The NANoREG Project

A common European approach
to the regulatory testing of nanomaterials

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Presenter: Keld Alstrup Jensen (NRCWE)

NANoREG Partners

Total budget ca. 50 Mio €
(ca. 67.5 Mio $); 20% from EU

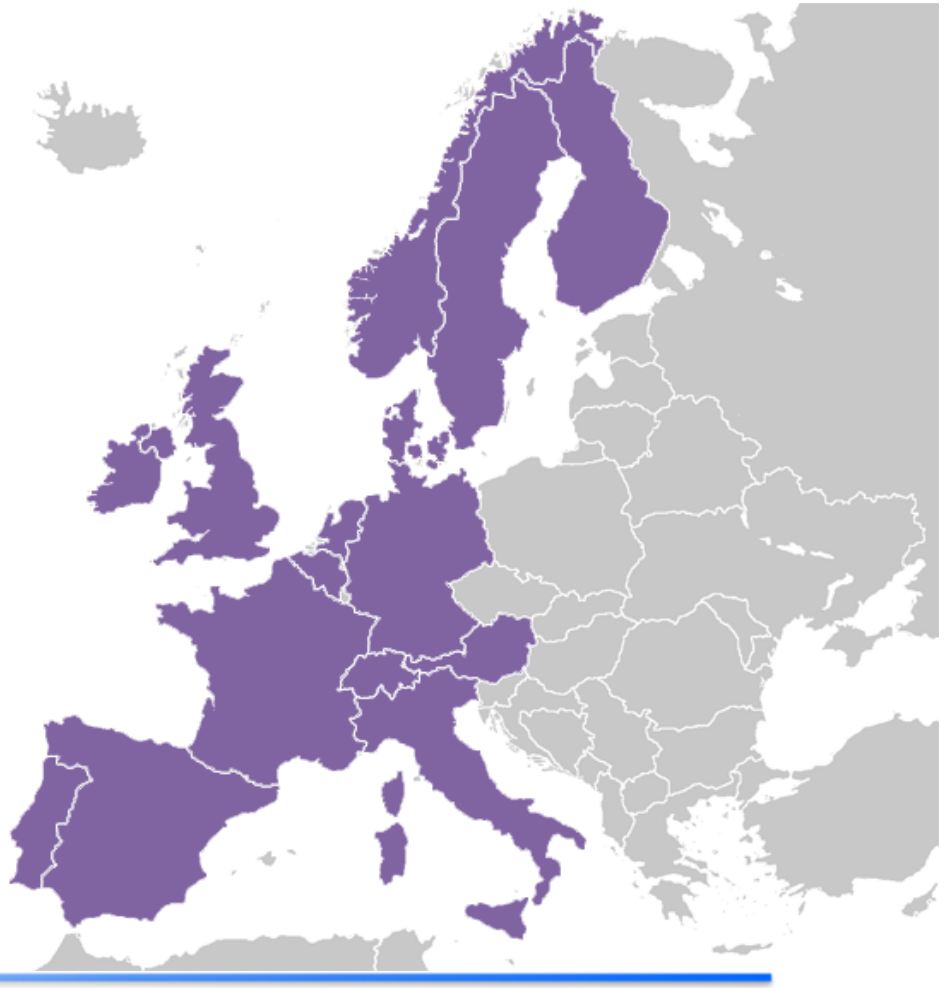
Project duration: 42 Months
(started March 2013)

61 partners from
15 European countries

13 are EU member states
(AT, BE, DE, DK, ES, FI, FR, IR, IT, NL, PT, SE, UK)
2 associated states
(CH, NO),
and 1 PAN-EU JRC

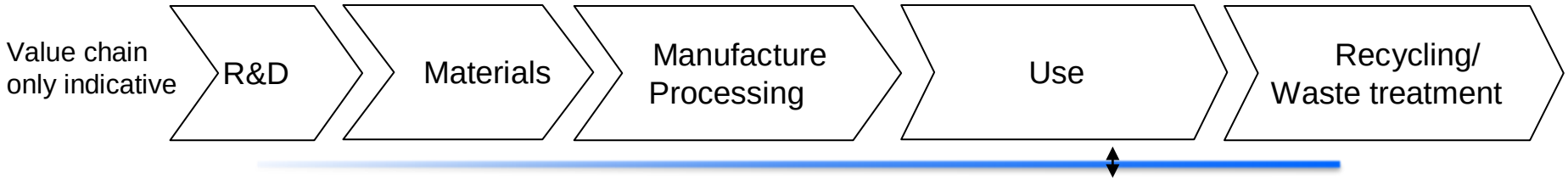
Incoming: TK

„International“ collaboration

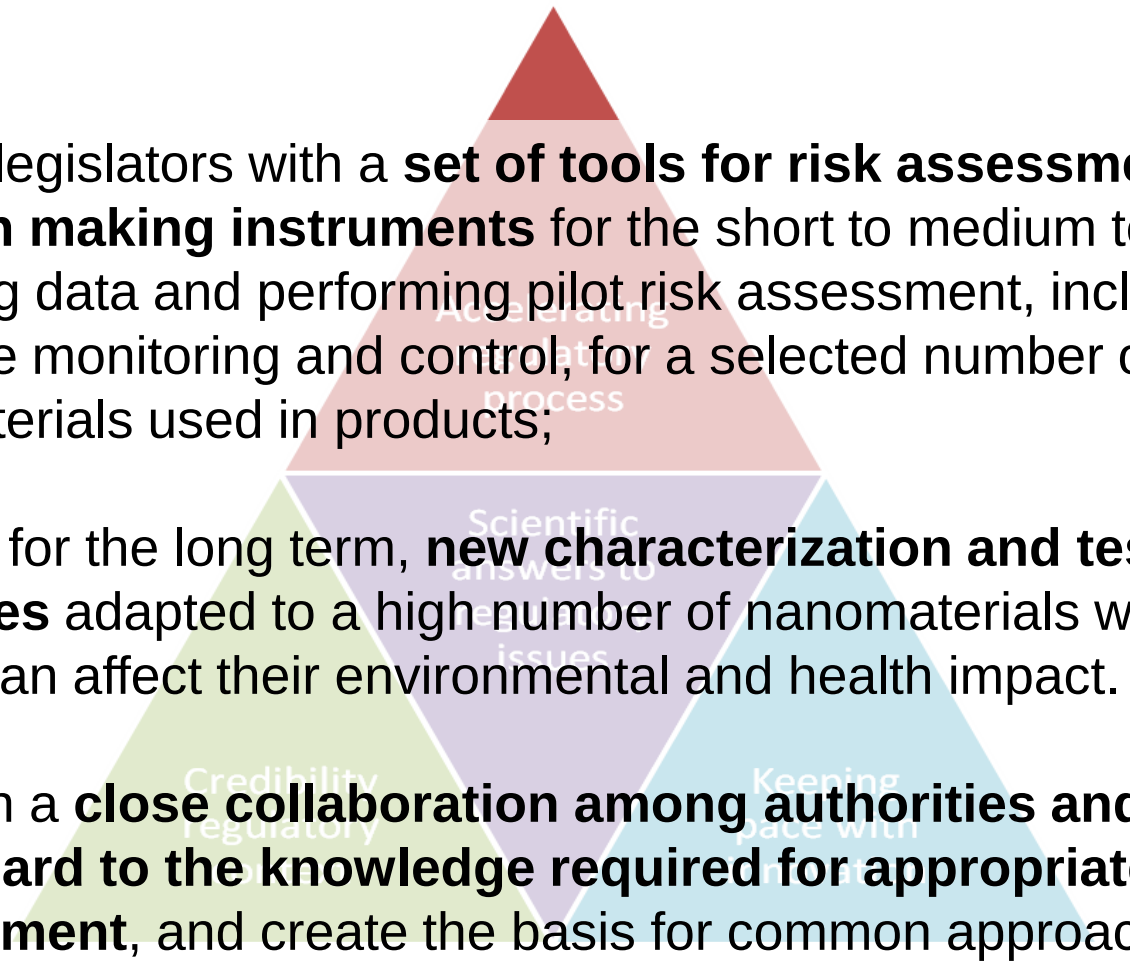


Basic data

- A project intended to combine the “all” aspects of **societal needs, innovation, exploitation & industry**
- **Structured to deliver answers on regulatory questions** coming from the **member states and organization (e.g., OECD WPMNM)**
- Specific focus will be on **the nanosafety methodology**
- Aim is to **identify, harmonize, and apply “reliable” methods** for characterization, testing, risk assessment and management
- Aim is to establish a **grouping paradigme for MNM based on phys-chem and toxicity** to enable faster, but still reliable risk assessment
- Lessons and demonstration will be made through NANoREG **Value Chain Studies**



Overall objectives



- Provide legislators with a **set of tools for risk assessment and decision making instruments** for the short to medium term, by gathering data and performing pilot risk assessment, including exposure monitoring and control, for a selected number of nanomaterials used in products;

- Develop for the long term, **new characterization and testing strategies** adapted to a high number of nanomaterials where many factors can affect their environmental and health impact.

- Establish a **close collaboration among authorities and industry with regard to the knowledge required for appropriate risk management**, and create the basis for common approaches, mutually acceptable datasets and risk management practices.

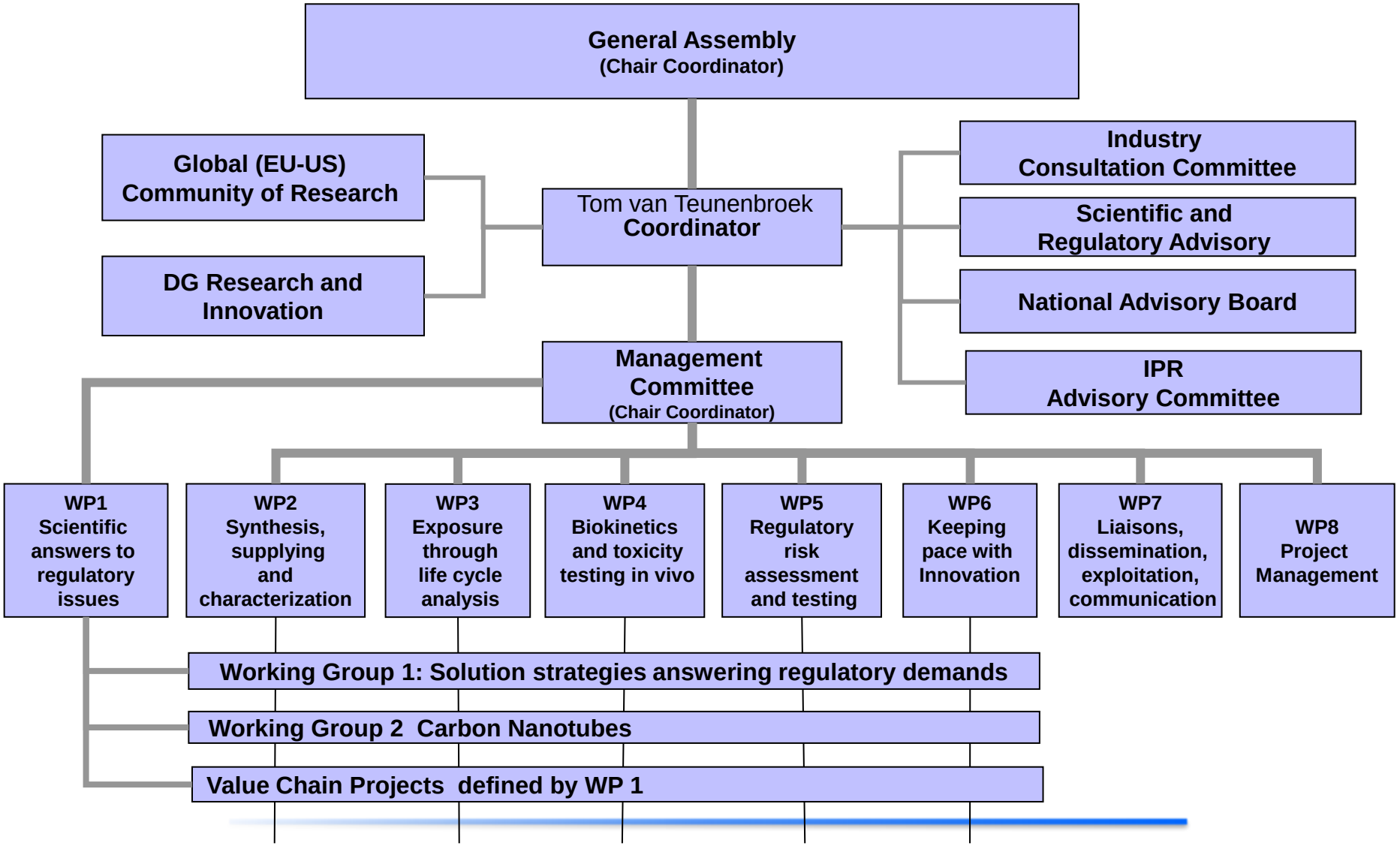
Main expected results and impact

- Will **contribute to a safe and controlled market** entrance of new nanomaterials and nanomaterial based products
- Help **fill the gaps and shortcomings in current evaluation methods** for new materials
- Include risk analysis in the start phase – **promote Safe by Design**
- Support an EU wide **integrated risk policy**
- Aim: find common **denominator for implementing guidelines**
- Aim: **Develop or modify SPSF** (Standard Project Submission Form) procedures and **TGs (Technical Guidelines)**

Grouping, regulating, and risk management

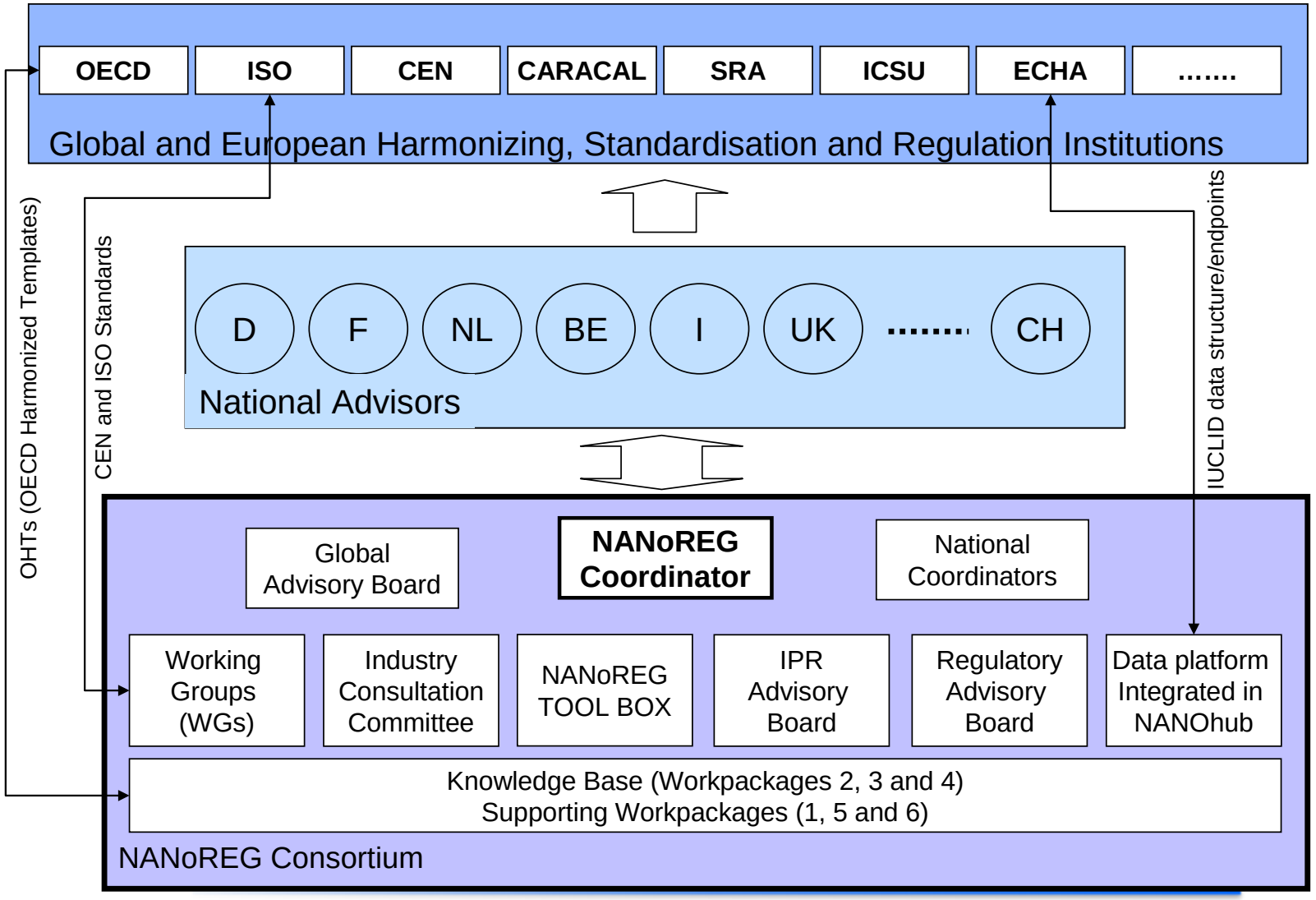
NANoREG's Organisational Structure

A common European approach to the regulatory testing of nanomaterials



NANoREG's European/global workflow

A common European approach to the regulatory testing of nanomaterials



Global Position

- Already forms a EU contribution to the **EU-US axis on global regulation of nanomaterials**
- Strong **interest shown by several OECD countries** to participate on the basis of their own financial support – **Japan, Korea, Australia, Canada, Turkey**
- Strong **interest shown by several other countries** to join on an own cost basis, now under evaluation – **China, Russia, Brazil**
- Links to other organisations (**ECHA, OECD, ISO,** etc)
- **Links and collaboration with ongoing projects** and initiatives based on areas of common interest:
  - FP7: MARINA, GUIDENANO, SUN, NANOVALID, NANOFUTURES
  - CEFIC-LRI project on grouping (upcoming),
  - PEROSH (DUSTINANO NEN/CEN Mandate 416),
  - OECD WPMN activities,
  - US-CEINT (U.S. Life Cycle Inventory (LCI) Database)

Expected Results, Impact and Uptake from the individual WPs

NANoREG's Organisational Structure

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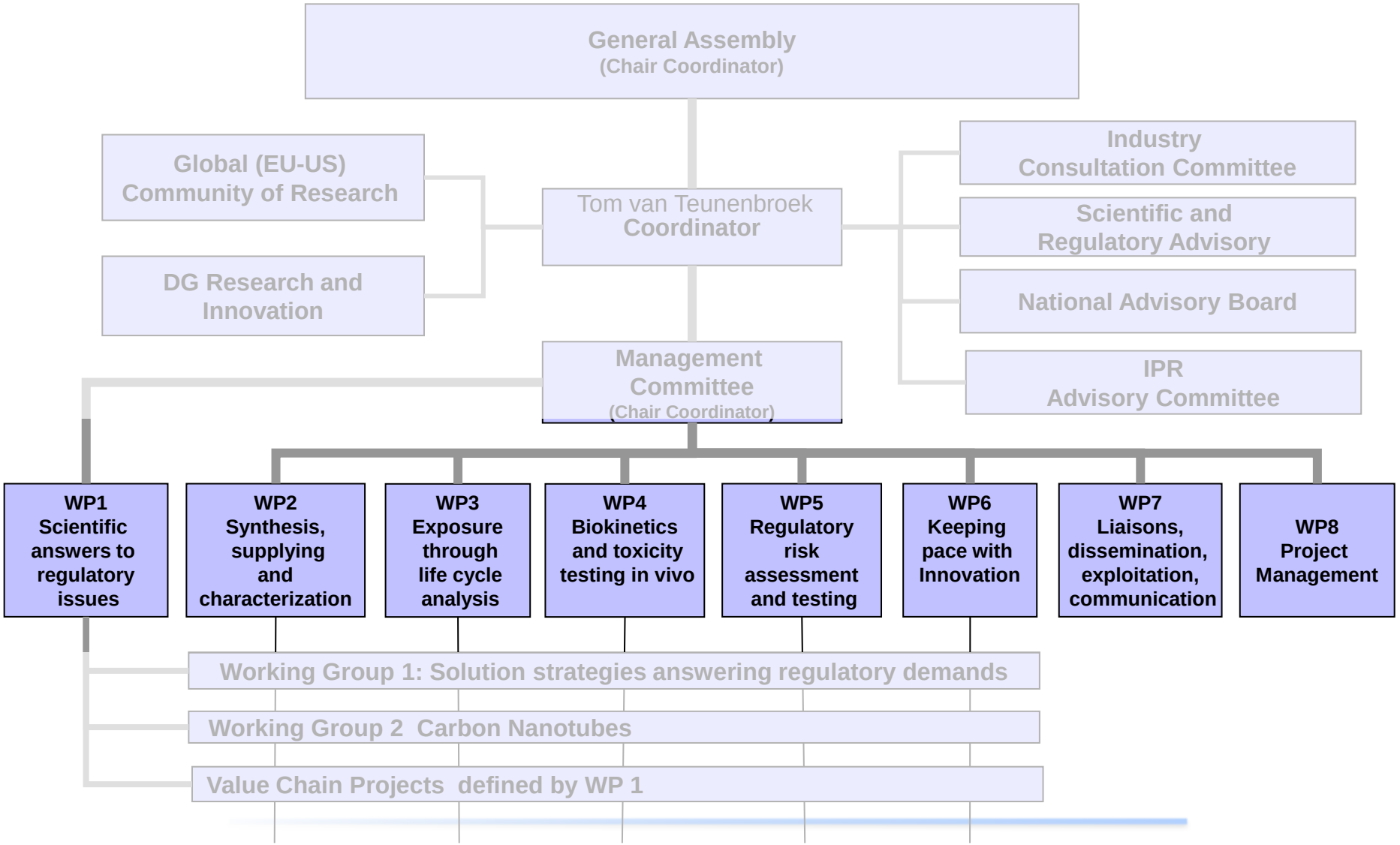


Main objectives of WP1

- **Identify, formulate and prioritize issues/questions regarding regulatory safety assessment and management of MNM as demanded from relevant authorities and stakeholders**
- **Formulate answers to selected issues/questions using information collected/generated by WP2 to WP6**
- **Ensure an iterative development of answers to regulatory questions**
  - **Consolidates the information produced by the other WPs in order to develop:*an* *overall framework* to address safety of nanomaterials**
  - **Establishes a *toolbox* to support the application of the framework**
  - **Establish a *data platform* to integrate NANoREG and other intitiatives**

In close collaboration with
WP7 (**Karl Höhener (TEMAS, CH)**): Liaisons, dissemination, communication)

Regulatory questions addressed

Regulatory question
1. Measurement and characterization: ID according to EC definition
2. Measurement and characterization: Characterization through LCA
3. Characterization and transformation: After entry into body and the environment
4. Metrology and dose metrics (for Risk Assessment); Hazard, exposure, LCA
5. Extrapolation and grouping: Investigate read-across from bulk or grouping due to properties, expo, MoA
6. Fate, persistence and long-term effects: MN (+coated) in humans, environment, environmental species, the food chain; link to bulk?
7. Kinetics and fate, determination: How and when should information on absorption be generated and used for hazard assessment?
8. Kinetics and fate, extrapolation: May kinetics and fate be predicted and used for grouping/read across for hazard assessment.
9. Mode of action: Which PC properties drive MN exposure and affect biological systems and should be known for risk assessment?
10. Hazard: Which methods should be used to assess the human and environmental toxicity?
11. Exposure: What are the main determinants for occupational and consumer exposure
12. Exposure: How should human and environmental exposure be assessed in practice?
13. Exposure and life cycle analysis: What scenarios may cause exposure, SOPs for MN release tests (powders/matrices)
14. Risk Assessment: NOEL or benchmark dose levels of long-term (low dose) exposures; ability to predict from acute and sub-acute tests
15. Risk Management: Exposure reduction, applicability of exisiting risk management measures, applicability of existing control banding tools.
16. Health surveillance: Feasability of biological monitoring or health surveillance
Transfer to regulatory system
Transfer to standardization and test guidelines

Main objectives of WP2

Synthesis and procurement

- availability and key characteristics of more than 60 MNM

Identification of MNM according to the EC regulatory definition

- number size-distribution, VSSA, MN categorization and nomenclature

NM Characterization SOPs for regulatory purposes

- SOPs supporting key OECD TGs and potential future methods

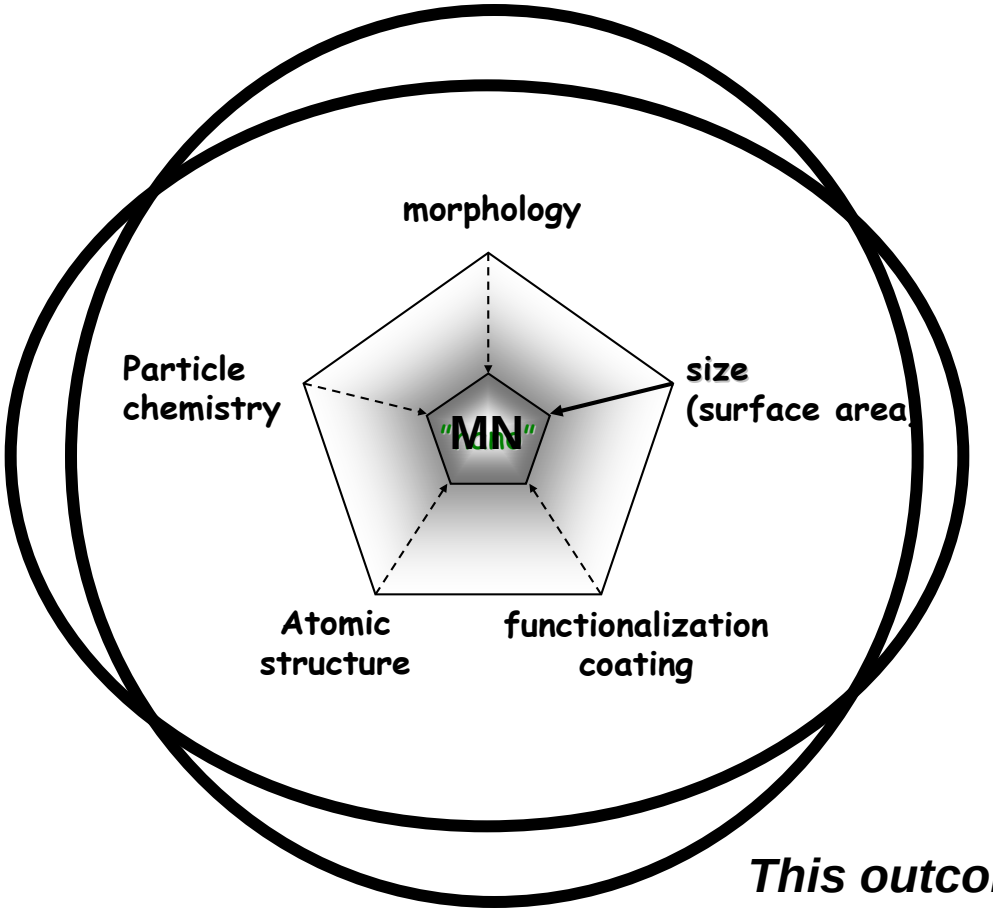
Test item preperation, exposure, dose and fate for regulatory purposes and toxicology

- in vivo inhalation and performance of selected in vitro and ecotox preperation protocols

Potential WP2 impact
SOPs for regulatory characterization needs

adsorption capacity (protein and organics)

Solubility in biofluids/biodurability



Reactivity (pH, Eh, ROS)

SOPs for EC definiiton of MNM
SOPs for revision of OECD TGs
SOPs for new CEN or TGs
SOPs for test item preperation
Methods for in vivo testing
Methods for in vitro testing
Methods for ecotox testing

<u>Intended uptake</u>
Transfer to NANoREG WPs
OECD
CEN
ISO
……

This outcome makes regulation operational

test item preperation
for toxicological testing

Currently 19 Mandatory Core MNM (ca. 70 MNM total)

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		TEM		BET	ICP-MS and/or EDS	GC-MS, HPLC-MS
Material Code	"Core material"	diameter (nm)	length (nm)	SSA (m2/g)	inorganic/coating	organic coat/associated
NM100	TiO2	110±57	NA	9	no	no
NM101	TiO2	6.0±0.7	NA	316	no	silanes, hexadecanoic and oxydecanoic acids
NM103	TiO2	24.7±2.3	NA	51	Al,Si,Fe	dimethoxydimethyl-silane, silane
NM110	ZnO	147±149	NA	14	no	no
NM111	ZnO	141±103	NA	18	no	triethoxicaprylsilane 130
NM200	silica	18.3±4.5	NA	189	Al,Na,S	no
NM203	silica	24.7±2.3	NA	204	Al,S	hydrates?
NM212	CeO2	33	33	28	pending	no
NM220	BaSO4	25	NA	38	pending	no
NM300K	Ag	16.7±4.0	NA	NA	NA	NA
NM300K dispersion	tween20/PEG	NA	NA	NA	NA	NA
NM302	Ag	200 (from vender)	3000 (from vender)	NA	NA	NA
NM302 dispersion	tween20/PEG?	NA	NA	NA	NA	NA
NM400	MWCNT	13.6±3.7	846±446	254	Al,Fe,Na,Ni	pyrolitically carbon coated (from vender)
NM401	MWCNT	64.2±34.5	4048±2371	18	Na, Fe, Al, Ni, Mg	no
NM410	SWCNT	2 (from vender)	pending	pending	pending	pending
Nanocellulose - A	Nanofibrillar cellulose	pending	pending	NA	pending	pending
Nanocellulose - B	Nanofibrillar cellulose	pending	pending	NA	pending	carboxymethyl (from vender)
Nanocellulose - C	Nanofibrillar cellulose	10 (from vender)	5000	NA	pending	pending
Nanocellulose - D	Nanofibrillar cellulose	7 (from vender)	1000	NA	pending	pending
Nanocellulose - E	Fibrous cellulose	pending	pending	NA	pending	pending

Main objectives of WP3

Characterize real exposure for workplace, consumer and environment

Identification of exposure scenarios; Emission potential data by dustiness testing; Pre-screening methodology (mesocosms); Conversion between metrics

Develop measurement and emission test strategies

Aging protocols; Instrumentation and methods (link with WP2)

Provide tools for exposure (risk) assesment

Evaluation of existing exposure modeling tools and development of new tools; Environmental exposure decision tree to categorize MNM and residues as entry point for (eco)toxicity assesment; Extended knowledge base; Effectiveness of control measures.

Tool to achieve these goals

- Value chain case studies

Potential impact

- **Input to the NANoREG Tool Box**
  - Exposure assessment model along the life.cycle
  - Emission potentials/release rates for specific compounds (powder CNT)

- **Input to horisontal tasks for improving the understadning of exposure**
  - Characterization and transformation
  - Environmental fate and persistence

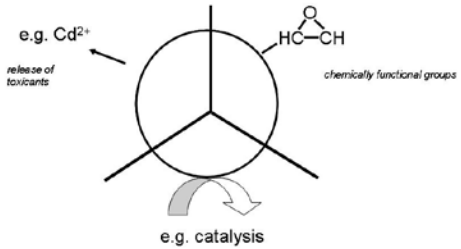
- **Potential implementation**
  - Within the NANoREG tool kit for making instruments for the regulators
  - Within REACH guidance for testing requirements
  - Within OECD test guidelines

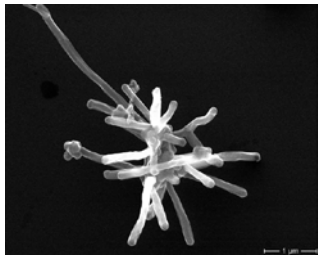
Main objectives of WP4

Study relevant materials (production volume and/or mode of action)

Investigate:

i) Distribution of NM in vivo
ii) Toxicological effects of NM
iii) Long(er)-term study whenever feasible





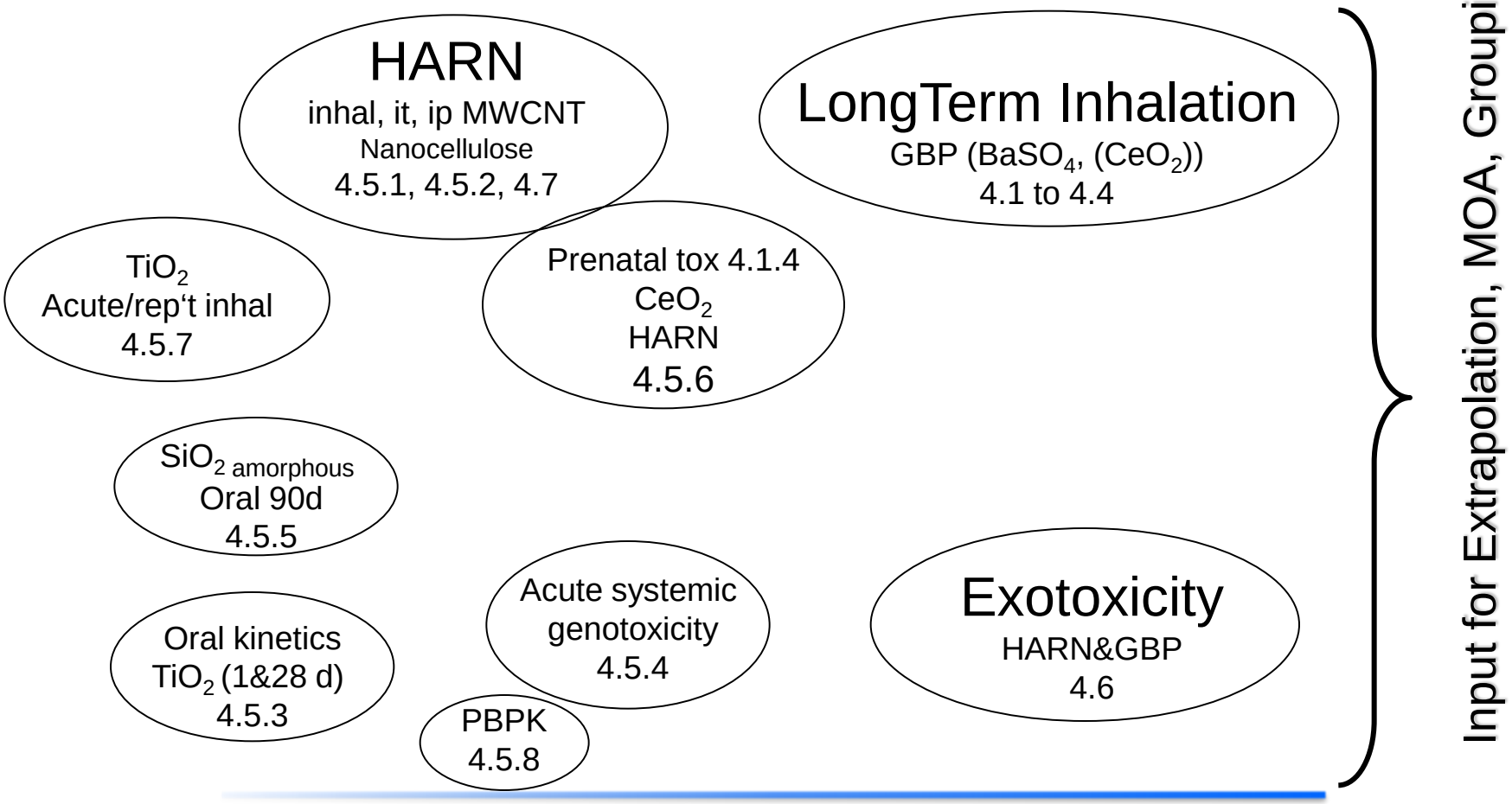
Potential outcome

- **Definition of overload exposure concentrations in rats (granular biopersistent particles)**
- **Basis for grouping according to mode of action**
- **Understanding effects and overload-concentrations for GBP**
- **Fibrous nanomaterials (HARN) – Sub-grouping according to functionalization?**

GBP, granular, biopersistent particles not specifically toxic; HARN, high aspect ratio nanomaterials

In vivo test projects

Approach: established regulatory protocols (e.g. OECD) as basis, add-on possible



Main objectives of WP5

Similarities between NM and Extrapolation

- Development of a proposal for grouping of nanomaterial in categories with similar biological, ecological and/or toxicological effects

Stability and elimination (biodurability/persistence)

- Development of a strategy for solubility testing

Alternative testing and predictive screening

- Development of an alternative predictive screening methodology

Decision Tree for Risk Assessment

- Development of a decision tree for hazard (risk) assessment based on results from WP2 and WP5

WP5 impact and implementation

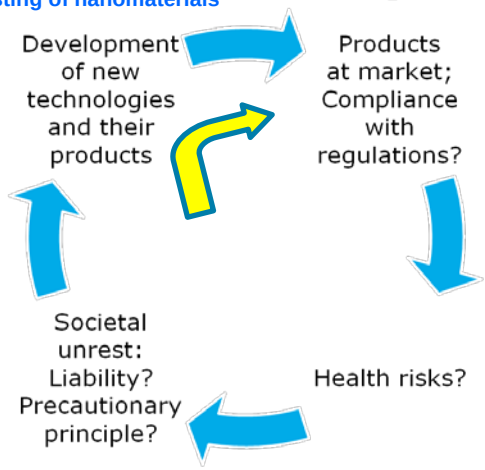
Potential impact

- Change from case by case risk assessment of nanomaterials to a testing strategy in which all information is used, including the possibility of extrapolation and grouping
- Strategic use of solubility, predictive in vitro toxicity assessment and high throughput screening methodology within the risk assessment of nanomaterials

Possible implementation:

- Within the NANoREG tool kit for risk assessment and decision making instruments for the regulators
- Within REACH guidance for testing requirements
- Within OECD test guidelines

Main objectives of WP6



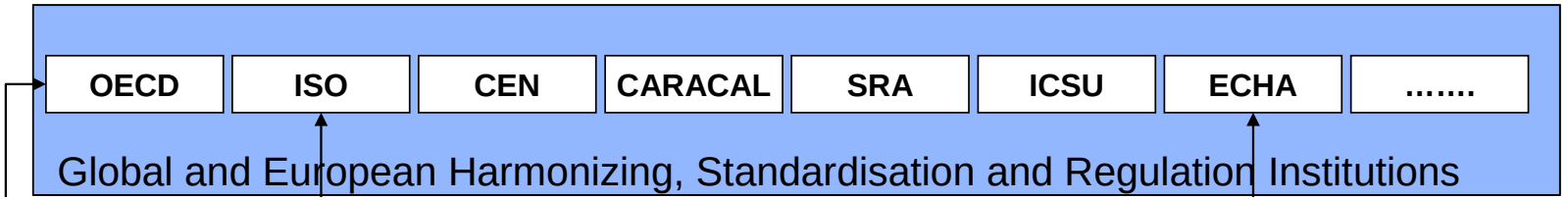
- **Linking risk analysis to innovation**
- **Safe by design**
  - Lessons learned from drug development
- **Safe by design: Practical approaches and examples**
- **Potential impact**
  - Decreased necessity for risk management activities
  - Stimulans for successful innovations by improved cooperation between innovators and safety researchers
- **Possible implementation**
  - Within the NANoREG toolkit for risk assessment and decision making instruments for the regulators

Most Regulatory Questions Addressed

A common European approach to the regulatory testing of nanomaterials

Regulatory question	WP1	WP2	WP3	WP4	WP5	WP6
1. Measurement and characterization: ID according to EC definition		X			X	
2. Measurement and characterization: Characterization through LCA		(x)			X	X
3. Characterization and transformation: After entry into body and the environment		(x)			X	
4. Metrology and dose metrics (for Risk Assessment); Hazard, exposure, LCA		(x)	X		X	
5. Extrapolation and grouping: Investigate read-across from bulk or grouping due to properties, expo, MoA		X	X	X	X	
6. Fate, persistence and long-term effects: MN (+coated) in humans, environment, environmental species, the food chain; link to bulk?		(x)	X	X	X	
7. Kinetics and fate, determination: How and when should information on absorption be generated and used for hazard assessment?				(x)	X	
8. Kinetics and fate, extrapolation: May kinetics and fate be predicted and used for grouping/read across for hazard assessment.				(x)	X	
9. Mode of action: Which PC properties drive MN exposure and affect biological systems and should be known for risk assessment?		(x)		X	X	X
10. Hazard: Which methods should be used to assess the human and environmental toxicity?		(x)		(x)	X	X
11. Exposure: What are the main determinants for occupational and consumer exposure			X		X	
12. Exposure: How should human and environmental exposure be assessed in practice?			X		X	
13. Exposure and life cycle analysis: What scenarios may cause exposure, SOPs for MN release tests (powders/matrices)			X		X	
14. Risk Assessment: NOEL or benchmark dose levels of long-term (low dose) exposures; ability to predict from acute and sub-acute tests				X	X	
15. Risk Management: Exposure reduction, applicability of exisiting risk management measures, applicability of existing control banding tools.			X			
16. Health surveillance: Feasability of biological monitoring or health surveillance						
Transfer to regulatory system	X	←	←	←	←	←
Transfer to standardization and test guidelines	X	(x)	(x)	(x)	(x)	

Aim and Wish: WOLRDWIDE collaboration!



Examples of areas of expected high interest

- A common regulatory understanding of MNM
- Harmonization of phys-chem. characterization methods (size-distributions, surface area …)
- Refinement of OECD TGs and new SPSFs(test and validation)
- Identify reliable toxicological test methods (e.g., exposure requirements, end-points, grouping, predictive screening)
- Methods and agreement on the use of emission potentials for exposure assessment (e.g., powder dustiness)
- Principles to achieve Safe-by-Design
- Harmonization of regulatory risk assessment paradigms (or data requirements)

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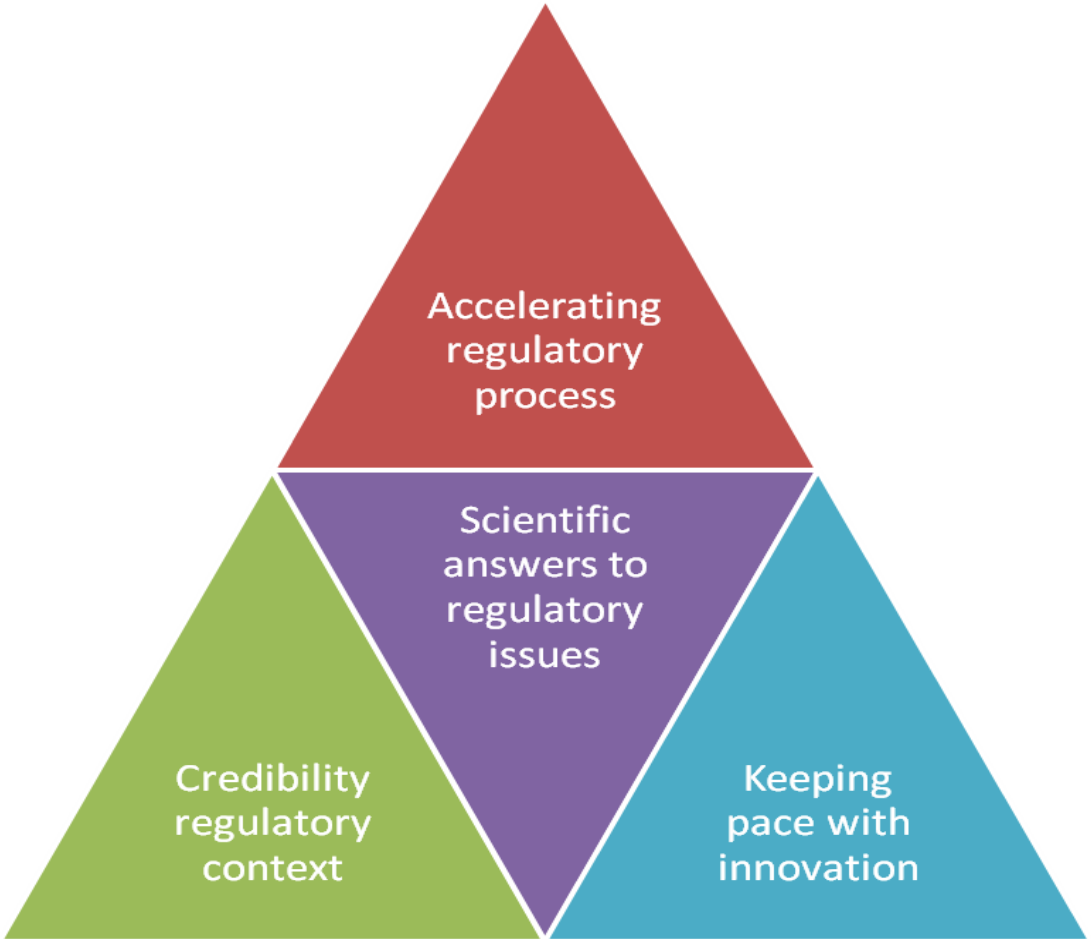
Accelerating regulatory process
Scientific answers to regulatory issues
Credibility regulatory context
Keeping pace with innovation

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