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Paradigm shift in chemical risk assessment: NAMs and the Changing Landscape of Exposure Data Collection

Exposure Data Production: Human Biomonitoring (HBM) working group
Progress and future direction

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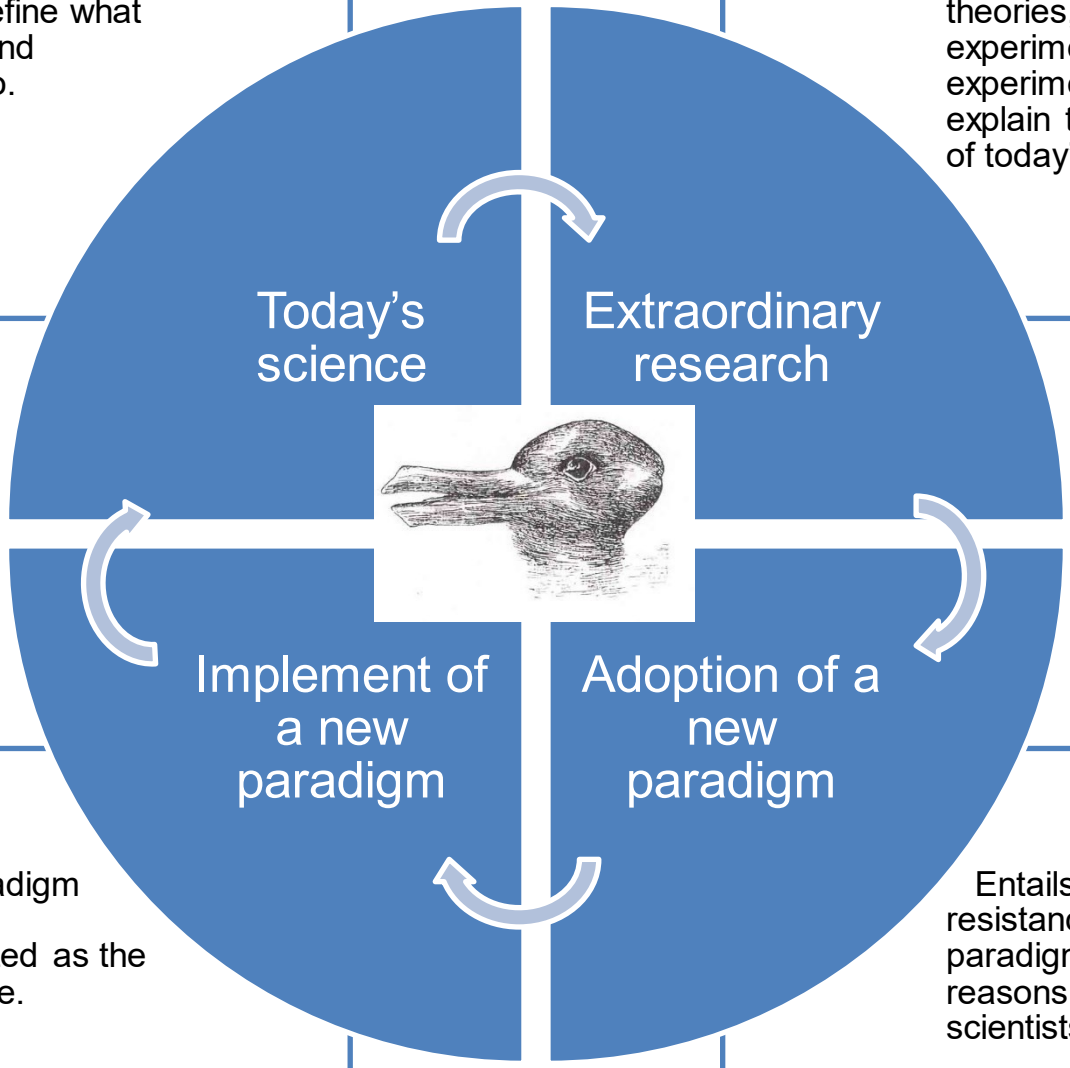
Paradigm shift in exposure science

- a set of theories and ideas that define what is possible and rational to do.

- Production of new theories, thought experiments, and experiments to explain the anomalies of today's research.



Kuhn used the duck-rabbit optical illusion, made famous by Wittgenstein, to demonstrate the way in which a paradigm shift could cause one to see the same information in an entirely different way

- the new paradigm becomes institutionalized as the dominant one.

Entails both resistance to the new paradigm, and reasons for why some scientists adopt it.

Paradigm shift in generating data for refined Hazard assessment

Today's science use traditional animal-based models in chemical exposure assessments

New Approach Methodologies (NAMs) are moving to innovative methods

Adoption of NAMs

Implementation in the future

NAMs roadmap highlights five key areas requiring more scientific and regulatory focus

1. **Toxicodynamics** (TD), making use of in silico tools and in vitro mechanistic and multi-omics data, high throughput screening, high content screening to identify Mode of Action (MoA) and inform AOPs;

2. **Toxicokinetics** (TK), using existing chemical data and modelling internal dosimetry, applying in silico tools, enhanced data models, TKTD modelling and QIVIVE, e.g., to be implemented in TK-plate;

3. **Exposome** data to inform exposure assessment, using epidemiological information and occupational or environmental human exposure including human inter-individual differences in metabolism and biomonitoring;

4. **Susceptible human population**, evolving the risk assessment paradigm through the integration of hazard and exposure drivers in mechanistically informed risk assessments for the identification of susceptible population groups;

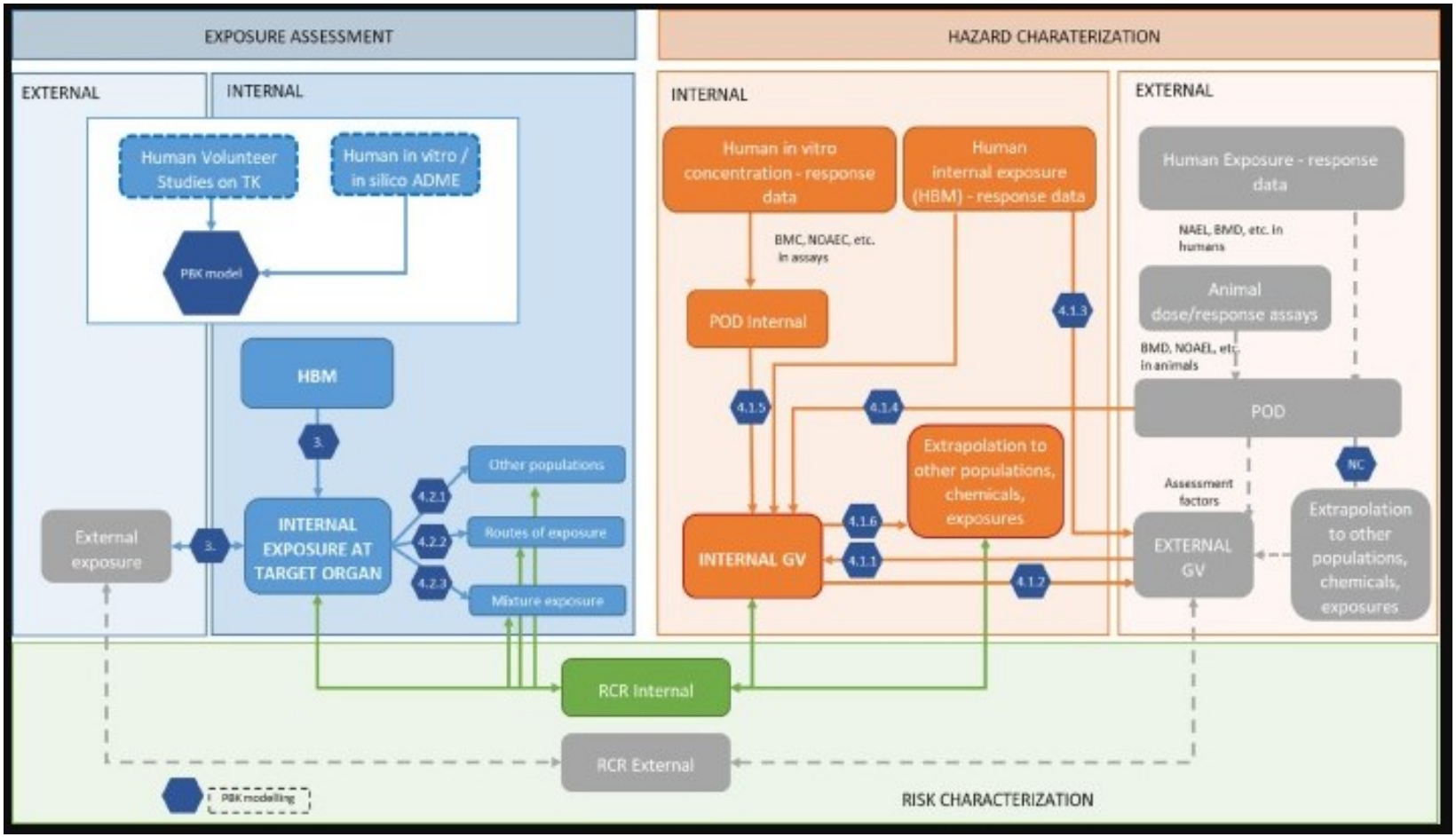
5. Data implementation, templates and tools are needed to facilitate the implementation of NAM data and their reporting into risk assessment dossiers.

Paradigm shift in generating data for refined risk assessments Hazard + Exposure = Risk

- Integration of NAMs into risk assessment is increasingly recognized in regulatory frameworks and supports a progressive shift towards Next Generation Risk Assessment (NGRA).
  - Roadmap for Action on NAMs in Risk Assessment of the European Food Safety Authority (EFSA)
  - Associated projects (e.g. ADME4NGRA) in dietary exposure to chemicals, i.e., food safety within the EU

- A key aspect of this shift is the **integration of physiologically based kinetic (PBK) modelling**
  - PBK mathematical models incorporating data from multiple routes and sources of exposure;
  - PBK models are parameterized using ***in vitro*, *in vivo*, and *in silico*** methods to generate internal exposure estimates in target organs over time.
  - PBK models in chemical risk assessment (CRA) can fill data gaps, reduce uncertainties, and enhance chemical safety evaluations.
  - PBK model validation can be performed with **human biomonitoring (HBM)** data.

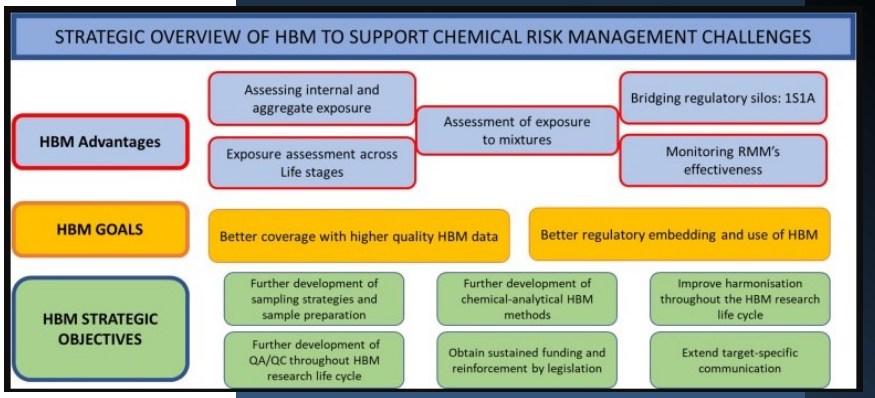
The interface between toxicological hazards and human exposures



Paradigm shift in generating data for refined Exposure assessment

- **Internal exposure** estimations or measurements give
  - a picture of simultaneous exposures to multiple chemicals and help in assessing associated risk for human health.
  - reflects exposures from all sources and routes of exposure as a steady state concentration for chemicals with long half-lives or as concentration over-time for short-lived chemicals.

- **Human biomonitoring** is an approach where internal exposures are measured



HBM improves chemical risk assessments

- HBM provides **comprehensive internal exposure** data and is currently being integrated within existing legal structures but also extends beyond.

- A key aspect of this shift is the **incorporation of HBM within NAMs**, bridging the gap between external and internal exposure data. HBM data respecting the FAIR principles (Findable, Accessible, Interoperable and Reusable) refine existing risk assessments by using human exposure data.

Leveraging HBM effectively across a chemical's life cycle examples

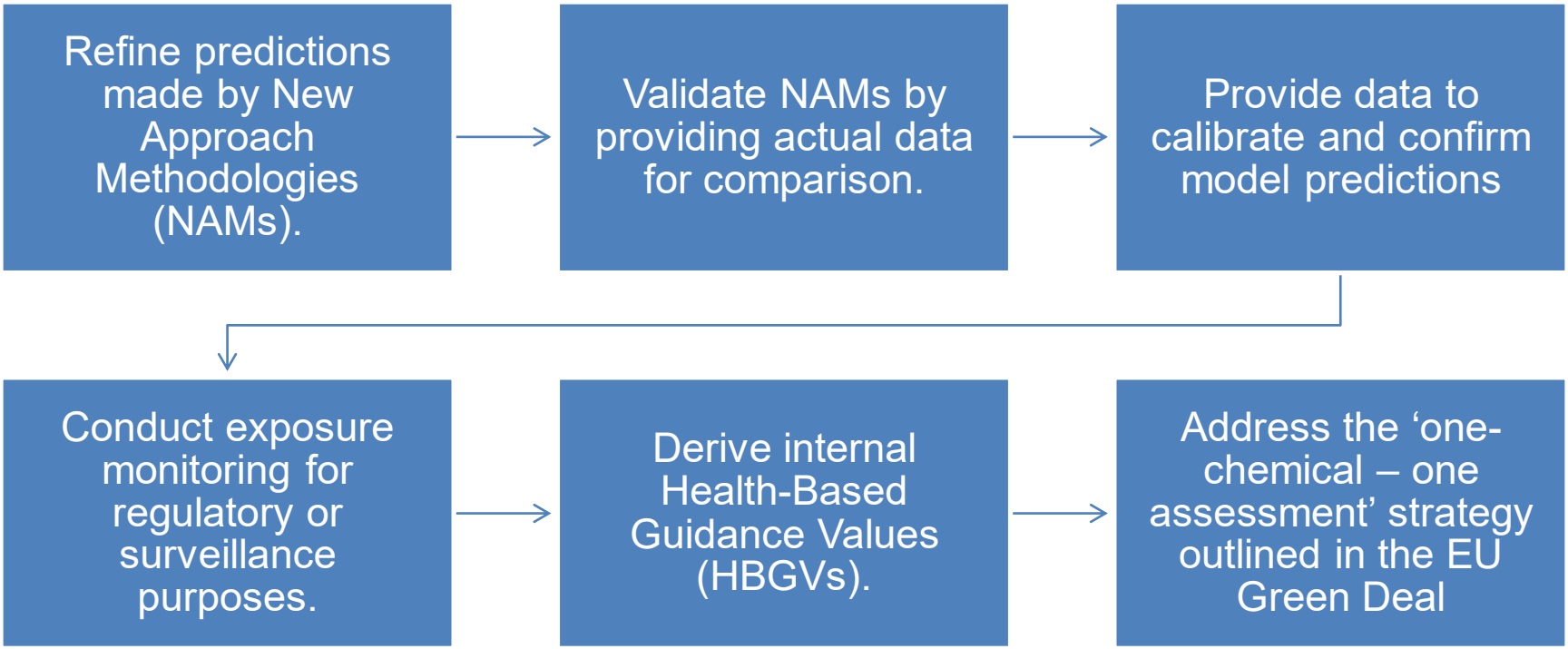
Ex. Exposure encompasses more than mere concentration or dosage; it is the product of concentration and time (C x T) that initiates the Molecular Initiating Event (MIE) within an Adverse Outcome Pathway (AOP).

At present the AOP starts at MIE but how much and how fast the chemical enters AOP is excluded. HBM and PBK models can help understand dose and ultimately, the likelihood of a toxic event.

Ex. Exposure encompasses more than mere one chemical.

At present mixture risk assessment are developed without considering results with HBM data

HBM is crucial for the practical assessment of internal exposures



our subgroup's initial HBM-NAMs framework

- Bridge the gap between hazard and exposure using HBM.
- Develop a strategy to enhance the collection and utilization of exposure data within the paradigm of NAMs Risk Assessment exploring the role of HBM.
- Characterize the role of HBM in the new NAMs risk assessment paradigm.
- Develop advanced HBM tools compatible with the NAMs framework
- Facilitate a holistic understanding of exposure scenarios, thereby enhancing the effectiveness and accuracy of exposure assessments across diverse environments.
- Ensure sustainability as well as rapid and effective responses to the challenges from future emerging chemicals.
- Develop data integration platforms to correlate external exposure with internal biomarkers from research on toxicokinetics and HBM.
- Develop user-friendly modelling tools for extrapolating HBM data to broader populations.
- Aligning exposure data with biological responses to better anticipate health risks and thereby assuring safe and sustainable across their entire life cycle.
- Recommend ways that mixture risk assessments can integrate combined exposure to multiple substances using HBM data, thus, capturing the complexity of actual chemical exposure.