CHIASMA - Accessible Innovative Methods for the Safety & Sustainability Assessment of Chemicals & Materials

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1. Introduction

The CHIASMA Project aims to devise and demonstrate a comprehensive set of **New Approach Methodologies (NAMs)** for chemicals and advanced materials, and integrate these into a user friendly, reliable and robust framework to perform human and environmental safety evaluation in a regulatory context. The **CHIASMA SSbD (Safe & Sustainable by Design) Assessment** will be based on an iterative approach that leverages on different consecutive assessment steps based on **chemocentric models**, **biocentric tools, and experimental NAMs**.

The CHIASMA NAMs, alone or combined into IATAs, will be developed to answer specific regulatory needs, focusing on regulatory requirements for human and environmental safety and assessment, aiming at applying it to the EU's SSbD approach in terms of defining safety and sustainability along the complete life cycle of a substance/material. A harmonised composition of the project consortium encompassing academic and research centres as well industry and regulators will ensure CHIASMA's value at continental level and beyond. The Project will ensure development and implementation of innovative NAMs to support EU strategies, such as the EU Chemicals Strategy for Sustainability (CSS), the JRC Safe and Sustainable by Design (SSbD) framework, and the AMI3030 initiative (to name but a few).

CHIASMA will promote EU leadership in the sector and provide a significant advance in the research field. The CHIASMA's link to industry and to EU and global regulators and policy makers (e.g. OECD, EURL ECVAM, ECHA, EFSA, US-EPA, and US-FDA) will ensure the relevancy and applicability of the developed approaches, which will be tested on three test cases, namely PFAS, (nano-)pesticides, and 2D chemicals/materials for energy applications, demonstrating regulatory relevance and trans-domain applicability of the CHIASMA-framework.

2. The CHIASMA Project

The CHIASMA Project is fully aligned with the EU strategies for the development of the SSbD Framework to ensure safety and sustainability of enabling and emerging technologies – including those based on chemicals and materials, as addressed in the

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EU's CSS, in the European Green Deal and in the Advanced Materials 2030 Initiative. CHIASMA will focus on developing NAMs and improved **Life Cycle Impact Assessment** (LCIA) approaches and strategies, to ultimately integrate these into the **CHIASMA Framework** for the combined assessment of SSbD to support REACH (regulation for the Registration, Evaluation, Authorisation and Restriction of Chemicals), CLP (regulation for Classification, Labelling and Packaging of chemicals) and other relevant regulations, such as the (proposed) Ecodesign for Sustainable Products Regulation and the EU Ecolabel regulation.

The resulting integrated **CHIASMA SSbD Assessment** (for safety- and environmental-assessment), will be successively built on the coherent development, refinement and demonstration of NAMS based on both ***in silico*** and '**experimental**' methods (*i.e.,* CHIASMA's collective term for ***in vitro* methods, human *ex vivo* methods and non-mammal *in vivo* methods**), in order to enable risk assessors, SMEs, large enterprises and regulators to address REACH and CLP relevant endpoints using human-centric and 3R-compliant approaches. The developed NAMs, refined and demonstrated by CHIASMA will be deployed as 'Swiss army knife' to generate data (e.g., newly generated or as the result or re-processing of existing data), and including *in silico, in vitro* and *in chemico* approaches that will be used alone or in combined approaches, such as Integrated Approaches to Testing and Assessment (IATAs), to generate specific regulatory relevant results for the EU SSbD Framework.

The CHIASMA SSbD Assessment and the *in silico* and experimental NAMs will be 'in-project' validated against three groups of socially and environmentally relevant chemicals and materials groups:

a) Demo-Case 1: Polyfluoroalkyl Substances (PFAS),
b) Demo-Case 2: (nano)-pesticides, and
c) Demo-Case 3: 2D materials for energy applications.

The focus on these three groups is justified by their high health impact, environmental persistence, and large industrial use, which lead to high societal concern. CHIASMA builds on many years of research and innovation (R&I) and knowledge pooling in chemical safety and nanosafety, development and implementation of computational models and of advanced biological models for prediction of safety and environmental impact, generation of conceptual frameworks for assessment formed through European and international collaborations.

CHIASMA will contribute to the global efforts towards the green and digital transition, ensuring **more robust and more ethical regulatory-ready methods** to enable stakeholders to achieve the ambitious European goals for a sustainable and toxic free society. CHIASMA will boost the efforts of the scientific community and authorities to **generate, validate and implement new alternative methods and strategies for the animal-free assessment of chemicals and materials**.

3. The CHIASMA R&I Approach

The **CHIASMA R&I approach to testing and assessment** (see Figure 1) aims to provide regulators with an integrated framework (the CHIASMA SSbD Assessment) allowing human and environmental safety and environmental impact assessment using an iterative multi-step approach based on next generation safety assessment (NGSA) approaches. The CHIASMA SSbD Assessment combines the elements, corresponding to the numbers in Figure 1:

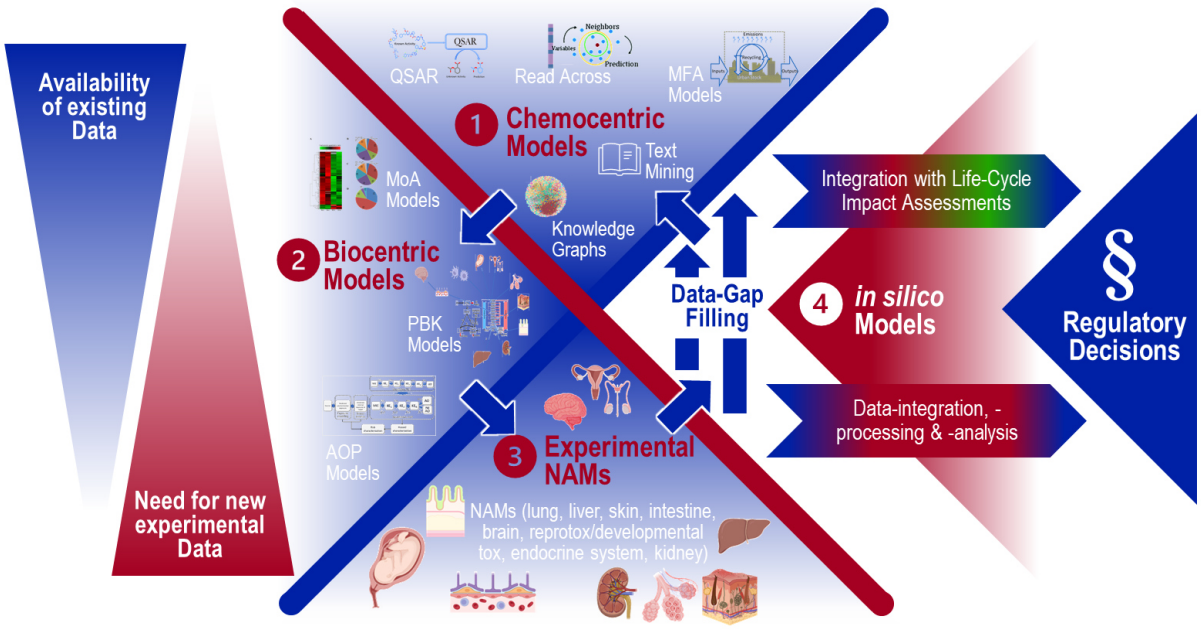

Figure 1: Illustration of the CHIASMA R&I approach to testing and assessment of materials using an iterative approach based on the integration of (1) chemocentric, (2) biocentric and (3) new experimental models into a conceptual framework for data-integration and -processing.

1. **Chemocentric models**, powered by **state-of-art artificial intelligence**, including:
   - Chemocentric models for the prediction of behaviour and properties of chemical systems.
   - Quantitative Structure-Activity Relationship (QSAR) models relating chemical features to biological effects.
   - Material Flow Analysis models (MFA) to predict chemical/material releases along the products' life cycle.
   - Text mining tools to process, analyse, and extract valuable information from large amounts of text data.
   - Knowledge Graph to capture, structure and analyse existing data, inferring new links and conclusions.
   - Read Across to predict properties for the target substance(s) based on properties of analogous substances.
2. **Biocentric models**, consisting of:
   - Physiologically-Based Kinetic models (PBK) to predict behaviour and distribution of chemicals in the body.
   - Adverse Outcome Pathways models (AOPs) to provide a systematic and comprehensive understanding of key events (KEs) and molecular initiating events (MIEs) that lead to an adverse outcome following exposure.
   - Mechanism of Action (MOA) models that describe the molecular biology processes and interactions following exposure to identify the specific targets, pathways, and interactions that are involved.
3. **Optimised experimental NAMs**, representative of the following human biological systems:

- Human organs and systems (brain, reproductive/developmental and endocrine systems, kidney, and liver).

- Human internal biological barriers (blood-brain-barrier (BBB) and blood-placental-barrier (BPB).
- Human external barriers (lung alveolar barrier, skin and small intestine).

4. **Data integration, processing and analysis modules** that will also include innovative Life Cycle Impact Assessment (LCIA) methods for better integration of toxicity in human and environmental assessment.