Regulatory Research Roadmap
NanoSafety Cluster

Vicki Stone and Adrienne Sipps
v.stone@hw.ac.uk     adrienne.sips@rivm.nl
Regulator Research Roadmap Team

Input from:
Vicki Stone
Jacques-Aurelien Sergent
Enrico Bergamaschi
Susan Dekkers
Wilson Engelman
Katrin Halling
Sonja Hartl
Andrej Kobe
Niklas Luhmann?
Serli Önlü

Agnes Oomen
Adriele Prina-Mello
Juan Riego-Sintes
Phil Sayre (US EPA)
Monita Sharma
Adrienne Sips
Ulla Vogel
Tom van Teunenbroek
Martie van Tongeren
Wilson Wengelmann
Regulatory Research Roadmap Purpose

• To identify and structure the research required to deliver effective regulation of nanomaterial safety
• Including
  – Consumer
  – Occupational
  – Sector specific issues
• Excluding
  – Nanomedicine
Stage 1 – Identifying activities relevant to the RRR

- ITS-NANO hexagon diagrams to illustrate research prioritisation (Vicki Stone)
- NANoREG gap analysis (Susan Dekkers)
- US research and regulatory development (Phil Sayes EPA)
- MARINA tiered approach for RA (Agnes Oomen)
- Nanonext.nl (Adrienne Sips)
  - Dutch nanotechnology development programme
  - Risk Analysis and Technology Assessment (RATA)
- NANoREG questions relevant for regulators (Juan Rigo-Sintes)
- Safety-by-Design – SUN and NanoGuide (Vicki Stone)
- REACH (Juan Rigo-Sintes, Wim De Coen)
- EU occupational and safety at work regulatory input (?)
- Educational framework (?)
Research Prioritisation to deliver an Intelligent Testing Strategy for Engineered Nanomaterials

http://www.nano.hw.ac.uk/research-projects/itsnano.html

Stone et al., Particle and Fibre Toxicology 2014, 11:9
Physicochemical Priorities

- Characterisation of NM transformation processes (during NM life cycle)
- Standardisation of reference materials
- Instruments and methods validation
- Standardised methods/certified protocols
- Inter-laboratory comparison, data validation
- Innovative PC endpoints
- Characterisation of NM in different matrices
- Instrument development (throughput and multimetrics)

- Identify PC properties including transformation (during NM life cycle)
- Identify PC properties influencing bioavailability and kinetics
- Identify PC properties influencing dose metric
- Identify PC properties influencing internal dose
- Tailored approaches for PC ID for different requirements, e.g., regulatory, industry, etc.
- Functional grouping based on NMs PC ID (what NMs go)
- Functional grouping based on NMs PC ID (what NMs are)
- Functional grouping based on PC ID (what NMs do)
- Functional grouping based on PC ID and Hazard parameters
- Hazard ID input

- Standard protocols for PC monitoring (during NM life cycle)
- Standard protocols for PC measurement in different matrices
- Standard protocols for in situ PC ID measuring in vitro and in vivo
- Inter-laboratory comparison, data validation
- Tailored approaches for PC ID for different requirements, e.g., regulatory, industry, etc.
- Hazard ID input

Diagrams also generated for Hazard ID and Exposure ID
ITS-NANO hexagon approach

Regulatory research priorities

Core priorities

Product to market research priorities

Current position

Future
The Plan

- Convert NANoREG Regulation Research Gap analysis into a hexagon diagram.
- Colour code the hexagons by identifying which research priorities are relevant or common to both road maps.
- Interrogate the diagram using the Regulatory Questions from NANoREG and edit as appropriate.
- Interrogate the diagram in relation to current EU regulations (in particular REACH) and edit as appropriate.
- Compare and contrast the hexagon diagram generated with US activities and edit as appropriate.
- Generate one paragraph of text to outline each hexagon/priority and link to the relevant references, reports and projects.
- Put together the final text that introduces the roadmap, provides the roadmap diagram, the short description for each hexagon/priority with references, and the final conclusions.
Implement nano-relevant RA strategies in regulatory frameworks

- Develop nano-relevant RA strategies (interpolation)
- Develop nano-relevant RA strategies (grouping)
- Develop nano-relevant RA strategies (exptrapolation)
- Develop nano-relevant RA strategies (read across)

Identify characteristics that influence:
- Release
- Fate and kinetics
- Exposure
- Hazard

Generating high quality data
- Exposure and kinetics data using representative NMs
- Hazard data using representative NM
- Exposure data using representative NMs

Understanding of uncertainty of current data for:
- Risk assessment
- Decision making
- Risk governance

Finalisation of an Intelligent Testing Strategy

Interim Regulations I (or Guidelines)

Refinement of the definition to relate to nano-relevant risk

Implementing relationship between physchem and NM behaviour into RA

Implementing relationship between physchem and NM behaviour into RA

Ideal regulatory approach
RRR diagram so far

• 50 Research priority hexagons identified
• 21 methods
• 11 data generation
• 16 Refinement of RA strategies
• 1 Identify nano-relevant safety issues – key decision point

• 1 implement nano-specific RA strategies in regulatory frameworks
• 3 interim regulations generated over time lead to a final fourth ‘ideal regulatory approach’
We can’t wait 15 years before identifying and acting upon nano-relevant regulation needs…….

Regulatory approaches could increase in sophistication with time as the knowledge base increases - ‘something is better than nothing’
### Generalisation of a solar definition

A clear definition of nanomaterials is necessary to enable a well-structured, accurate and consistent approach to the assessment and management of these materials. In order to simplify understanding and communication, a clear definition of nanomaterials is essential.

The European Commission (EC) published a report on "Nano- and Non-Nano-Based Materials: A Guide for Practitioners" in 2012. This document provides guidance on the identification and classification of nanomaterials, as well as the development of a risk assessment framework. The guidance is intended to ensure consistency and comparability across different applications and jurisdictions.

The guidance highlights the importance of considering the specific characteristics and properties of nanomaterials, including their size, shape, composition, and surface chemistry. It also emphasizes the need to consider the potential exposure pathways and the potential impact on human health and the environment.

### Standard methods for NM preparation for toxicity and effects studies

There is a need for standard methods for testing nanomaterials, particularly for toxicological and environmental assessments. Such tests are necessary to determine the potential risks associated with exposure to nanomaterials. The standard methods aim to provide a consistent and reproducible approach to testing, allowing for better comparison and interpretation of results.

#### Potential effects of nanomaterials

- **Health effects:** Long-term exposure to nanomaterials may lead to adverse health effects, including respiratory tract irritation, skin sensitization, and systemic toxicity. The potential for accumulation and long-term retention in the body remains a concern.
- **Environmental effects:** The release of nanomaterials into the environment can have significant implications for ecosystems and human health. The potential for bioaccumulation and the impact on biodiversity need to be considered.

#### Strategies for risk management

- **Engineering controls:** Implementing engineering controls, such as local exhaust ventilation systems, can help reduce exposure to nanomaterials. This is particularly important in workplaces where nanomaterials are handled directly.
- **Personal protective equipment:** Providing adequate personal protective equipment (PPE) is crucial for protecting workers from direct contact with nanomaterials. PPE should be selected based on the specific hazards and the level of protection required.
- **Training and awareness:** Providing training and awareness programs for workers can help reduce the risks associated with nanomaterials. This includes educating workers about the hazards and proper handling practices.

### Finalization of an intelligent testing strategy

- **Validation of test methods:** Ensuring the accuracy and reliability of test methods is essential for obtaining meaningful results. This involves regular validation and calibration of test equipment and procedures.
- **Interpretation of results:** Interpreting the results of tests requires a clear understanding of the specific test methods used and the implications of the results. This is crucial for making informed decisions about the potential risks and benefits associated with nanomaterials.

### Incorporating transformation into RA and regulatory frameworks

- **Regulatory harmonization:** Efforts to harmonize regulatory frameworks across different jurisdictions can help ensure consistent and comparable risk assessments. This is particularly important for nanomaterials, where the potential for global use is high.
- **Public engagement:** Engaging with the public and stakeholders is crucial for ensuring that regulatory frameworks are developed in a way that aligns with societal values and priorities.

### Strategies for RA of novel NPs

- **Risk assessment:** Conducting thorough risk assessments for new nanomaterials is essential for identifying potential risks and developing appropriate regulatory strategies. This involves considering the specific characteristics and properties of the nanomaterials, as well as their potential exposure pathways.
- **Risk management:** Developing and implementing effective risk management strategies is critical for minimizing the potential risks associated with nanomaterials. This includes the use of engineering controls, personal protective equipment, and training programs.

### Implement nanoscale-focused RA strategies into regulatory frameworks

- **Adaptation of existing frameworks:** Many existing regulatory frameworks are not fully equipped to address the specific characteristics and properties of nanomaterials. This requires adaptation and modification of existing frameworks to ensure they are effective for nanomaterials.
- **Proactive risk management:** Proactive risk management strategies can help prevent potential risks before they occur. This involves identifying and addressing potential risks at an early stage, before they have a significant impact on human health or the environment.
Text requirements

• Potential authors have been identified for all missing research priorities

• Each section needs to
  – Clarify why it is a research priority
  – Clarify what research is already encompassed within the priority
  – Generate recommendations relevant to the priority
  – Provide links to further information
Example

Generation of a clear definition – Why?

A clear definition of nanomaterial should
• be scientifically driven (i.e. evidence based),
• exhibit a well-defined scope
• be possible to implement
• be as uniform as possible across different legal frameworks and global locations, in order to prevent that a material is regarded as a nanomaterial in one framework and not in another.
Example

Generation of a clear definition – What?

The European Commission (EC) published a recommendation in 2011 on the definition of nanomaterial (2011/696/EU):


Most probably the most distinguishing aspect of the EC nanomaterial definition is the use of particle size distributions based on the numbers of particles, and not on the mass or volume of the particles, as the main classification feature.

Lately (August 2014) Joint Research Centre Institute for Reference Materials and Measurements published the second review report namely, Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 2: Assessment of collected information concerning the experience with the definition:

Example

Generation of a clear definition – Recommendation

An attempt by different regulators to align their definitions (e.g. via an OECD workshop) would be helpful.
Next steps

• Finish first draft of report for circulation to cluster members
• Interrogate the diagram using the Regulatory Questions from NANoREG and edit as appropriate.
• Interrogate the diagram in relation to current EU regulations (in particular REACH) and edit as appropriate.
• Compare and contrast the hexagon diagram generated with US activities and edit as appropriate.
Nanocluster input

• Next draft will be circulated for comment in April
Regulator Research Roadmap Team

Acknowledgements

Input from:
Vicki Stone
Jacques-Aurelien Sergent
Enrico Bergamaschi
Susan Dekkers
Wilson Engelman
Katrin Halling
Sonja Hartl
Andrej Kobe
Niklas Luhmann?
Serli Önlü

Agnes Oomen
Adriele Prina-Mello
Juan Riego-Sintes
Phil Sayre (US EPA)
Monita Sharma
Adrienne Sips
Ulla Vogel
Tom van Teunenbroek
Martie van Tongeren
Wilson Wengelmann