Qualification as a Tool to Speed up the Regulatory Implementation of NAMs –

Insights from EFSA NAMs4NANO Project

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Overview

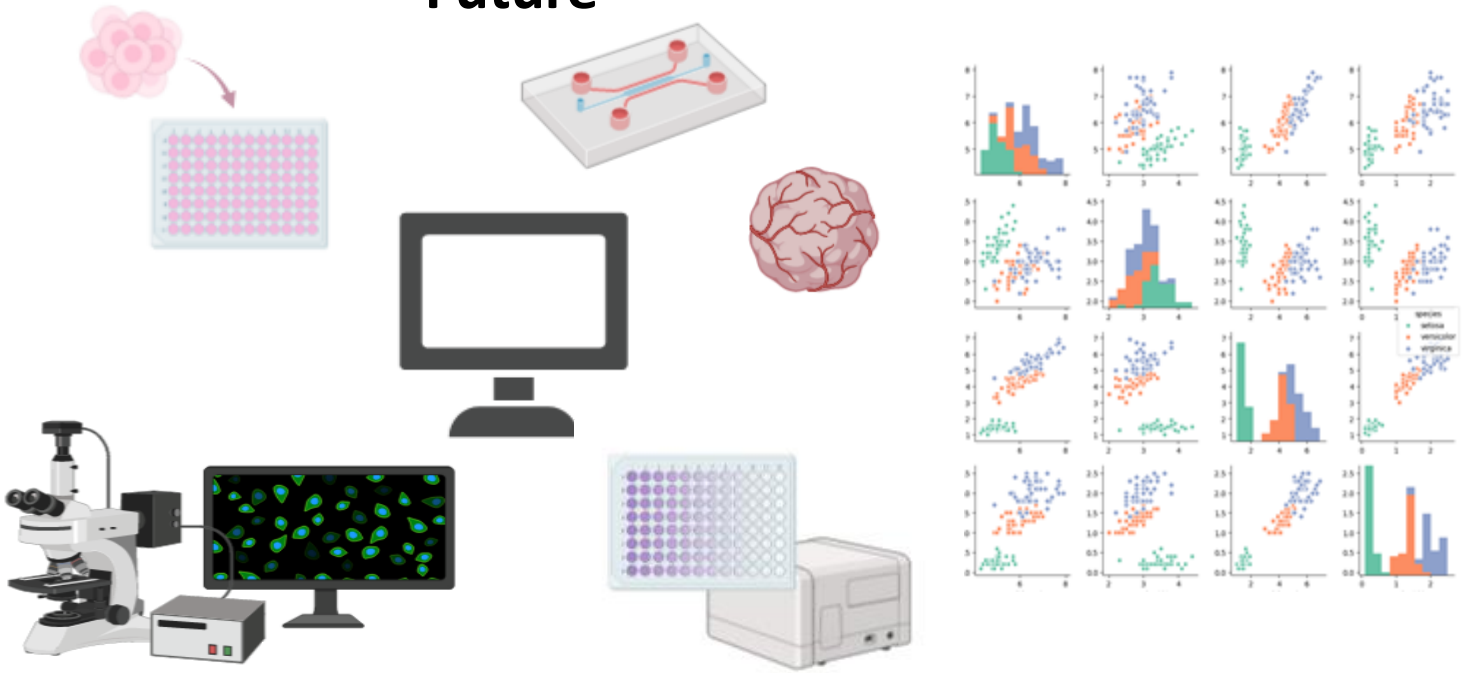
- **Risk Assessment: Paradigm Shift to New Approach Methodologies (NAMs)**
  - *Challenges and Possibilities*
- **Risk Assessment of Nanomaterials - a ”special case”**
  - *Challenges and Possibilities*
- **Insights from EFSA NAMs4NANO project**
  - *Qualification vs Validation*
  - *Proposed Qualification System*
  - *Overview on proposed criteria (reliability & relevance)*
- **Take Home Messages**

Paradigm Shift to Next Generation Risk Assessment (NGRA)

Vision: The transition to an animal-free system for chemical risk assessment based on human biology while keeping or increasing the level of protection

Today

Future



Risk Assessment: Integration of NAMs – the legal challenge

Example: Plant Protection Products (PPP)

Regulation	A.S. in PPP 283/2013	OECD TG#
Toxicokinetics		417
Acute Toxicity (oral, dermal, inhalation)		401-403, 423, 425
Skin irritation / corrosion		404, 431, 439
Eye irritation / corrosion		405, 437, 438, 467, 491, 492, 496
Sensitization (skin)		406, 429, 442, 497
Repeated dose, 28 d		407
Repeated dose, 90 d		408
Cronic toxicity		451
Carciongenicity		452, 453
(Screeningtest repro-tox)		422
Developmental toxicity (species 2)		414
Reproductive toxicity (EOGRTS or 2-Gen)		443, 416
(Developmental neurotoxicity)		426, (IVB)
Endocrine disruption		Diverse
Genotoxicity in vitro		e.g. 471
Genotoxicity in vivo		e.g. 474

REGULATIONS

COMMISSION REGULATION (EU) No 283/2013

of 1 March 2013

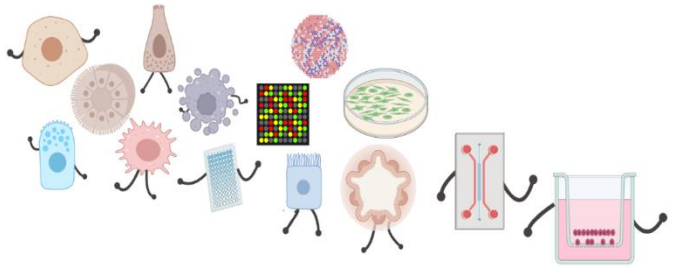
setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

Only altered by majority in EP, EC

Only altered if all OECD MS agree

BfR

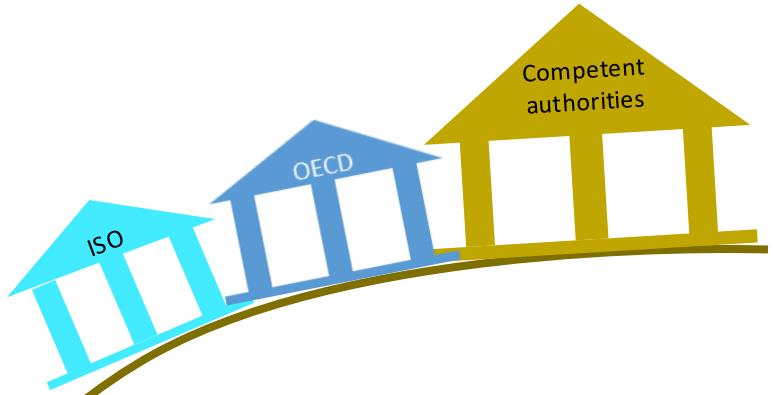
Risk Assessment: Integration of NAMs – the validation challenge



Issues…

- SOPs not fully developed
- Applicability domain lacking
- Unclear regulatory use/ demonstration of regulatory relevance lacking
- Lack of integration into existing data
- Lack of motivation for validation
- Lack of dedicated funding

…



In the last two decades >
300 projects
1billion Euro

Nanosafety cluster:
34 projects finalised
27 projects ongoing

Skin corrosivity
Skin irritation
Eye Damage
Genotoxicity
Sensitisation
ED

Test development | **Validation** | Test guidelines | Integration into regulatory practise

EFSA NAMs4NANO Overview

- **Improve general understanding on NAMs for risk assessments** (possibilities, challenges, uncertainties)
- **Apply selected NAMs in risk assessment case studies** mainly **for filling data gaps** by **integrating NAM data** with other types of data using **Integrated Approaches to Testing and Assessment (IATAs)**
- **Further improve selected NAM methodologies**

Budget:	5.3 Mill Euro (EFSA funding, GP/EFSA/MESE/2022/01)
Duration:	4 years (04.04.2023- 03.04.2027)
Consortium:	BfR (GER); ISS (IT); ANSES (FR); RIVM (NL); Sciensano (BE); WFSR (NL); LIST (LU)
Additional Partners:	JRC (EC); SFA (SING)
Subcontractors:	Fraunhofer ITEM (GER) – for Lot 1-3 Uni Auckland, New Zealand, Uni Hasselt, Uni Politècnica de València – only for Lot 3

Lot 1: Review, Qualification System, Implementation Plan	**Lot 2: Risk Assessment Case Studies**	**Lot 3: Methodological Case Studies**
Coordination: A. Haase (BfR)	Coordination: A. Haase (BfR)	Coordination: F. Cubadda (ISS)

„Nano“ in the food and feed chain

Engineered nanomaterials (according to Novel Foods Regulation EU 2015/ 2283)

“any **intentionally produced material** that has **one or more dimensions of the order of 100 nm or less** or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale”.

Conventional materials with a nanoscaled fraction following the Guidance on Particle-TR (2021)

Novel Foods (EU 2015/2283)	Nutrients (e.g. EC 1925/2006)	Flavourings (EC 1334/ 2008)	Food Additives (EC 1333/2008)
FCM (EC 1935/ 2004)	Plastic FCM (EU 10/2011)	Feed Additives (EC 1831/ 2003)	Pesticides (EC 2009/128)

Nano-related policies in the food and feed sector

1. **<u>Stepwise approach integrating NAMs</u>** to evaluate
   - Dissolution/ Degradation
   - Local Effects
   - Barrier Crossing/ Cellular Uptake

2. Suggested *in vitro* tests:
   - Genotoxicity
   - Cytotoxicity
   - Reactivity/ Oxidative stress
   - Inflammatory Potential
   - Integrity of intestinal barrier …

3. **<u>Lack of OECD TGs</u>**

4. Reporting of non-guideline *in vitro* assays should follow OECD GD 211

“Nano” Risk Assessment by NAMs - Example IHAT

Example: Assessment of iron hydroxide adipate tartrate (IHAT)

- **iron hydroxide adipate tartrate (IHAT)**: novel (nanosized) food, source of the nutrient iron
  - assessed by EFSA Nutrition, Novel Food and Food Allergens Panel (EFSA NDA Panel, 2021)
- **Applicant presented evidence utilizing NAMs** demonstrating that:
  - this nanosized iron source is taken up as particles by the enterocytes
  - however, it enters the intracellular iron pool and behaves similarly to dietary iron
  - importantly it does not bypass homeostatic control (hence does not lead to possible bioaccumulation and adverse effects)
- **Generalisation: AOP-based IATA approach for a nano-enabled nutrient outlined** (Schoonjans et al., 2023)

For “Nano” Risk Assessment, risk assessors must deal with non-guideline data on a daily basis
(not only in the food & feed sector)

“Nano” Risk Assessment: Opportunities/ Challenges for NAMs

Nanomaterials (NMs) are easily manufactured in plenty of variants, urgently demanding for NAMs

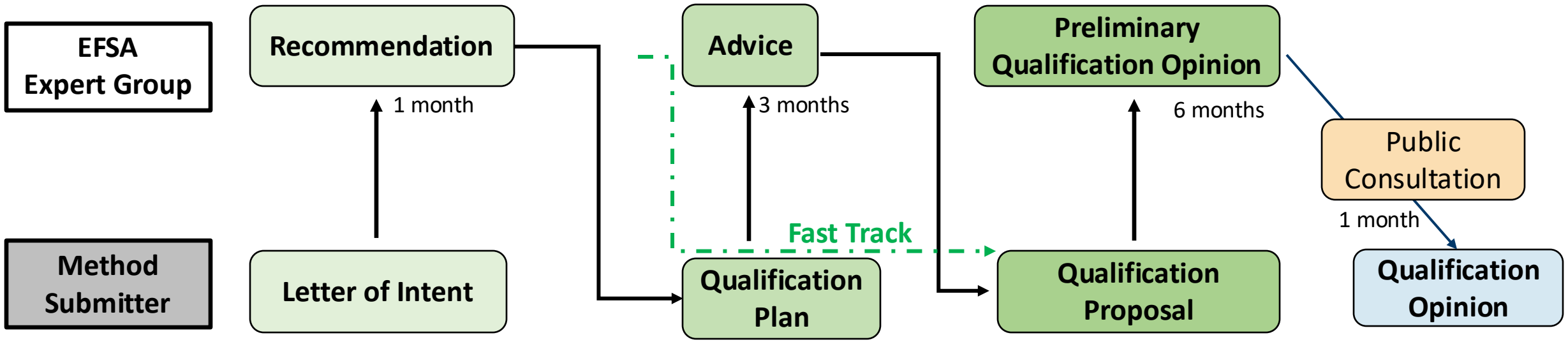
Opportunities

- Existing OECD TGs mostly not suitable as such - require adaptations, in addition new OECD TGs are needed
- Essential elements for “Nano” risk assessment (e.g., barrier crossing) are technically easier to implement *in vitro*
- Nanotechnology as an area with high innovation has established dialogues of different stakeholders - new concepts receive attention early on

Challenges

- Particulate nature requires sophisticated physicochemical characterization, not only of the pristine materials
- Complex transformations need to be considered (e.g. agglomeration, dissolution, biomolecule corona)
- Particulate nature renders *in vitro* assays more challenging (e.g. dispersion stability, interferences, dosimetry)

Qualification System: Proposed Process (updated scheme)



- **Method Description: General**
- **Self-evaluation** of method "readiness" (RRL)
- **Intended context-of-use**
  - ✓ How does NAM fit in regulatory framework?
- **Relevance for context-of-use**
  - ✓ Biological Relevance

- **Method Description: Details**
  - ✓ Standard Operating Procedures (SOPs)
  - ✓ Experimental raw data & metadata
  - ✓ Data analysis (evaluation & interpretation)
- **Reliability (within-Lab)**
- **Relevance for context-of-use**
  - ✓ Explain underlying scientific principle
  - ✓ How firm is the evidence?

- **Method Description: Further Details**
  - ✓ Limitations, issues, troubleshooting
  - ✓ Acceptance criteria
  - ✓ Reference chemicals/ benchmarks
- **Reliability (Lab Transfer)**
- **Relevance for context-of-use**
  - ✓ *In-vivo* anchorage
  - ✓ Human relevance
  - ✓ Orthogonal method(s) *(if applicable)*

Validation and Qualification

Validation

- ✓ **Validation studies** based on internationally recognised principles (OECD GD 34)
- ✓ **Validation bodies** or other actors (e.g. method developers, public-public or public-private partnerships)

Qualification

Proposal for a **qualification system for NAMs** for nanoparticles risk assessment in the **food and feed chain**

- ✓ **Voluntary,** practical tools **aiming toward faster regulatory implementation** of non-guideline methods

Test method definition/description/SOPs

Relevance

Within-lab reproducibility

Between-lab reproducibility

Optional, but must demonstrate transferability to at least one lab

OECD Test Guidelines

- ✓ **Standard methods** for safety testing of chemicals
- ✓ **International use**
- ✓ **Internationally agreed regulatory readiness**

Mutual Acceptance of Data (MAD)

Qualification Opinion

- ✓ **Expert opinion** based on pre-defined criteria
- ✓ **EFSA context-specific regulatory readiness**

Context of use (e.g., one legal framework)

Reliability and Relevance (different stages of the process)

	Letter of Intent	Qualification Plan	Qualification Proposal
Relevance *(for context-of-use)*	**Initial considerations on biological relevance**	**Underlying scientific principle** (e.g. AOP anchoring for a biological NAM) **Initial considerations on plausibility of evidence** (e.g. AOP endorsed by OECD?)	**Weight-of-Evidence** Comparison to • existing "gold standard" method *(if applicable)* • *in vivo* evidence *(if available)* • other similar/orthogonal methods *(if applicable)* **Human Relevance**
Reliability	Not expected in LoI*	**Within-lab reproducibility** • over time • different user	**Transferability of Method**

Methodology towards Implementation Plan

1. Feedback from Public Consultation
2. Dialogues with Key Stakeholders (e.g. EMA, ECHA, SCCS, EC JRC, US FDA, OECD)
3. Feedback from Industry/ Business Operators
4. Testing the Readiness Criteria
    - Within the Consortium
        - 12 NAMs (Lot 2) selected for LoI
        - 2 NAMs for testing Qualification Plan & Qualification Proposal
    - By external Stakeholders
        - EU nanoPass Consortium
        - EU SUNRISE Consortium
        - AOAC Europe Section
5. Follow-up on Proposals for Co-development of the Readiness Criteria

Take Home Messages

- **Regulatory implementation of NAMs remains challenging:** *legal challenge, validation challenge…*
- "Nano" as an area with high innovation offers unique possibilities to explore the regulatory use of NAMs
- Many projects developed NAMs, released SOPs and verified some in ILCs – several **appear promising to be further explored for risk assessment in integrated approaches**
- **Qualification appears as a promising tool for faster regulatory implementation.**
- Our consortium published an initial proposal for qualification, which is currently discussed with key stakeholders & the readiness criteria are tested for selected NAMs (within the consortium & beyond)
- In parallel, our consortium explores promising NAMs in risk assessment case studies (Lot 2), and improves others in selected methodological case studies (Lot 3)

<u>Highest Priority NAMs for Nano</u>

- Degradation and Dissolution (in relevant biofluids)
- Cellular uptake/ barrier crossing
- Initial toxicity screening (genotoxicity, cell viability/ cytotoxicity, reactivity/ ox. stress, (pro-) inflammatory responses, barrier integrity)

Thank you very much! Questions?

Thanks to all NAMs4NANO partners!

Special Thanks to the Lot 1 Team

BfR: Shirin Usmani, Vera Ritz, Katharina Siewert
ISS: **Francesco Cubadda**, Olimpia Vincentini
JRC: Susanne Bremer-Hoffmann, Alessia Bogni, Deborah Stanco
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RIVM: Emily McVey, Anges Oomen
WFSR: Meike van der Zande
LIST: Tommaso Serchi, Kahina Mehennaoui

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External Scientific Report

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Review of New Approach Methodologies for Application in Risk Assessment of Nanoparticles in the Food and Feed Sector: Status and Challenges

Shirin M. Usmani[1], Susanne Bremer-Hoffmann[2], Karlien Cheyns[3], Francesco Cubadda[4], Verónica I. Dumit[1], Sylvia E. Escher[5], Valerie Fessard[6], Arno C. Gutleb[7], Thibaut Léger[6], Yuk-Chien Liu[1], Jan Mast[3], Emily McVey[8], Birgit Mertens[3], Daniela Montalvo[3], Agnes G. Oomen[8,9], Vera Ritz1, Tommaso Serchi[7], Holger Sieg[1], Katherina Siewert[1], Deborah Stanco[2], Eveline Verleysen[3], Olimpia Vincentini[4], Calvin W. S. Yeo[10], Dingyi Yu[10], Meike van der Zande[11], Andrea Haase[1]

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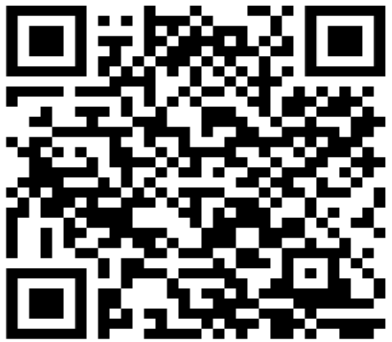


External Scientific Report

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Proposal for a qualification system for New Approach Methodologies (NAMs) in the food and feed sector: example of implementation for nanomaterial risk assessment

Andrea Haase[1], João Barroso[2], Alessia Bogni[2], Susanne Bremer-Hoffmann[2], Valerie Fessard[3], Arno C. Gutleb[4], Jan Mast[5], Emily McVey[6], Birgit Mertens[5], Agnes G. Oomen[6,7], Vera Ritz[1], Tommaso Serchi[4], Katherina Siewert[1], Deborah Stanco[2], Shirin M. Usmani[1], Eveline Verleysen[5], Olimpia Vincentini[8], Meike van der Zande[9], Francesco Cubadda[8]

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