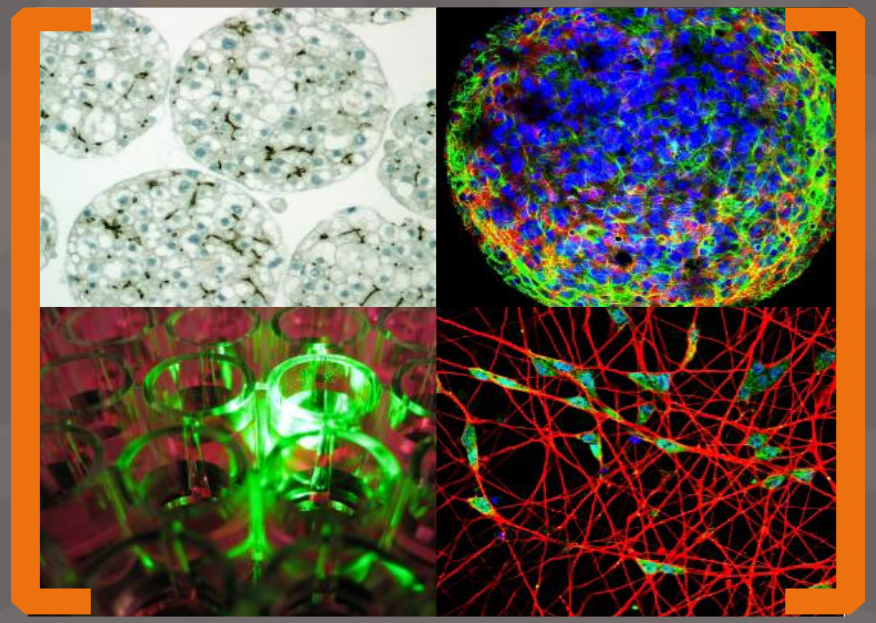
EU-ToxRisk Final Symposium,
Brussels, 3-4 November 2021

How will EU-ToxRisk impact on NAM regulatory acceptance?



Dr. Matthias Herzler

German Federal Institute for Risk Assessment (BfR)

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Disclaimer

The observations in this presentation are shared on a strictly personal basis, i.e. they **do not reflect**…

… a harmonised view of the EU-ToxRisk Regulatory Advisory Board (RAB) or

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Recent ECHA Statements on the Role of NAMs

Echa head: We are 40 years away from effective predictive toxicology

03 June 2021

Bjorn Hansen says decades of investment needed to make sufficient advances

https://chemicalwatch.com/275371/echa-head-we-are-40-years-away-from-effective-predictive-toxicology

"… Dr Hansen stressed that the **development of predictive toxicology methods has not significantly improved** in his 30 years of working on EU chemicals policy. […]"

"…advancing **test methods that inform regulatory requirements for complex endpoints**, such as the 90-day repeated dose toxicity test, is where the **main challenge** lies."

"**No alternative approaches** have been developed, according to Dr Hansen, that **fully predict** the outcome of these **complex and information rich studies**. […] The trend, he said, has been to focus on **mechanistic, specific toxicity, which can be very informative and bring new lines of evidence in safety management**, but this does not replace such tests."

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Recent ECHA Statements on the Role of NAMs

Echa: Animal testing for complex endpoints 'unavoidable' without regulatory change

21 October 2021

System is based on adversity, which NAMs do not measure directly, says senior agency scientist

https://chemicalwatch.com/356810/echa-animal-testing-for-complex-endpoints-unavoidable-without-regulatory-change

"[…] we are **regulating** chemicals on the basis of observed **adversities**." […] **NAMs do not measure those adversities** but rather the potential for them, he said. 'They are for measuring those early stages that may or may not lead to adversities.' "

"**NAMs** […] **for more complex endpoints** are **not directly applicable** under the **current regulatory framework** […]. If you want to make them more of use, and more successful, most probably you will need to consider **changing the legal framework**."

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A Number of Questions Arise…

Do these statements adequately reflect the **role of NAMs** under REACH today?

Did **EU-ToxRisk increase regulatory confidence** in NAMs under this system?

What are the **future challenges** of chemical risk assessment?

Do we need to **change the current system** for that?

Did **EU-ToxRisk** already **help** us to better understand how to address them?

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Current Role of NAMs Under REACH/CLP

Screening for/grouping of substances in need of regulation

→ e.g. ECHA uses a battery of in silico methods for this purpose

Predicting phys.-chem. parameters

→ e.g. phys.-chem. parameters, dermal/oral absorption, metabolism

Providing **mechanistic information**

→ e.g. ED identification (e.g. using ToxCast data), assessment of (absence of) human relevance

Reduce/replace/refine animal testing

→ e.g. grouping/read-across, replace standard animal tests for irritation/corrosion and skin sensitisation, indicators for study design (EOGRTS)

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Current Pre-Requisites: REACH Annex XI Requirements for NAMs

Scientific validity needs to be established.

Adequate and reliable **documentation** of the applied method needs to be provided.

However, to really **replace** a standard *in vivo* animal test, NAMs also need to be **adequate** for the purpose of **classification and labelling** and/or **risk assessment**.

→ **coverage of the „key parameters“** of the in vivo test (also **exposure duration**, if relevant).

→ key parameters include adversity-based **„Points-of-Departure“ (PoDs)** for risk assessment, but no requirement to **measure** adversity, animal tests are predictive models for human toxicity, too!

If we want, NAMs can already replace studies for complex endpoints today.

But ECHA is also correct in that we do not have such methods yet.

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How Has EU-ToxRisk Contributed to Regulatory NAM Acceptance?

Connecting research and regulatory domains

→ With its openness towards regulatory needs, EU-ToxRisk has greatly fostered mutual understanding.

Better account for **regulatory requirements**

→ **Great progress** in standardising NAM documentation (e.g. Krebs et al., 2019)

Methodology

→ Improvement of currently employed methods (Read-Across, e.g. Escher et al., 2019, RAx AD)

→ Groundwork for future developments (e.g. „ab initio“ case studies/NGRA, e.g. Moné et al, 2020)

Dissemination

→ Significant number of high-quality papers, outreach to OECD

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How Will That Help Us in the Future?

Excerpt from http://uploads6.wikiart.org/images/john-william-waterhouse/the-crystal-ball-1902.jpg

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The Commission‘s „Chemicals Strategy for Sustainability“ (CSS)

Despite a **strong EU policy** […] adopted 10 years ago, **which makes full replacement of animal testing its ultimate goal**, animals are still required to be used systematically for testing in the field of chemicals.

“…need to **innovate** in order to **reduce dependency on animal testing** but also to **improve** the **quality, efficiency and speed** of chemical hazard and risk assessments.”

→ “establish and update a **research and innovation agenda for chemicals**, […] that would also **promote the regulatory uptake of research findings**;”

→ “foster multidisciplinary research and digital innovations for **advanced tools, methods and models, and data analysis capacities** to also **move away from animal testing**;”

→ “much **knowledge** to be acquired by authorities on the intrinsic properties of a **vast majority of chemicals**, including polymers and chemicals that are **not manufactured in high volumes**.

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Areas of Future Work – Mechanistic and ADME Data

To support, *inter alia*:

→ ED, PMT, PBT identification

→ Grouping for risk assessment and regulation

→ Data-driven mixture risk assessment

- Generic „MAF“ ignores mechanistic prerequisites
- Upcoming EFSA guidance…
- BfR paper…(Tralau et al., 2021)

DOI: 10.1038/s43016-021-00316-7

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Areas of Future Work – Complex Endpoints

Methods to cover a **broad range of biological targets**

→ For **risk assessment**, but also for „**SSbD** “ chemicals

→ Need to integrate with existing data → „**big data** toxicology“

→ **Screening** level, but eventually **definitive** risk assessment → „**NGRA**“

→ **Omics** methods have the potential, but much work to be done

BfR/UFZ symposium „Challenges in Public Health Protection in the 21st Century: New Methods, Omics and Novel Concepts in Toxicology“

Nov 15-17, 2021, free registration open until Nov 8. https://www.bfr-akademie.de/english/events/nam-omics.html

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My Ultimate Learning from EU-ToxRisk…

EU-ToxRisk has started to address these future issues…

… and RISK HUNT3R will continue down this road!

But there are also structural problems we need to address, e.g.

- **Regulators** leaning back and waiting for industry to deliver NAMs that perfectly fit the existing system;
- **Industry** leaning back and waiting for regulators to tell them what to do.

Both „sides“ need to step up their engagement, but also more incentives and enforcement are needed („sticks and carrots“)!

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PARC (Partnership for the Assessment of Risks from Chemicals)

400 million € public-public partnership involving EU Member State authorities, affiliated entities, European agencies, and the Commission

Submitted 09/2021, project duration: 7 years, kick-off (pending approval): May 2022

Strong focus on **HBM**, **NAMs** and **NGRA**

Part of the "**research and innovation platform**" mentioned in the CSS

Dedicated WP for "a **common science-policy agenda**"

There will be lots of opportunities to interact, to ensure that cutting-edge science meets regulatory and policy goals, including the transition away from animal testing.

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Thanks for your attention

matthias.herzler@bfr.bund.de