Topic 3: Metrology and dose metrics for hazard and exposure assessment throughout the life cycle

State-of-the-science in Metrology & Metrics for Nanomaterials Regulation

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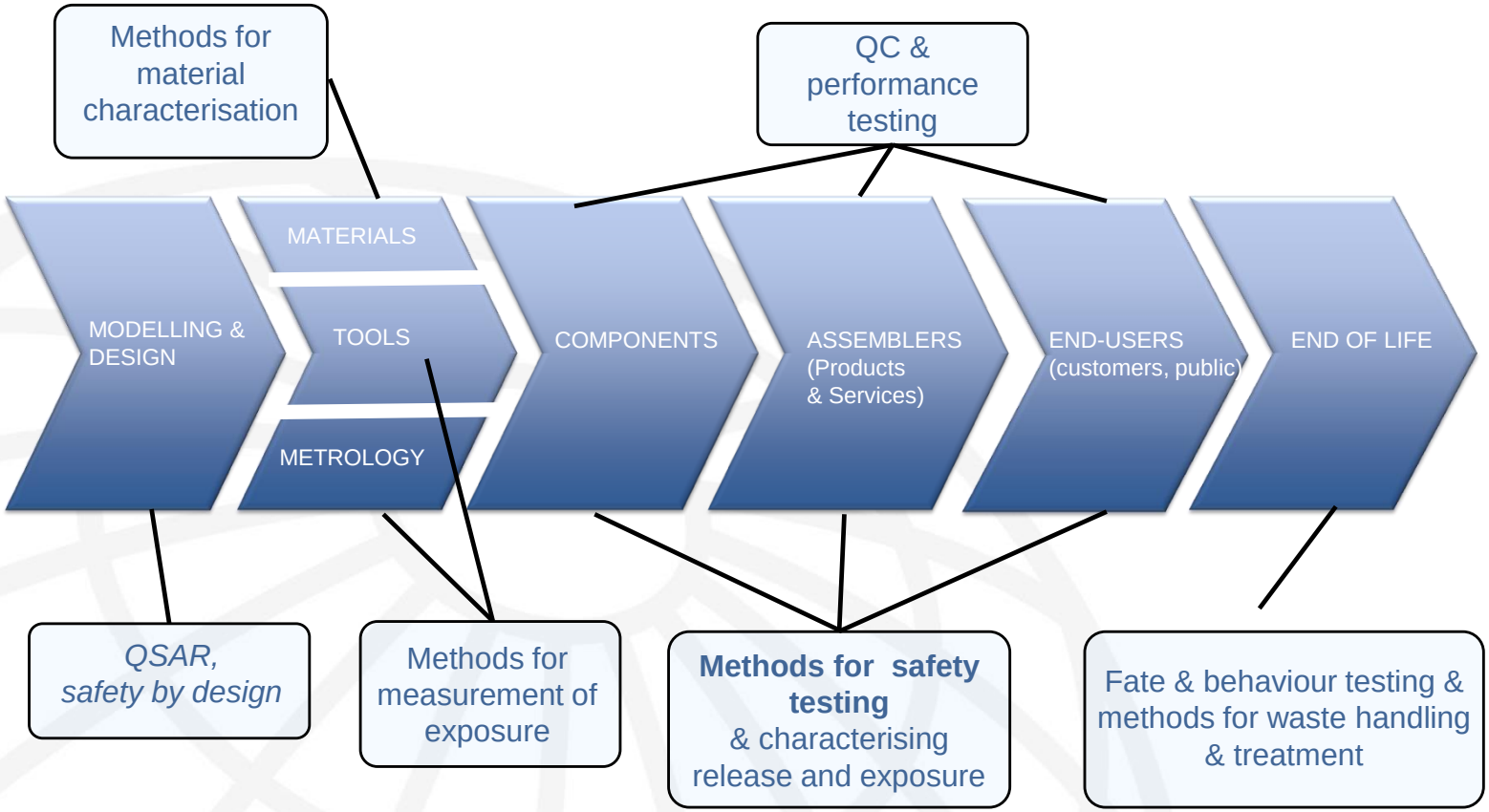
What is metrology (characterisation) data for?

- EC Regulations & Directives
  - REACH & CLP, Cosmetics, Food…
- Mandatory Reporting/Notification Schemes
  - France, Belgium, Denmark,… US,…
- Labelling requirements
- Quality control
- Product & Process R&D

Metrology along the Value Chain

Testing requirements & methods are being applied to the ‘value chain’ / ‘innovation pathways’ in the development of new technologies, materials & products:



Metrology (characterisation) in Risk Assessment

- Substance Identification (composition, structure)
- Categorisation
  - 'Concern' identification?
  - Exposure-based waiving?
- Informing the selection of techniques & interpretation of
  - benchmarked hazard assessment
  - exposure assessments
  - 'functional assays' showing the behaviour of a substance's property or properties in systems
- Facilitating consideration of read-across
- …

Building bridges between communities

- Know *what* you are trying to achieve, and *why* it's important/necessary
- Work from *solid foundations*, iteratively, starting from a beachhead
- Evolve from methods that are understood and reliable, to achieve the overall goal

Regulatory challenges (historic) for nanomaterials

- Current formal regulatory frameworks *may* not be ideally suited to identify nano-specific issues -
  - relevance of notification triggers, information requirements etc.
- Information on nanomaterials currently on the market is incomplete
  - important knowledge gaps in the toxicology, physico-chemical characteristics and exposure data, making *highly-informed* risk assessment and risk management challenging;
  - appropriate *precautionary* measures are necessary.
- A number of activities aim to improve regulation & governance of nanomaterials.

REACH Implementation Projects on Nanomaterials (RIP-oNs) - 2010

Main aim was to develop recommendations for changes to the **REACH guidance** which take account of specific issues in relation to current generation nanomaterials.

RIP-oN 2

1. Develop specific advice on how REACH information requirements on ***intrinsic properties*** of nanomaterials can be fulfilled
   - Address and advise on appropriateness of relevant test methods and outline specific testing strategies

2. Develop specific advice on the ***information needed*** for **safety evaluation and risk management** of nanomaterials
   - In particular, if information is needed beyond current REACH Information Requirements listed in Annexes VI-X.

RIP-oN 2: Sources of Information

- 89 published reports and standards from key organisations;
- 54 reports and standards under development from key organisations;
- 161 reports and publications from EU FP6/7 and other relevant international projects;
- 557 reports and publications reviewed in the ENRHES literature review (FP7 CSA review project);
- 931 additional publications from the peer-reviewed literature.

RIP-oN outcomes

Appraisal of the scientific evidence base pertaining to nanomaterials in the context of the existing REACH *process*:

- Current Articles of the REACH regulation
- Current published ECHA Guidance
- Accepted methods and available Standards

ECHA's Guidance is now much more fit-for-purpose for nanomaterials (and other particulate-based substances), but the RIP-oNs made **no appraisal** of the ***value*** of the Information Requirements to the ***outcome and benefit*** of the regulatory process.

Key considerations & recommendations in RIP-oNs: Metrics

- No unique response to the question of which is the “best” metric for nanomaterials
- Mass based metrics are embedded in regulatory testing
- At least for inhalation, surface area and number based metrics are also important in some circumstances
- Insufficient evidence for these additional metrics in relation to environmental exposure and ecotoxicology
- Measurement approaches are available
- Conversion between metrics is challenging
- Sufficient characterisation to support conversion should be encouraged

R&D Recommendations from RIP-oN 2

- Existing phys-chem IRs
  - Relative density
  - Surface tension
  - Water solubility
  - Partition coefficient
  - Flammability
  - Explosive properties
  - Granulometry
  - Adsorption / desorption
  - Dissociation constant

Data is needed to demonstrate the applicability / suitability of a test method

Review of *informative* soon-to-be-published standards

- Additional specific intrinsic properties
  - Shape
  - Surface area
  - Porosity
  - Surface energy
  - Surface chemistry
  - Surface acidity
  - Surface charge
  - Redox potential
  - Cell-free ROS/RNS production capacity

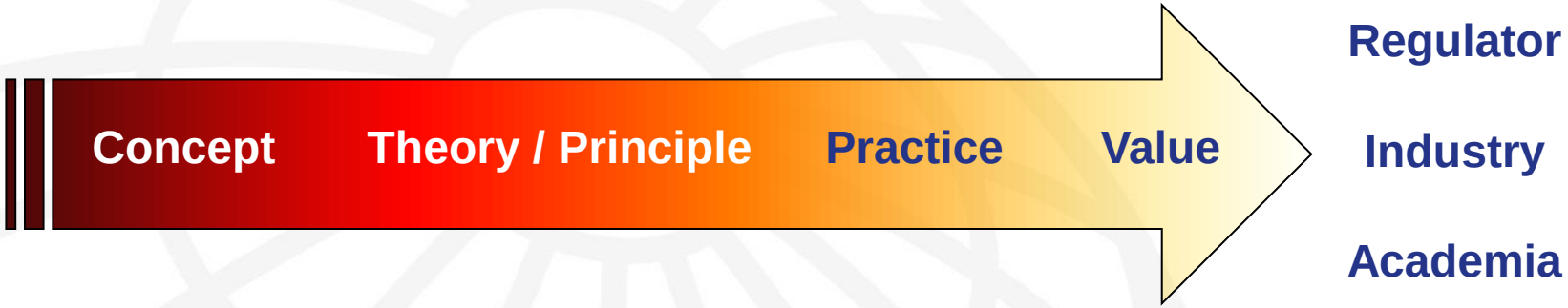
Review of *informative* soon-to-be-published standards

Fundamental research of the relationship between properties and endpoints.

- General aspects (e.g. characterisation, standards, protocols etc)

The $6M (€4.6M) questions are…

Is this data *appropriate* for risk assessment?
Can registrants *meaningfully* gather and report it?
Does it *inform* regulatory decision-making?



Developments since the RIP-oNs…

- **Publication of the EC definition of a nanomaterial**
- **EC's review of the REACH legal text**
- **Broader/deeper evidence gathering:**
  - EC Service contract reports
    - *"Scoping possible modifications across the breadth of EU safety & health at work legislation for nanomaterials" (2011, not yet published)*
    - "Scientific technical support on assessment of nanomaterials in REACH registration dossiers and adequacy of available information" (Nano Support Project - Task I)
    - "Scoping the impact on industry, consumers, human health & the environment from possible options for changing the REACH regulation" (Nano Support Project - Task II)
    - "Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 1: Compilation of information concerning the experience with the definition"
  - Public consultations
    - EC Consultation on the modification of the REACH Annexes on Nanomaterials (21.06.2013 to 13.09.2013)

Developments since the RIP-oNs…

- **Broader/deeper evidence gathering (continued):**
  - FP7 research
    - On-going nanomaterials risk projects
    - ITS-Nano
    - NANoREG
  - Experiences from Member State registers/reporting schemes

- **EC's Second Regulatory Review of Nanomaterials**

- **New ISO Standards published**

- **Outcomes from the OECD Sponsorship Programme and ongoing WPMN discussions & expert workshops**

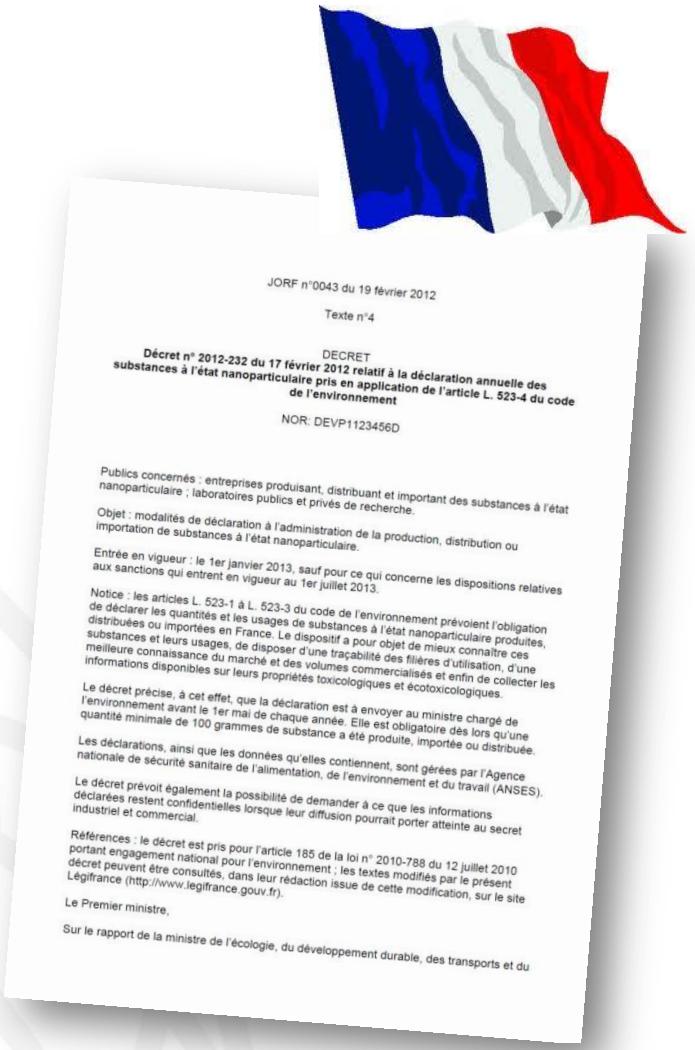
French Decree on Nanomaterials Reporting

In February 2012, the French Government introduced a national decree for mandatory reporting of nanomaterials (Décret n° 2012-232 du 17 février 2012), the first of its kind to be introduced in Europe.

The decree applies to nanomaterials on their own or included in a mixture or another material, and requires an annual declaration to be submitted to the French National Agency for Food Safety, Environment and Labor (ANSES) in May of each year, commencing from May 2013.

The declaration is mandatory as soon as 100g of nanoscale substance has been produced, distributed or imported over the previous year.

Non-compliance to this mandatory registration scheme would lead to financial penalties.



JORF n°0043 du 19 février 2012

Texte n°4

DECRET

Décret n° 2012-232 du 17 février 2012 relatif à la déclaration annuelle des substances à l'état nanoparticulaire pris en application de l'article L. 523-4 du code de l'environnement

NOR: DEVP1123456D

Publics concernés : entreprises produisant, distribuant et important des substances à l'état nanoparticulaire ; laboratoires publics et privés de recherche.

Objet : modalités de déclaration à l'administration de la production, distribution ou importation de substances à l'état nanoparticulaire.

Entrée en vigueur : le 1er janvier 2013, sauf pour ce qui concerne les dispositions relatives aux sanctions qui entrent en vigueur au 1er juillet 2013.

Notice : les articles L. 523-1 à L. 523-3 du code de l'environnement prévoient l'obligation de déclarer les quantités et les usages de substances à l'état nanoparticulaire produites, distribuées ou importées en France. Le dispositif a pour objet de mieux connaître ces substances et leurs usages, de disposer d'une traçabilité des filières d'utilisation, d'une meilleure connaissance du marché et des volumes commercialisés et enfin de collecter les informations disponibles sur leurs propriétés toxicologiques et écotoxicologiques.

Le décret précise, à cet effet, que la déclaration est à envoyer au ministre chargé de l'environnement avant le 1er mai de chaque année. Elle est obligatoire dès lors qu'une quantité minimale de 100 grammes de substance a été produite, importée ou distribuée.

Les déclarations, ainsi que les données qu'elles contiennent, sont gérées par l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES).

Le décret prévoit également la possibilité de demander à ce que les informations déclarées restent confidentielles lorsque leur diffusion pourrait porter atteinte au secret industriel et commercial.

Références : le décret est pris pour l'article 185 de la loi n° 2010-788 du 12 juillet 2010 portant engagement national pour l'environnement ; les textes modifiés par le présent décret peuvent être consultés, dans leur rédaction issue de cette modification, sur le site Légifrance (http://www.legifrance.gouv.fr).

Le Premier ministre,

Sur le rapport de la ministre de l'écologie, du développement durable, des transports et du

French Decree on Nanomaterials Reporting

Information about the properties of the nanomaterial produced, used and distributed, including:

- Chemical identification of the substance. The declarant must specify if the substance is: on its own; or included in a mixture or incorporated into a material and potentially extracted or released upon use;
- The physical state (solid, liquid, gas or powder) of any mixture;
- Commercial name (where applicable);
- Mean particle size and method used to quantify this parameter;
- Particle number size distribution and method used to quantify this parameter;
- Degree of aggregation and/or agglomeration;
- Particle shape and method used to determine this parameter;
- Description of substance coating (if applicable);
- REACH Registration number (if the substance has already been registered);
- Contaminants level (if applicable);
- Crystalline structure (if applicable);
- Surface area and method used to determine this parameter;
- Surface charge (zeta-potential and associated pH).

The $6M (€4.6M) questions (again) are…

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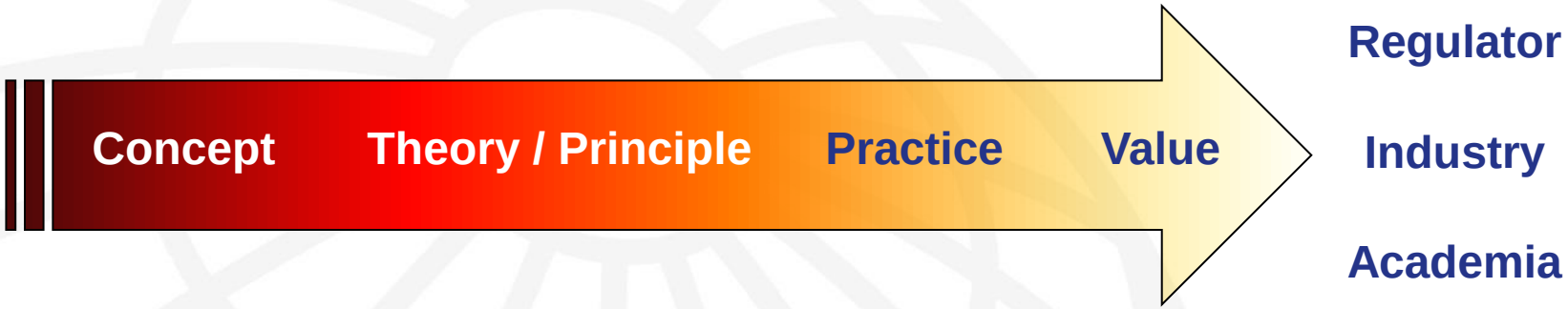
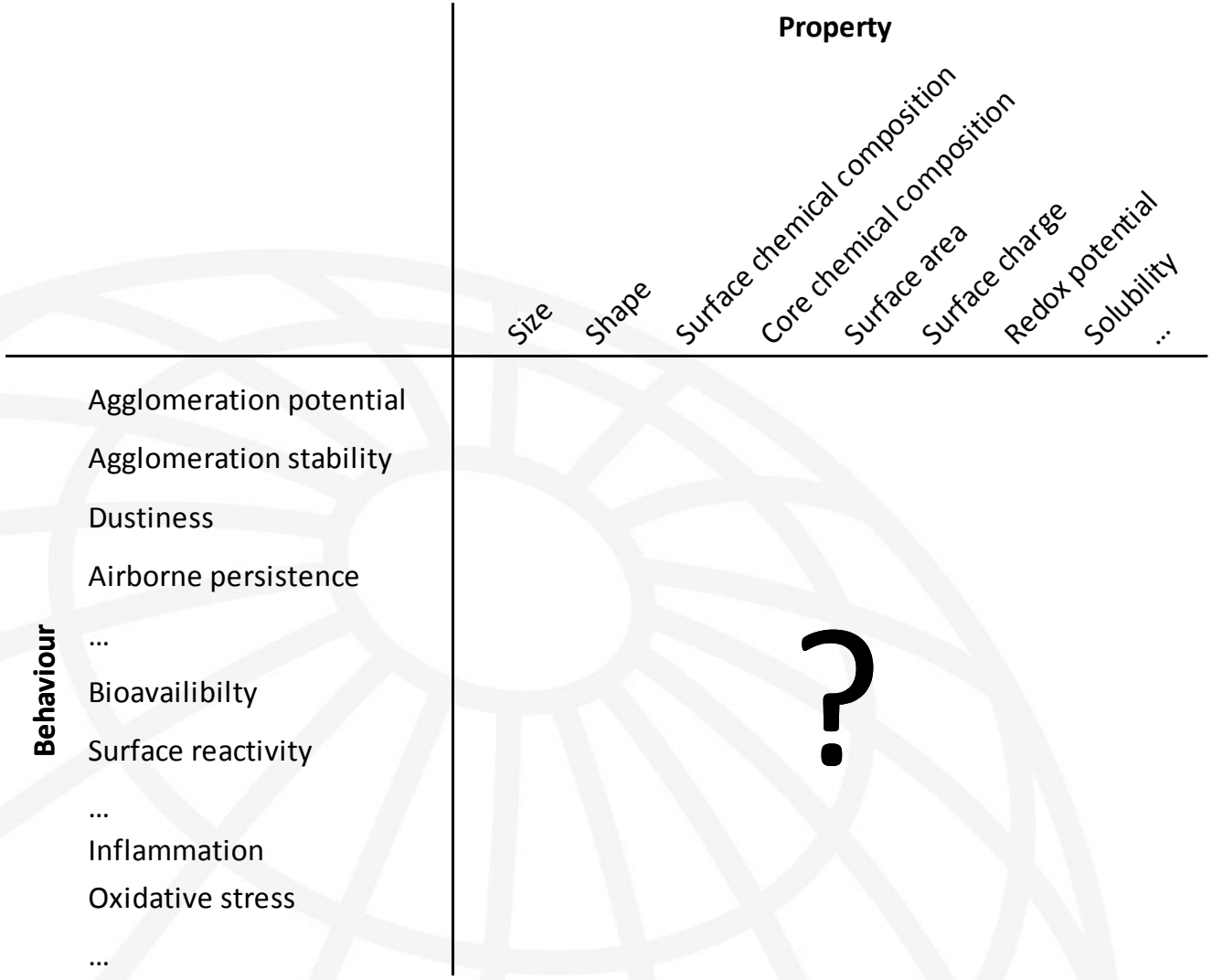


Would mapping properties *meaningfully* to behaviours build a substance profile and help inform regulatory risk assessment?



Building bridges between communities

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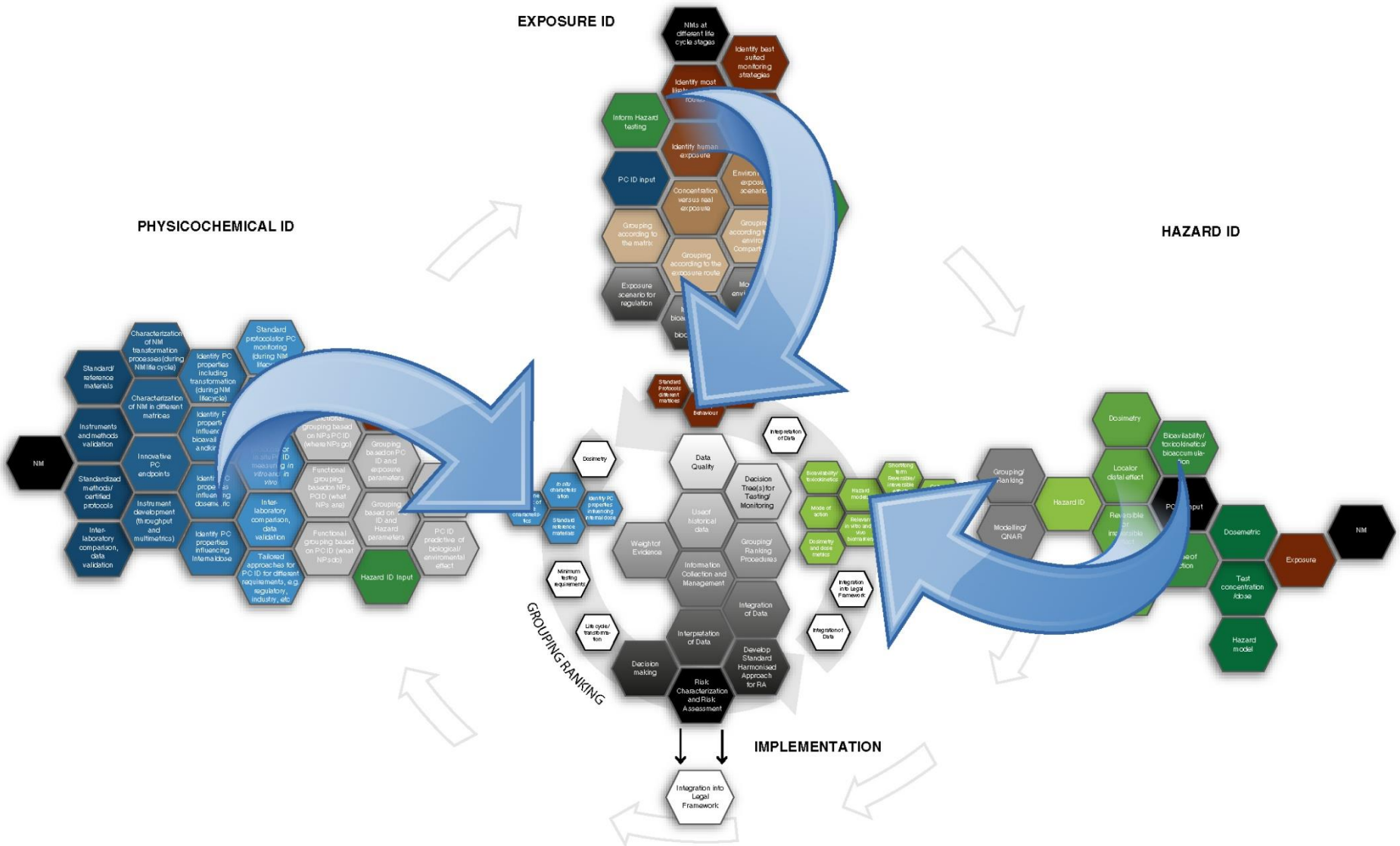
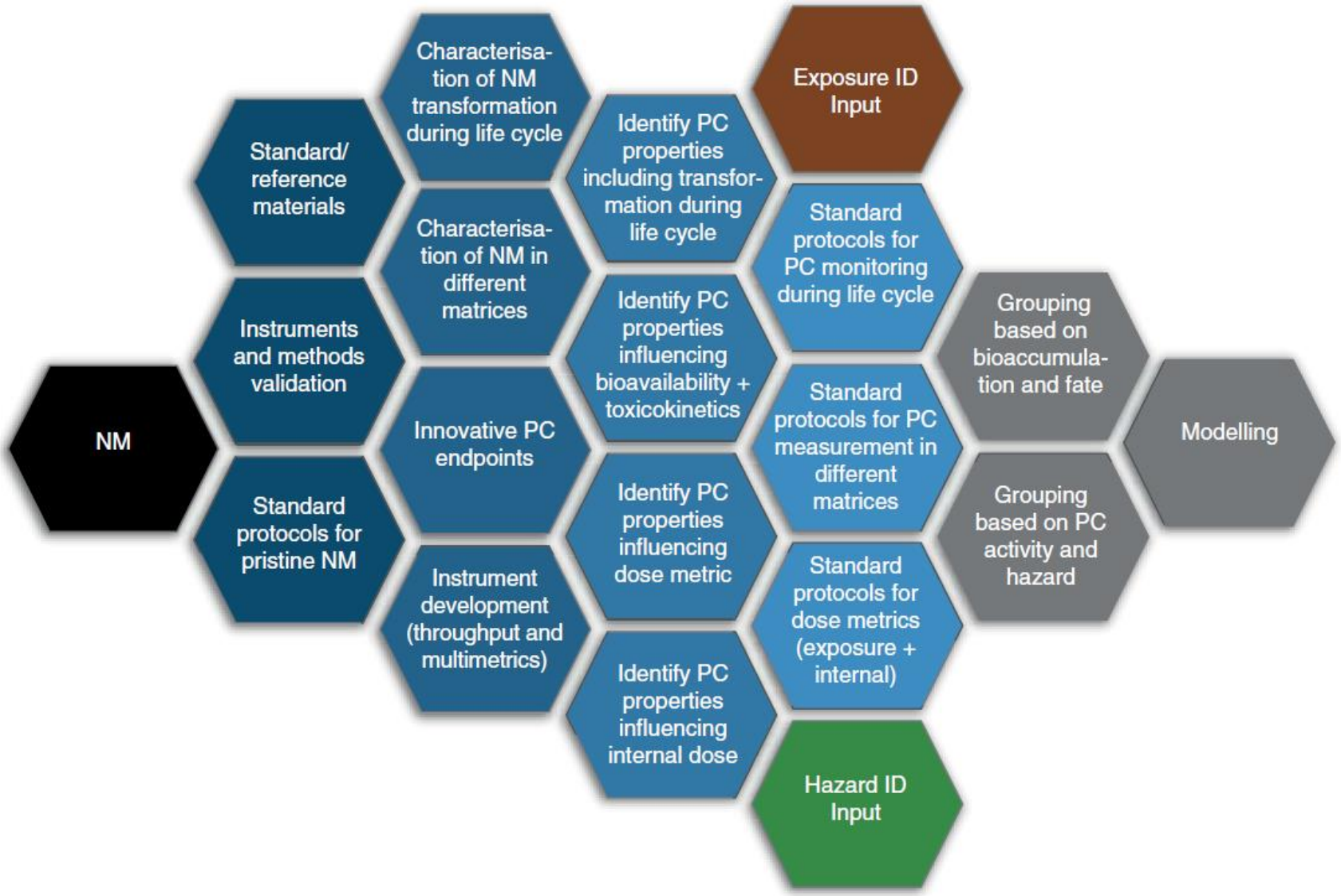
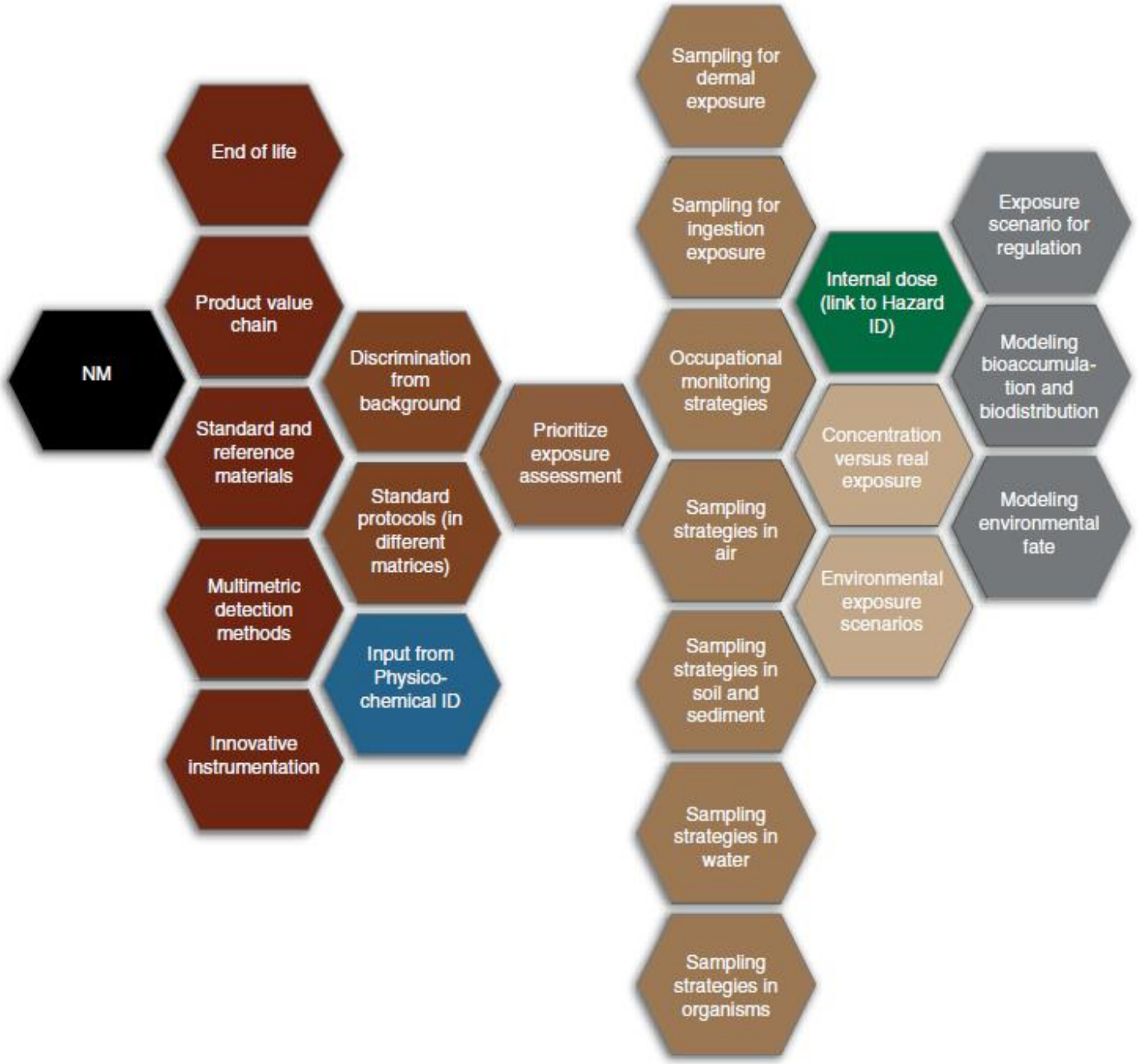
ITS-Nano: A *blueprint* for a 'bridge'

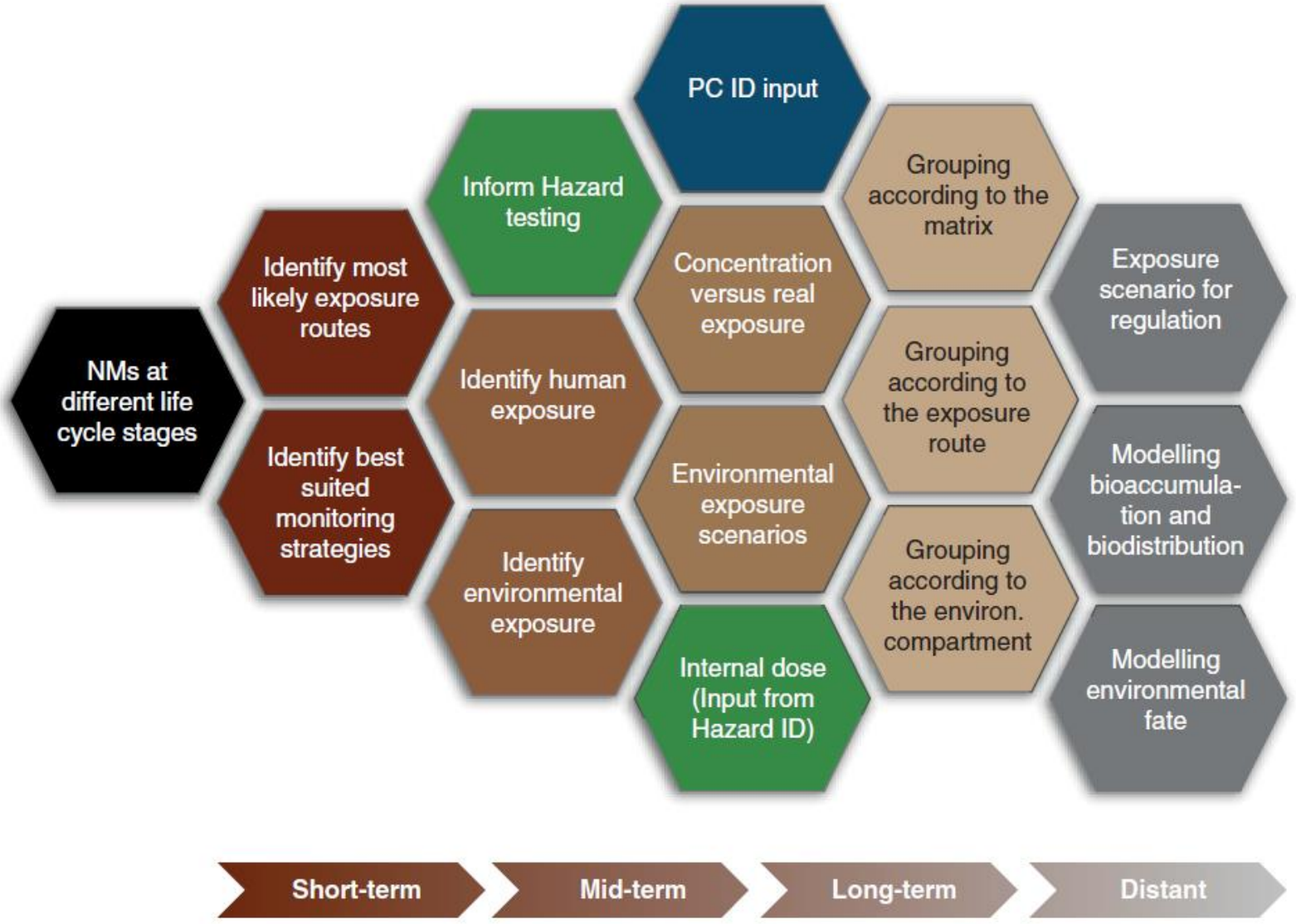


ITS-Nano: Metrology stepping-stones

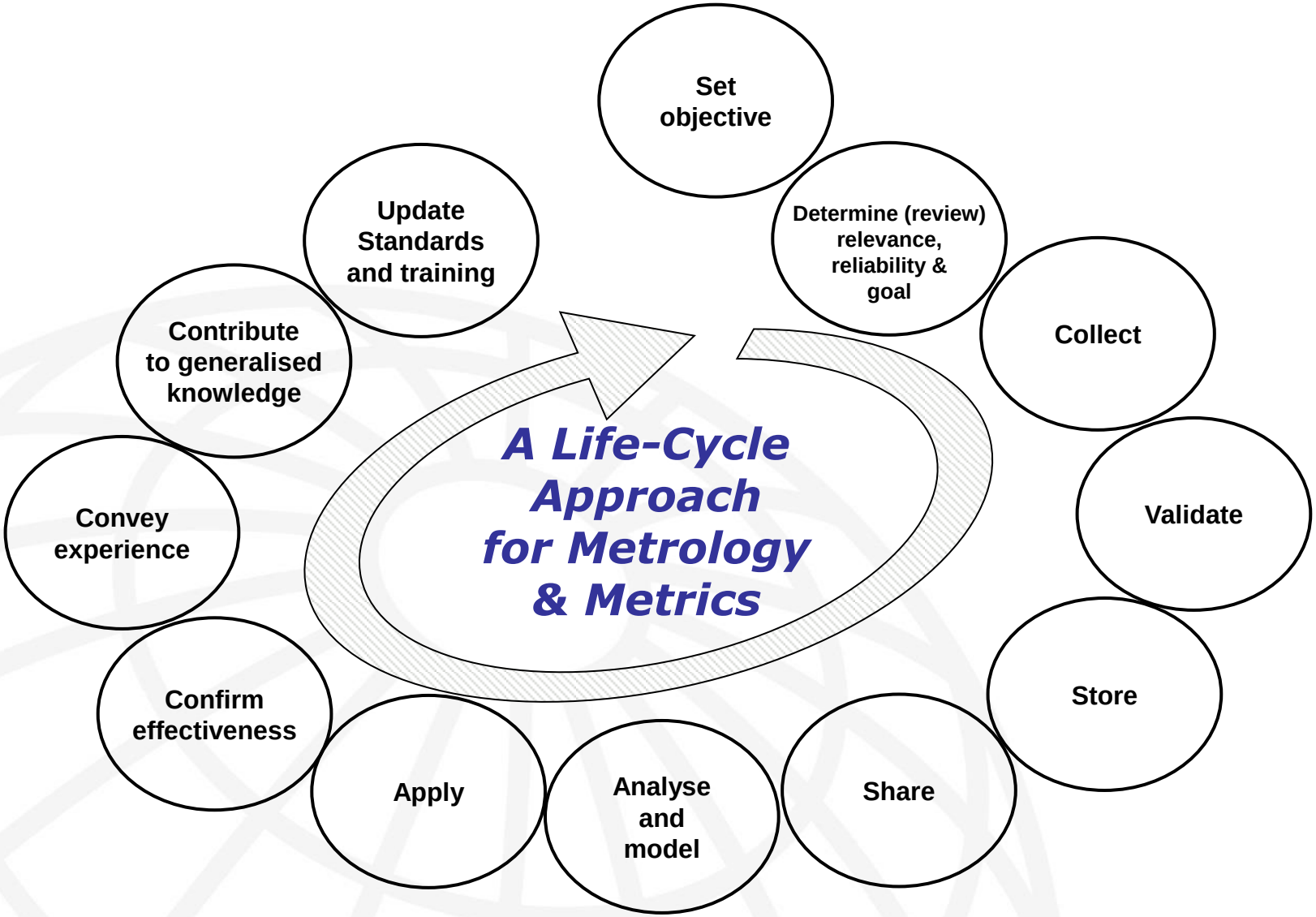



NM
End of life
Product value chain
Standard and reference materials
Multimetric detection methods
Innovative instrumentation
Discrimination from background
Standard protocols (in different matrices)
Input from Physico-chemical ID
Prioritize exposure assessment
Sampling for dermal exposure
Sampling for ingestion exposure
Occupational monitoring strategies
Sampling strategies in air
Sampling strategies in soil and sediment
Sampling strategies in water
Sampling strategies in organisms
Internal dose (link to Hazard ID)
Concentration versus real exposure
Environmental exposure scenarios
Exposure scenario for regulation
Modeling bioaccumula-tion and biodistribution
Modeling environmental fate

But does regulation want us to run before we can walk?



A model for systematically developing metrics



Adapted from Hoover and Cox, 2011

Summary

- Metrology has an essential role to play in the development of nanomaterials, not least in facilitating and integrating the interpretation of components of risk assessments.
- The aspirations of categorisation and read-across in risk assessment will depend on robust metrology.
- Data is being gathered on nanomaterials, and the experiences in doing so are emerging, but its value for regulatory risk assessment is perhaps some time away.
- It is arguable whether unlinked data on a substance's properties and behaviours can meaningfully inform regulatory risk assessment decision-making.
- A strategy for enhancing the components of nanomaterials risk assessment exists (ITS-Nano) and needs wide-spread consideration, further development of operational processes, and adoption for successful implementation.

Thank you for your attention

We can build good bridges, but can't keep them free of occasional fog!