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Advanced Characterisation Methodologies to assess and predict the Health and Environmental Risks of Advanced Materials

Interim Results of the MACRAMÉ R&I Approach – Ensuring regulatory Alignment in the Research & Innovation of five market-relevant Advanced Materials
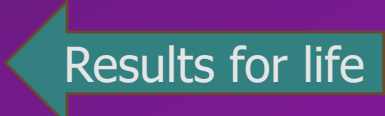
NanoTox 2024
23. – 25. September 2024, Venice (Italy)

How to ... *ensure regulatory Alignment in the Research & Innovation of five market-relevant Advanced Materials*

1. Choose your market-relevant Advanced Materials (AdMa)
   a) Conduct a gap-analysis

2. Set an R&I strategy (incl. benchmarks & workflow)
   a) Define possible LCA exposures (→ MACAMÉ Exposure Points)
   b) Agree on a language / terminology (or invent one)

3. Develop sampling approaches & methodologies (→ MACRAMÉ Sampling Protocols)

4. Set a reference (→ MACRAMÉ Control Material Library)

5. Develop a data collection method (→ MACRAMÉ Instance Map)

6. Write a roadmap (→ MACRAMÉ Harmonisation & Standardisation Roadmap) ◄ MACRAMÉ Results

7. ... start working down the list above

8. ... realise that there is no way you get everything done in three project years ◄ Results for life

9. ... set up more projects to continue the work ◄ NanoTox Community Results
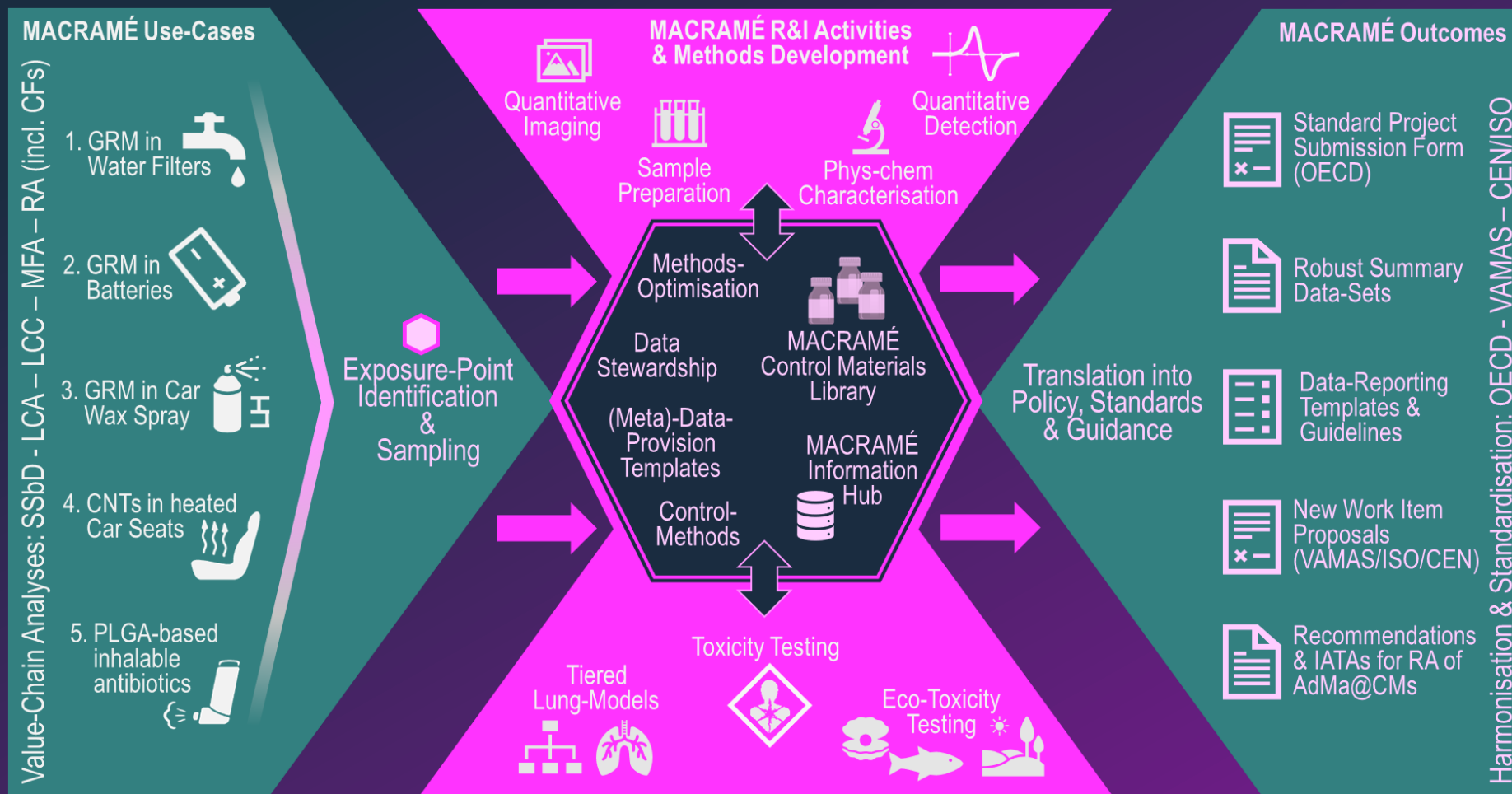
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The MACRAMÉ R&I Approach

Illustration of the MACRAMÉ R&I Approach (AdMa@CMs: Advanced Materials in complex matrices; CF: Characterisation Factor; GRM: graphene-related material; IATA: integrated approaches to testing and assessment; LCA: Life-Cycle Assessment; LCC: Life-Cycle-Costing; MFA: Material-Flow Analysis; RA: Risk-Assessment; SSbD: Safe-&-Sustainable-by-Design).

Harmonisation & Standardisation of Nanomaterials

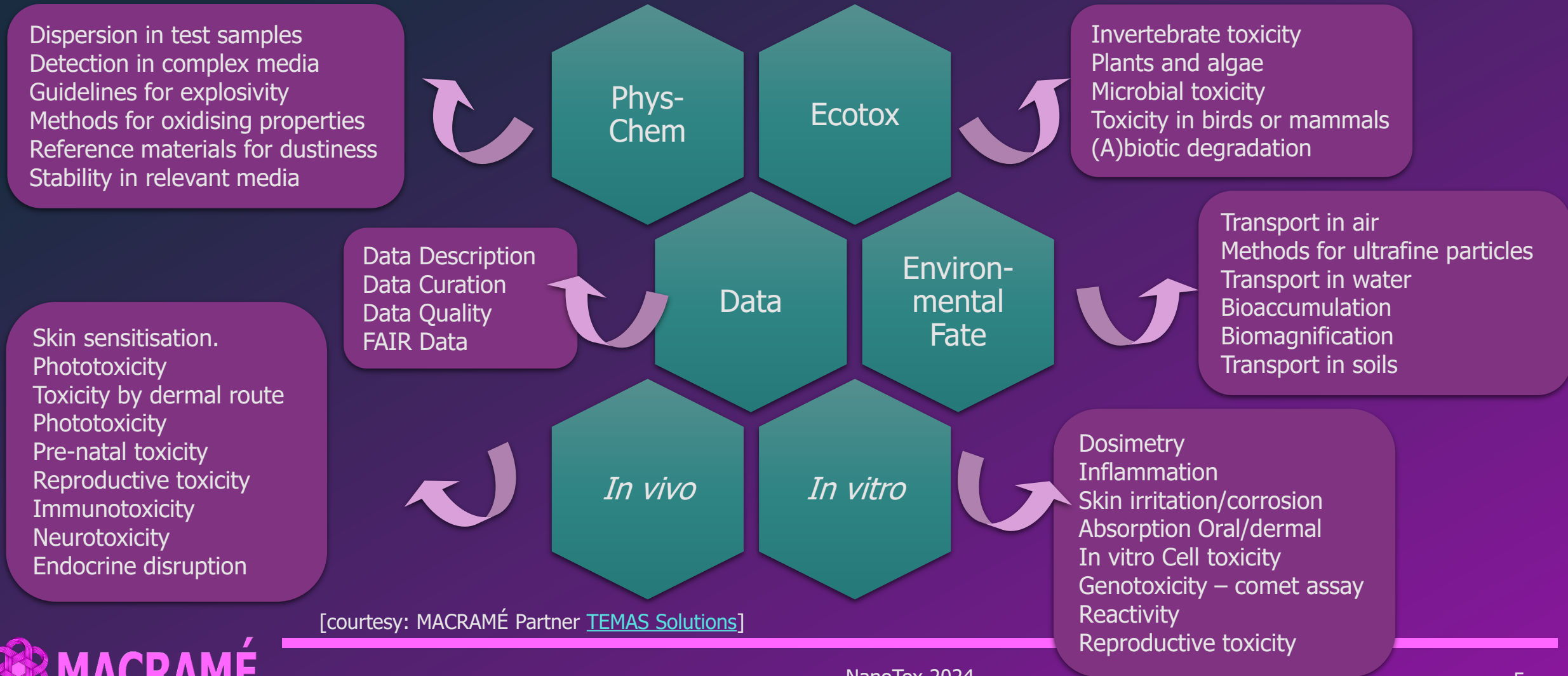|					
ISO	**Terminology** Achieved 18 On-going 7	**Measurement** Achieved 8 On-going 6	**Characterisation Graphene** Achieved 13 On-going 8	**Characterisation (Other)** Achieved 27 On-going 2	**Exposure and Risk** Achieved 23 On-going 11	**Performance Evaluation** Achieved 3 Ongoing 3
CEN	**Terminology** Achieved 7 On-going 5	**Measurement** Achieved 5 On-going -	**Characterisation (Other)** Achieved 1 On-going 3	**Exposure and Risk** Achieved 19 On-going 11	**Other** Achieved 4
OECD	**Physico-chemical Characterisation** Achieved 5 On-going 5	**Human Toxicology** Achieved 5 On-going 5	**Environmetal Toxicology** Achieved 1 On-going 4	**Environmental Fate** Achieved 1 On-going 3	**End of Life** Achieved 1 Ongoing 1

215 Standards! ➡ *But we still have gaps*

[courtesy: MACRAMÉ Partner TEMAS Solutions]

(Nano)Materials Standardisation Gaps (September 2023)

Dispersion in test samples
Detection in complex media
Guidelines for explosivity
Methods for oxidising properties
Reference materials for dustiness
Stability in relevant media

Invertebrate toxicity
Plants and algae
Microbial toxicity
Toxicity in birds or mammals
(A)biotic degradation

Data Description
Data Curation
Data Quality
FAIR Data

Transport in air
Methods for ultrafine particles
Transport in water
Bioaccumulation
Biomagnification
Transport in soils

Skin sensitisation.
Phototoxicity
Toxicity by dermal route
Phototoxicity
Pre-natal toxicity
Reproductive toxicity
Immunotoxicity
Neurotoxicity
Endocrine disruption

Dosimetry
Inflammation
Skin irritation/corrosion
Absorption Oral/dermal
In vitro Cell toxicity
Genotoxicity – comet assay
Reactivity
Reproductive toxicity

Phys-Chem
Ecotox
Data
Environ-mental Fate
In vivo
In vitro

[courtesy: MACRAMÉ Partner TEMAS Solutions]
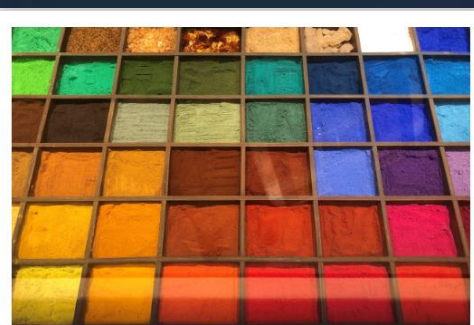
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Exposure-Point Definition in real-life Value-Chains ...

MACRAMÉ Exposure Points [Samples & Constituents]	Pristine AdMa Manufacture	AdMa (Un-)Bagging & Transport	Product Manufacture	Reactor/ Machine Cleaning	(Un-)Bagging & Transport	(Professional) Intended Use	End-of-Life		
							Shredding	Incineration	Release/Leakage
	[AdMa]		[AdMa] - [AdMa@CPM] - [CPM]				[AdMa@EoL(CPM)] - [CPM(EoL)]		
UC1: GO in Water-Filters	Pristine GO, polysulfone (matrix)		GO@Polysulfone-Fibre, Water from the spinning-process			(filtered water) *	-		Incineration products: Fly-ash, Flue-gas
UC2: FLG in BMS	Pristine FLG, epoxy resin		FLG@epoxy (non-reticulated (liquid samples) and reticulated (solid samples))**			FLG@epoxy (overheated)	FLG@epoxy (shredded)		
UC3: GRM-bearing Sprays	-					GRM@aerosol	GRM@aerosol (in container), EoL according to container material and/or special instructions		
UC4: CNTs in Polymer Foils	Commercial CNTs (NanoCyl SA), polyurethane (PU) matrix		CNTs@PU (masterbatch & cured composite)			CNTs@PU (overheated, abraded (Taber))	CNTs@PU (shredded)		Incineration products (O$_2$-depletion): Fly-Ash, Flue-gas
UC5: PLGA-based inhal. Antibiotics	PLGA-particles (different sizes) Ciprofloxacin		ciprofloxacine@PLGA controls: Au@PGLA, Fe$_x$O$_y$@PLGA, PLGA (labelled with Lumogen red®)				-		ciprofloxacine@PLGA
Characterisation - Detection – Imaging (by Attributes) [Samples & Constituents]	All UCs: • characterisation; • aerosol generation & characterisation; • stability in environmental & biological matrices; • high resolution imaging in cells		All UCs: • Aerosol generation for *in vitro* exposure • Characterisation of the generated aerosol • Stability and release in environmental & biological matrices				All UCs: • EoL leaking from container/matrix • Aerosol generation for *in vitro* exposure • Stability and release in environmental & biological matrices		
			UC1, UC2, UC4, UC5: • Identification, quantification & characterisation	UC1, UC2, UC4, UC5: • Identification of (form of) release during cleaning	UC3: • Identification: presence of GRM ➢YES: quantification, characterisation	UC2, UC4: • characterisation after mechanical abrasion (Taber) • characterisation of release at heating	UC1, UC2, UC4: • characterisation after mechanical abrasion	UC1, UC2, UC4: • characterisation of flue-gas & fly-ash	UC1, UC2, UC4: • Identification of release of EoL-products (in land-fill)
	[AdMa] - [AdMa@EM] - [AdMa@BM]		[AdMa@CPM] - [AdMa@CPM@EM] – [AdMa@CPM@BM]				[AdMa@EoL(CPM)] – [AdMa@EoL(CPM)@EM]		
Human Toxicity Testing (in-vivo – ex-vivo) [Samples & Constituents]	In case of inhalable release: Scheduled Tiered Lung-Model Approach (see Section 1.2, III.vii)								
	[AdMa@BM]		[AdMa@CPM] [AdMa@CPM@BM]- [AdM@BM] - [CPM@BM]				[AdMa@EoL(CPM)]		
Ecotoxicity Testing [Samples & Constituents]	Ecotox Testing Strategy (see Figure 5)								
	[AdMa@EM]		[AdMa@EM] – [AdMa@CPM@EM] - [CPM@EM]				[AdMa@EoL(CPM)]	[AdMa@EoL(CPM)]	

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Terminology:

- AdMa = Advanced Material
- CM = Complex Matrix
- EM = Environmental Matrix
- BM = Biological Matrix
- CPM = Complex Product Matrix
- EoL = End-of-Life
- AdMa@CMs
  - AdMa@EM
  - AdMa@BM
  - AdMa@EoL(CPM)
  - AdMa@EoL(CPM)@EM

References – the MACRAMÉ Control Materials Library

Launch of the MACRAMÉ Control Material Library

July 1, 2023

To support development, harmonisation, and benchmarking of testing methods applied within the HorizonEurope-funded Project, a MACRAMÉ Control Material Library (CML) has been established. The Library contains representative materials with largely known properties impacting the in vitro test development and of materials to be investigated in the MACRAMÉ Use Cases (UCs).

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<u>Exemplary Excerpt</u>: Table 2: Materials of the CML selected for the development and validation of controlled aerosol generation (Task 2.2).

	Name	Supplier	Link to Product	Criteria for the selection	Interesting Features	Also used in other projects
Nanotubes						
MWCNT test material	ARIGM001	BAuA Repository		Serves as default testing material for method development, available in large quantities	High dustiness, medium degree of entanglement, mean diameter ~35 nm, mean length ~1-2µm	CarboLifeCycle,
Graphitised MWCNT	NM401	OECD Repository		Positive control for fibre paradigm (rigid), test with µ-Dishes	Rigid and long fibres, easy to disperse, >20% WHO fraction	NanoGRAVUR, InnoMat.Life, HARMLESS, NanoHarmony
MWCNT	Baytubes C150P	BAuA Repository		Negative control for fibre paradigm (NM400 not a real one), test with µ-Dishes		older BAuA projects
Aligned flexible MWCNT	NG01AM0102	nanografi	Link	Thin commerical CNTs marketed as beeing produced in such way that they are aligned and bundled, test with µ-Dishes	Bundles are very long up to 95 µm.	not yet
MWCNT 30-50 nm	NG01MW0501	nanografi	Link	Presumed to be a mixture of more flexible and less rigid MWCNTs (proportions), test with µ-Dishes		not yet

→ https://macrame-project.eu/launch-of-the-macrame-control-material-library/

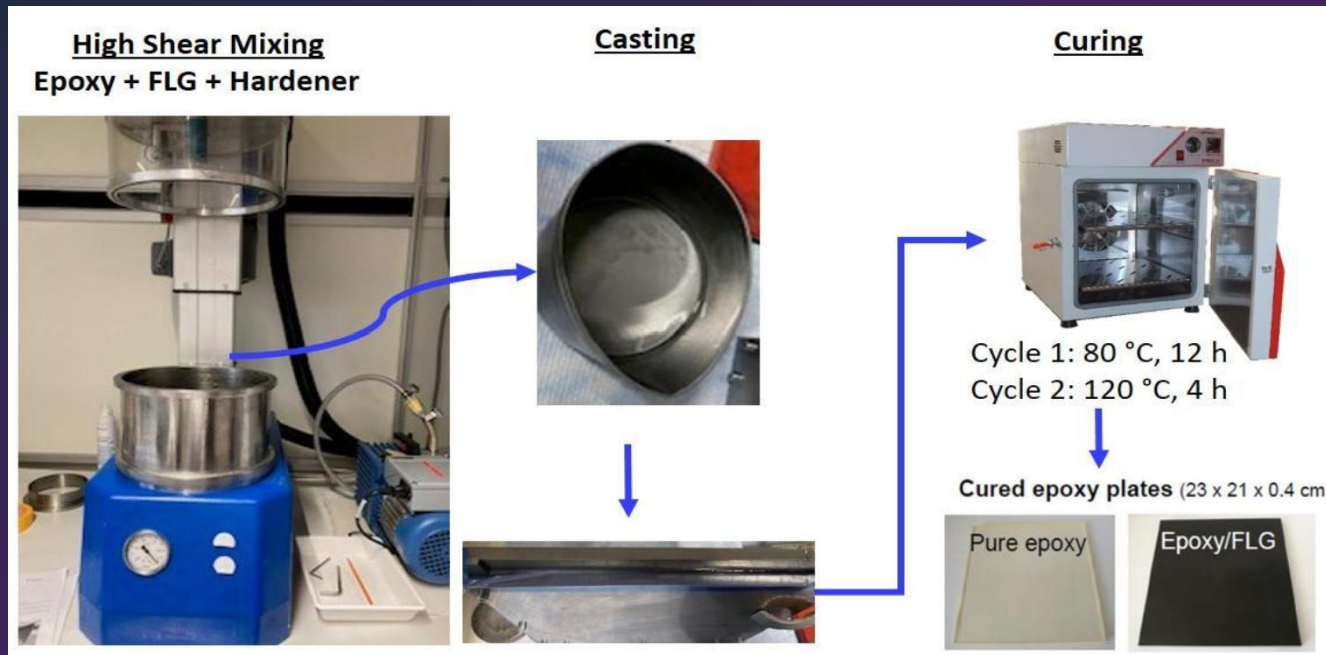MACRAMÉ

MACRAMÉ Sampling Approaches & Protocols

Sampling & Sample-Provision Protocols for AdMas in complex Matrices

March 1, 2024

The MACRAMÉ Project has published its first set of 'Sampling & Sample-Provision Protocols for AdMas in complex Matrices', in order to guide the sample collection that needs to be performed at the MACRAMÉ Use-Case (UCs) sites prior to sending the samples to MACRAMÉ laboratories for testing. Such sample collection is

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High Shear Mixing
Epoxy + FLG + Hardener

Casting

Curing

Cycle 1: 80 °C, 12 h
Cycle 2: 120 °C, 4 h

Cured epoxy plates (23 x 21 x 0.4 cm)

Pure epoxy | Epoxy/FLG

Exemplary Excerpt (Use-Case 2: BMS): Figure 3: Fabrication of Epoxy-FLG composite plates. Epoxy alone or epoxy-FLG composite are mixed with hardener (Baxxodur EC 301), moulded and then cured in the oven at indicated temperature cycles. The plates obtained after curing were used for abrasion.

Exemplary Excerpt (Use-Case 5: PGLA): Figure 12: PCL-samples.

→ https://macrame-project.eu/sampling-sample-provision-protocols-for-admas-in-complex-matrices/

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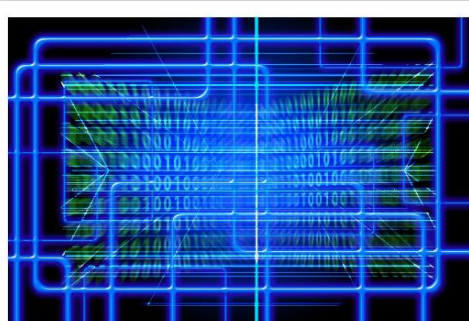# Data Collection – the MACRAMÉ Data Shepherd

MACRAMÉ Data Shepherding – an Approach to the centralised Management of Research Information & Knowledge

June 1, 2023

As a part of its open science philosophy, MACRAMÉ is implementing high quality knowledge and data management using state-of-the-art data sharing concepts, approaches and tools and constantly improving research output/data documentation towards full implementation of the FAIR (findable, accessible, interoperable and re-usable) and FAIR for Research Software (FAIR4RS) principles. This

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MACRAMÉ Data Shepherding Part 2– Harmonisation towards a common Data Schema

January 18, 2024

In the first part "MACRAMÉ Data Shepherding – an Approach to the centralised Management of Research Information & Knowledge", the principle data management concept of MACRAMÉ were outlined, including an elaboration of MACRAMÉ's implementation of the FAIR principles for internal data sharing, and two new data management tools (i.e. (a)

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Protocols
- Access and sharing of methods
- Collection of metadate in the experimental procedure
- Tracking details on the steps performed
- Linking of methods with results
- Comparison of the experimental design
- Searchable and easy to filter database

Sample Preparation · Measurement · Data Treatment — Protocols

Original Sample · Prepared Sample · Raw Data · Processed Data

Data
- Selection and use of methods added in the protocol database
- Creation and saving of the full workflow
- Support of intra- and inter-laboratory reproducibility goals
- Documentation of all steps performed on a sample from identification to final characterisation results
- Storage and sharing of data

Schematic illustration of the interdependencies between the two main sections of a Knowledge Infrastructure (Protocols and Data).
'Metadata stewardship in nanosafety research: learning from the past, preparing for an "on-the-fly" FAIR future', T. E. Exner *et al.*, Front Phys. 2023 (11), https://doi.org/10.3389/fphy.2023.1233879.

→ https://macrame-project.eu/macrame-data-shepherding-an-approach-to-the-centralised-management-of-research-information-knowledge/

→ https://macrame-project.eu/macrame-data-shepherding-part-2-harmonisation-towards-a-common-data-schema/

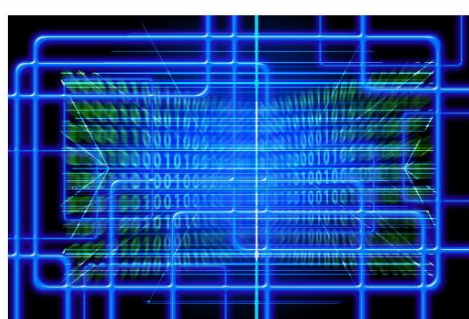# Data Collection – the MACRAMÉ Data Shepherd

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'[…] a highly topical issue in the science community: that of research data management and FAIR data.'

[Peer-Reviewer 1]

'One has to hope that the nano community reads this article and that the article gets out of the FAIR data community.'

[Peer-Reviewer 2]

'Metadata stewardship in nanosafety research: learning from the past, preparing for an "on-the-fly" FAIR future', T. E. Exner *et al.*, Front Phys. 2023 (11), https://doi.org/10.3389/fphy.2023.1233879.

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→ https://macrame-project.eu/macrame-data-shepherding-part-2-harmonisation-towards-a-common-data-schema/

# MACRAMÉ Harmonisation & Standardisation Roadmap

MACRAMÉ Harmonisation & Standardisation Roadmap – a Summary Report of five important Destinations

June 3, 2024

The MACRAMÉ Project just published an important milestone report: the 'MACRAMÉ Harmonisation & Standardisation Roadmap Summary Report for MACRAMÉ Methods and Models'-report combines and summarises the Project's activities in the field of 'Development and Advancement of Characterisation- & Test-Methods &-Protocols' (Project work package 2) with the activities pertaining to the

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... main results: A project is not an island
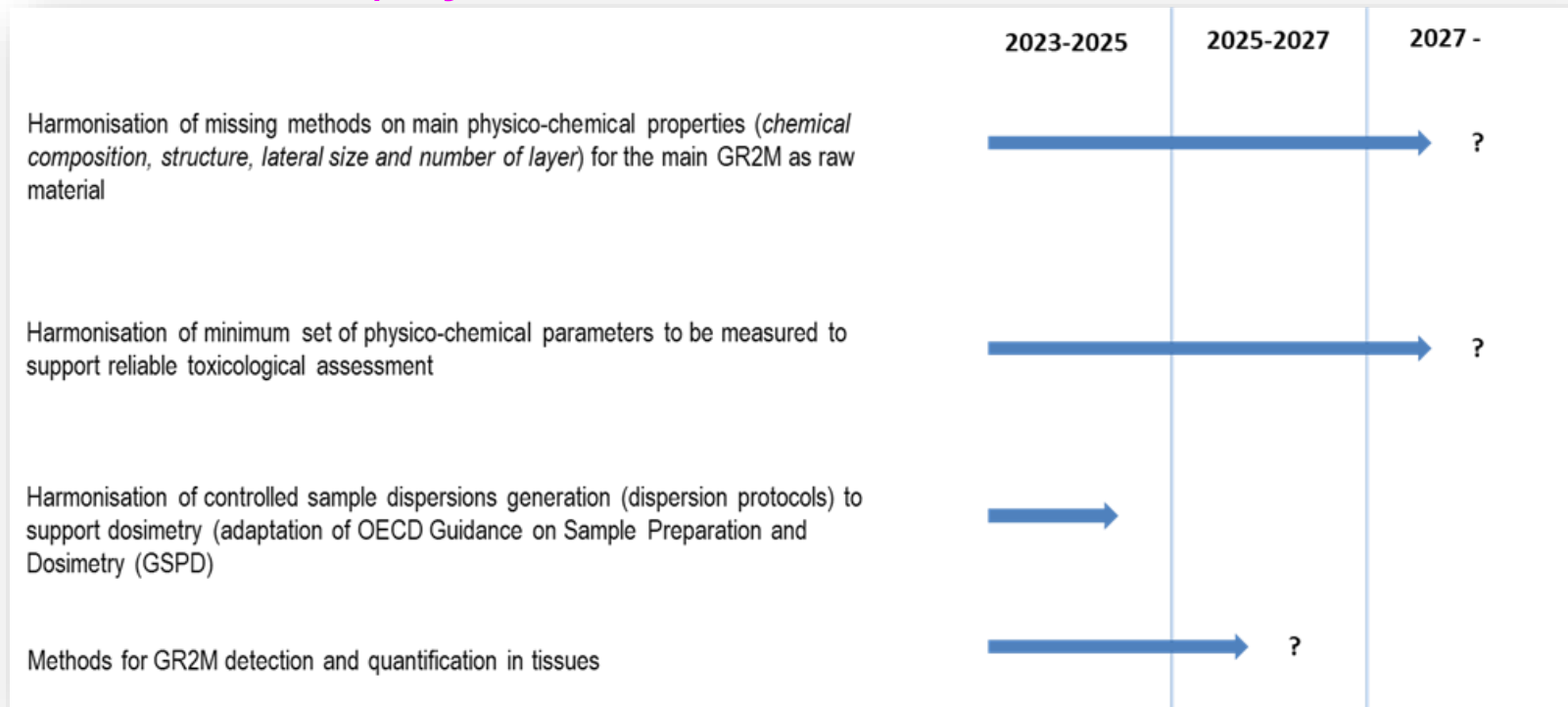
Exemplary Excerpt: Figure 5: Tentative overview of gaps identified in MACRAMÉ and tentative timeline to move them towards standardisation during and beyond the MACRAMÉ Project.

→ https://macrame-project.eu/out-now-macrame-harmonisation-standardisation-roadmap/

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Commercial break:

... go to see the Poster:

'CHIASMA, INSIGHT and PINK (ChIPs): a European approach to animal-free Safe and Sustainable by Design'

... the one-&-only on '*Tools beyond Nano*' ...

(Session 4, Wednesday, 10:30 – 11:30)

MACRAMÉ's three Sibling Projects

HORIZON-CL4-2023-RESILIENCE-01-**21**: Innovative methods for safety and sustainability assessments of chemicals and materials (RIA)

+

HORIZON-CL4-2023-RESILIENCE-01-**22**: Integrated approach for impact assessment of safe and sustainable chemicals and materials (RIA)

+

HORIZON-CL4-2023-RESILIENCE-01-**23**: Computational models for the development of safe and sustainable by design chemicals and materials (RIA)

XCHIASMA

INSIGHT

>PINK

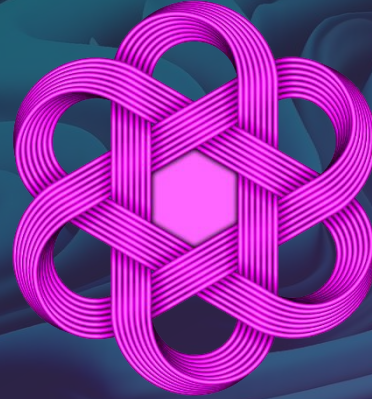>>> decreasing Experimental (lab) work >>>

>>> increasing *in silico* work >>>

Sharing of Case-Studies of specific Chemicals & Materials

Integration of shared computational Methods

total budget: € 23.2 Mio. (ca. ¾ from EU, ¼ non-EU) ♦ 37 individual Research Institutions; ♦ Jan. 2024 – Dec. 2027

MACRAMÉ

Steffi Friedrichs

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Thank you

www.macrame-project.eu

... The Context of the MACRAMÉ R&I Strategy

Harmonisation & Standardisation of (Nano)Materials – A brief History

§

'classic' Standardisation of Nanotechnology & Nanomaterials

ISO/TC229 Nanotechnologies (2005)

CEN/TC 352 Nanotechnologies (2005)

ASTM International Committee E56 on Nanotechnology (2005)

IEC/TC 113 Nanotechnologies for electrotechnical products and systems (2006)

Regulatory relevance of Nanomaterials Safety

OECD's Working Party on Manufactured Nanomaterials (2007)

NANoREG (2013 – 2017)

PROSAFE (2015 – 2017)

NANoREG II (2015 – 2019)

NanoHarmony (2020 – 2023)

Safe & Sustainable by Design (SSbD)

PARC (2022 – 2029)

SSbD Framework (by JRC) (2022)

MACRAMÉ (2022 – 2025)

CHIASMA (2024 – 2027)

INSIGHT (2024 – 2027)

PINK (2024 – 2027)

MACRAMÉ

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CHIASMA

INSIGHT

>PINK

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