs	0	0	5	1	4	7	3	1	0	1

"Current EU regulatory requirements for the assessment of chemicals and cosmetic products: challenges and opportunities for introducing new approach methodologies"

Pistollato et al., Archives of Toxicology (2021) 95:1867–1897

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Accelerating the Pace of Chemical Risk Assessment

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT




efsa EUROPEAN FOOD SAFETY AUTHORITY

EURL ECVAM

ENVIRONMENT

Agency for Science, Technology and Research SINGAPORE

UNIVERSITY OF BIRMINGHAM

rivm

Health Canada Santé Canada

ECHA EUROPEAN CHEMICALS AGENCY

EPA United States Environmental Protection Agency

NTP National Toxicology Program

- → International cooperation - strategic **common challenges**
- → Concrete **case studies** - specific regulatory needs
- → Early recognition – **regulatory** challenge is replacement of higher tier systemic toxicity testing
  - Main area of attention for ECHA
  - Multiple case studies – Diversity of needs and priorities

Health Canada

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Accelerating the Pace of Chemical Risk Assessment

Retrospective Study

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.

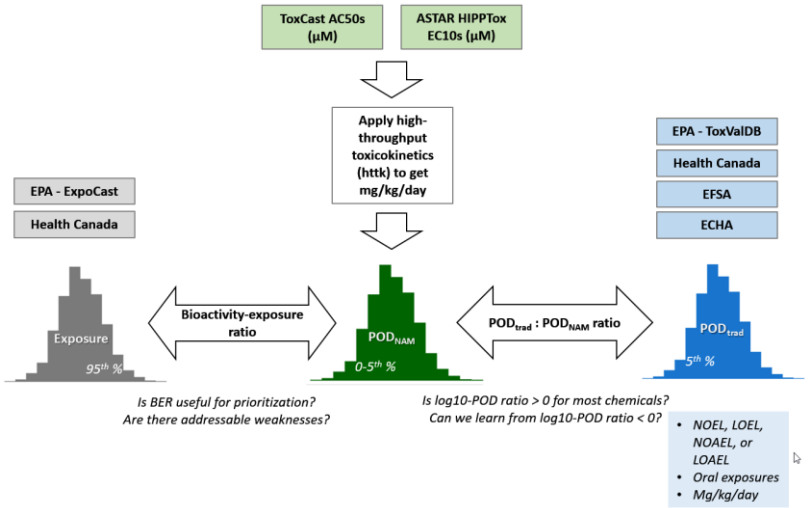
OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

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*

*National Center for Computational Toxicology, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC, 27711; [†]Healthy Environments and Consumer Safety Branch, Health Canada, Government of Canada, Ottawa, Ontario, Canada, K1A0K9; [‡]Innovations in Food and Chemical Safety Programme and Bioinformatics Institute, Agency for Science, Technology and Research, Singapore, 138671, Singapore; [§]Computational Assessment Unit, European Chemicals Agency, European Chemicals Agency Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Uusimaa, Finland; [¶]National Health and



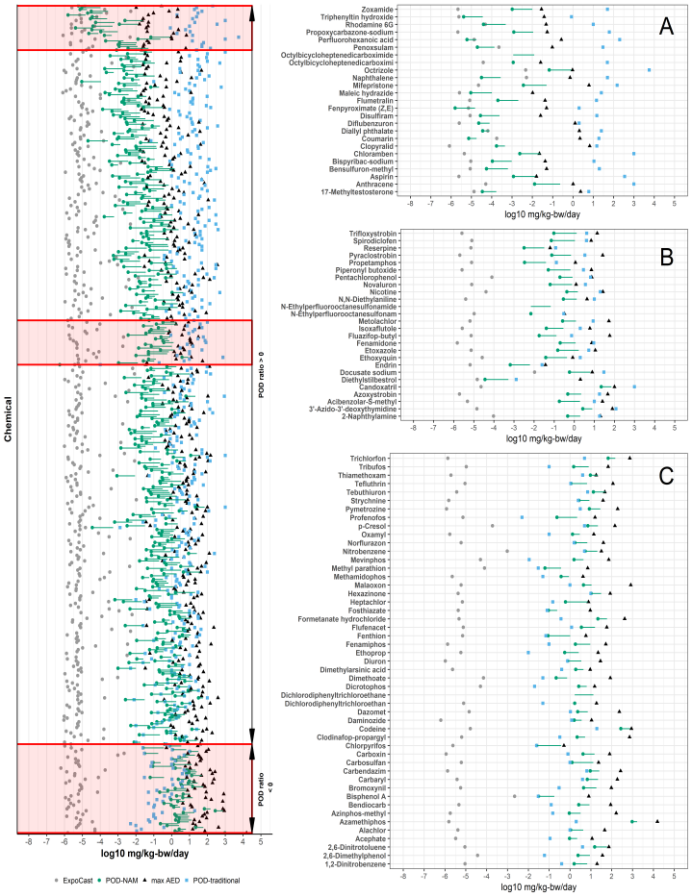
Katie Paul Friedman, et al.
Toxicol Sci. 2020 Jan 1;173(1):202-225. doi: 10.1093/toxsci/kfz201

Accelerating the Pace of Chemical Risk Assessment

Retrospective Study

Of the 448 substances, 89% had POD_{NAM} lower than traditional POD (POD_{trad})

Conclusion: NAM can be already used for conservative priority setting



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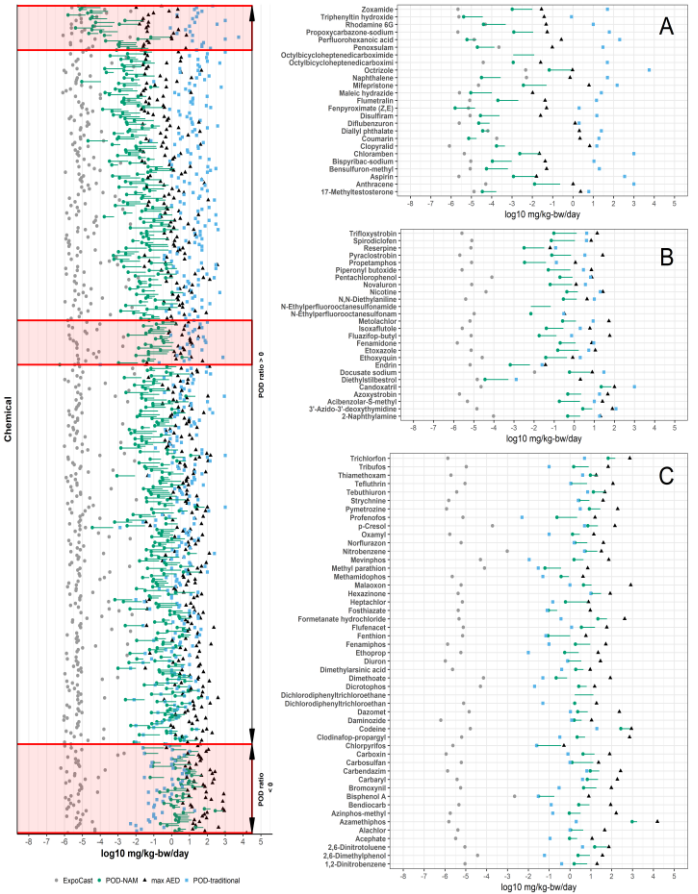
Accelerating the Pace of Chemical Risk Assessment

Retrospective Study

- Hazard estimates were over **conservative** in comparison to systemic in vivo data. Can we improve the accuracy of NAM estimates by applying an **optimised NAM battery**?
- Additional research to include expanded and improved high-throughput **toxicokinetics** and in vitro disposition kinetics. Would this help improve POD_{NAM} estimates?
- Specific types of chemicals may be currently outside the domain of **applicability.** How do we identify these in the future?
- Chemicals assessed (drugs, pesticides, biocides) bioactive, strong MoA. Will it work in a similar way for **less potent** compounds?



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APCRA prospective Study - Ongoing work

Objective

To identify a portable and scalable combination of toxicokinetic and toxicodynamic NAMs that provides a robust estimate of:

→ POD for wider range of systemic effects from RDT studies

→ Mechanistically-based RDT specific hazard flags/indications

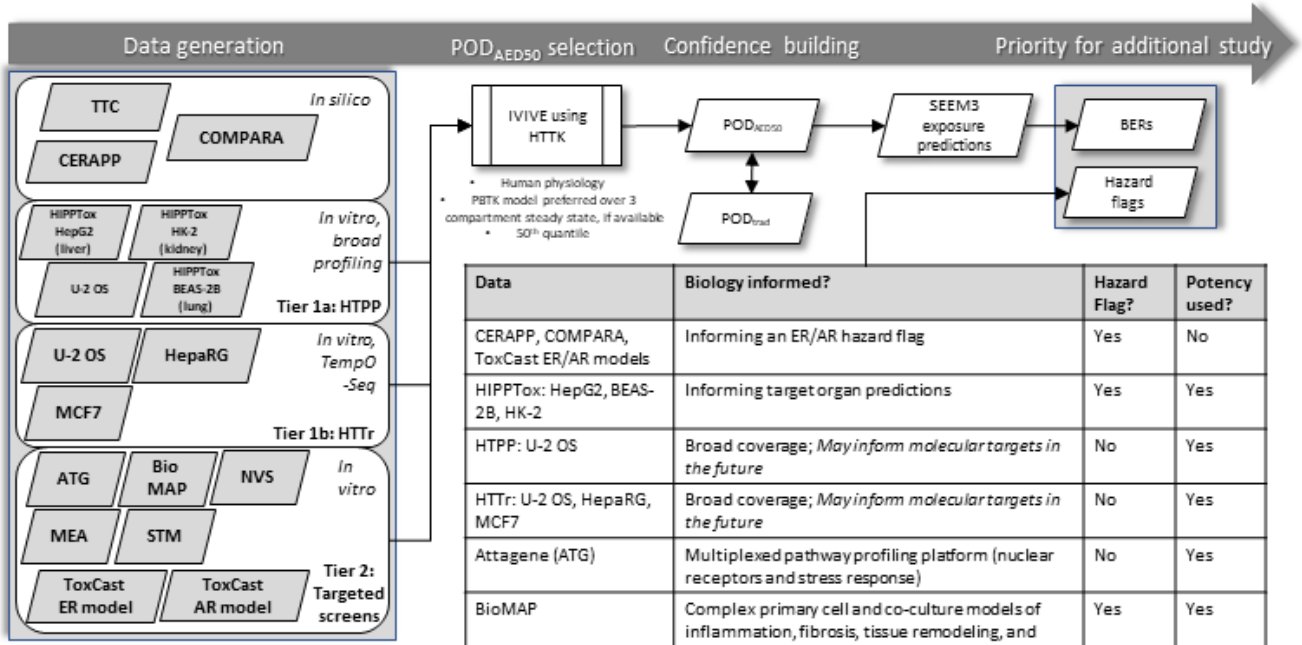
Design

- 200 chemicals from ToxCast library
- Generate data
- Derive POD_{NAM}
- Compare to exposure estimates
- Evaluate hazard flags
- Pick chemicals for further investigation

Led by
ECHA - **Tomasz Sobanski**
With substantial support
EPA – **Katie Paul Friedmann**
and valuable contributions from
NTP - HC- JRC - A*STAR

APCRA prospective Study - Ongoing work

Data integration Workflow



Data	Biology informed?	Hazard Flag?	Potency used?
CERAPP, COMPARA, ToxCast ER/AR models	Informing an ER/AR hazard flag	Yes	No
HIPPTox: HepG2, BEAS-2B, HK-2	Informing target organ predictions	Yes	Yes
HTPP: U-2 OS	Broad coverage; *May inform molecular targets in the future*	No	Yes
HTTr: U-2 OS, HepaRG, MCF7	Broad coverage; *May inform molecular targets in the future*	No	Yes
Attagene (ATG)	Multiplexed pathway profiling platform (nuclear receptors and stress response)	No	Yes
BioMAP	Complex primary cell and co-culture models of inflammation, fibrosis, tissue remodeling, and immune function	Yes	Yes
NovaScreen (NVS)	Suite of cell-free binding and biochemical assays	No	Yes
Microelectrode array (MEA)	Indication of acute effects on neuronal cells and their electrical function	Yes	Yes
Stemina (STM)	Stem-cell based screening with metabolomic indicator of developmental toxicity	Yes	Yes

Katie Paul Friedman, et al. APCRA
Unpublished

APCRA prospective Study - Ongoing work

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

→ Build a broad NAM-informed framework for the prediction of in vivo effects, with more biological information

→ Implement a chemical safety assessment workflow that is extensible and available for iterative improvement

→ Investigate the potential value of bioactivity estimates and hazard flags together in different scenarios

→ Estimate the accuracy of the derived PODs

→ **Deploy the best available science to address well focused regulatory questions for a common objective**

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Final remarks

- → The 117(3) report shows our efforts to promote NAMs and presents an outlook towards an animal-free system
- → ECHA is proactive to promote NAMs, and our activities in this respect are going beyond the regulatory implementation
- → Short-term opportunities should be seized to better integrate NAMs in the current system
- → Long-term: full replacement requires advancement in science and policy changes
- → It is a collective effort and requires buy-in by all stakeholders, including the public

Thank you

mounir.bouhifd@echa.europa.eu

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