National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Towards Harmonisation of Testing of Nanomaterials for EU Regulatory Requirements on Chemical Safety – A Proposal for Further Actions

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Introduction

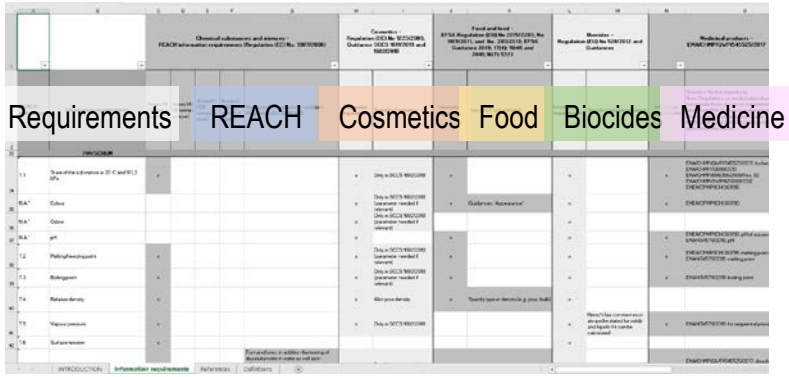
- Nanomaterials fit within the existing regulatory frameworks
  - their specific properties should be taken into account in their risk assessment[1]
- OECD Test Guidelines and Guidance Documents have been adapted or developed
- So far focus has been on needs for EU REACH regulation
- What about other (EU) regulatory areas?
  - Overview compiled

- Aim to identify and to prioritise further work on the development and adaptation of OECD TGs/GDs for nanomaterials

[1] OECD Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials (OECD/LEGAL/0400)

Bleeker et al 2023 (doi: 10.1016/j.yrtph.2023.105360)

What did we do?



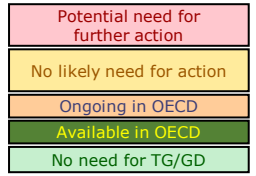
- **Overview of information requirements:**
  ca. 140 identified across industrial, cosmetics, biocides, food and feed, and (veterinary) medical area

- **For each requirement:**

  RIVM: assessment of ongoing actions, published documents and **potential need for further action** to accommodate nanospecific issues

  EU experts: reflection on analysis.

  Expert representation from research, EU regulatory bodies and each regulatory area.
  Experts involved in EU projects/OECD harmonisation programmes (NL, AT, DE, DK, ES, UK, and EC)



- Identification of potential **priority needs** and **overarching issues –** Expert comments & Relevance

EU Legislation

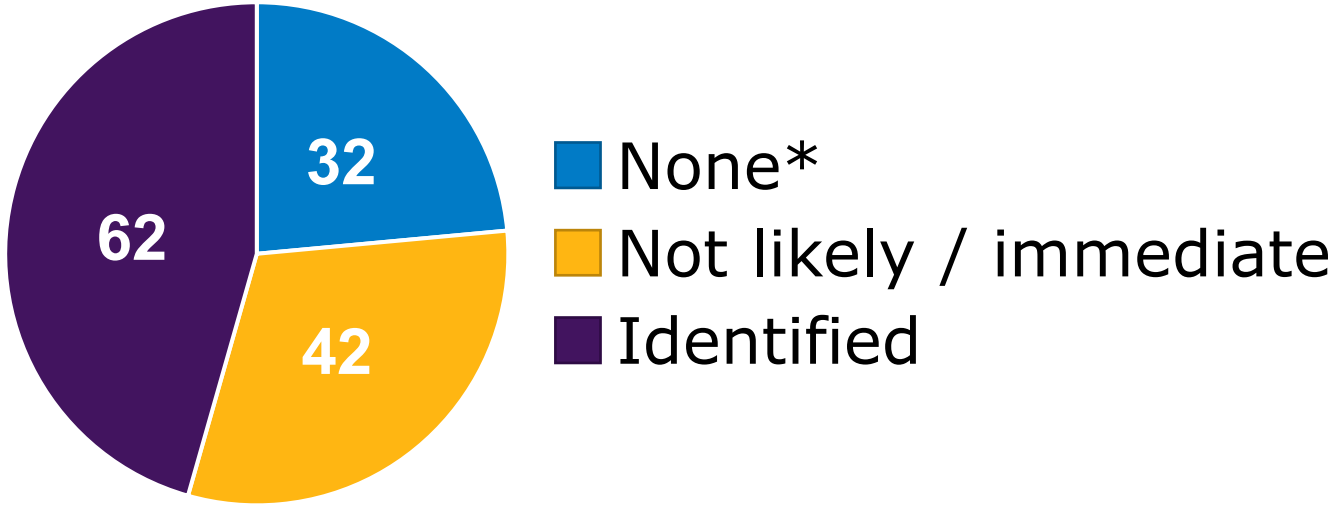
- **Biocides** (Regulation (EU) 528/2012)
- **Cosmetics** (Regulation (EC) 1223/2009)
- **Food & Feed** (Regulation (EC) No 178/2002)
  - Information to consumers (Regulation (EU) 1169/2011)
  - Contact materials (Regulation (EC) 450/2009)
  - Novel foods (Regulation (EC) 2015/2283)
  - Additives (Regulations (EC) 1331/2008, (EC) 1332/2008, (EC) 1333/2008, (EC) 1334/2008)
  - Feed (Regulations (EC) 1831/2003, Regulation (EC) 429/2008)
- **Medicinal products** (Directive 2001/83/EC, Regulation (EC) No 726/2004, …)
- **Veterinary medicinal products** (Regulation (EC) No 2019/6, …)
- **Medical devices** (Regulation (EU) 2017/745, Regulation (EU) 2017/746)
- **Chemicals (REACH)** (Regulation (EC) 1907/2006, Regulation (EU) 2018/1881)

focus on non-clinical for medical area

- Regulatory requirements among regulatory areas are very similar
- Shows benefits of closer collaboration ("one substance, one assessment")

Bleeker et al 2023 (doi: 10.1016/j.yrtph.2023.105360)

Needs for further action



* No need identified where OECD TGs are available or under development
(www.oecd.org/chemicalsafety/nanomet/status-report-test-guidelines-guidance-documents-nanomaterials.pdf)

Bleeker et al 2023 (doi: 10.1016/j.yrtph.2023.105360)

OECD TG/GD activities for NMs (since 2017)

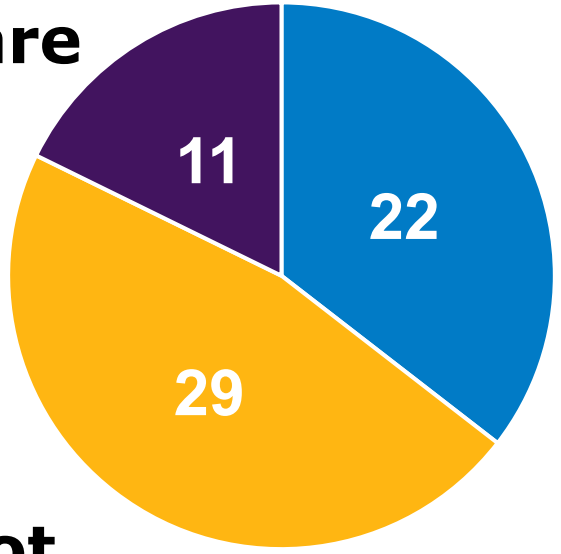
Section 1 Physical Chemical Properties	Section 2 Effects on Biotic Systems	Section 3 Env. Fate and Behaviour	Section 4 Health Effects
VSSA **PSD** TG 124: Determination of the Volume Specific Surface Area of Manufactured Nanomaterials *(EU)* TG 125: Nanomaterial Particle Size and Size Distribution of Nanomaterials *(DE)* TGP Project 1.5: Guidance Document on Determination of solubility and dissolution rate of nanomaterials in water and relevant synthetic biological media ***(DK/DE)*** TGP Project 1.6: Guidance Document on Identification and quantification of the surface chemistry and coatings on nano- and microscale materials ***(DK/DE)*** **Hydrophobicity index** TGP Project 1.7: TG on determination of the hydrophobicity index of manufactured nanomaterials through water affinity measurement *(EU)* TGP Project 1.8: TG on Dustiness of Manufactured ***(DK/FR)*** TGP Project 1.10: Development of a new Guidance Document on the determination of concentrations of nanoparticles in biological samples for (eco)toxicity studies ***(UK)***	***Aquatic/ Sediment Toxicity*** No. 317 Guidance Document on Aquatic and Sediment Toxicity Testing of Manufactured Nanomaterials *(US)* WPMN Project: Adaptation of OECD TGs 201, 202 and 203 for the determination of the ecotoxicity of MNs ***(FR/ES)***	**Dispersion stability** TG 318: Dispersion Stability of Nanomaterials in Simulated Environmental Media *(DE)* ***Dissolution & Dispersion*** No. 318 Guidance Document for the Testing of Dissolution and Dispersion Stability of Manufactured Nanomaterials in Simulated Environmental Media for Ecotoxicological Testing and Assessment *(DE)* ***Waste water treatment*** No. 340 Study Report on a test for removal in wastewater treatment plants of gold manufactured nanomaterial (NM) spiked in sludge (adapted OECD TG 303A) *(DE)* ***Leaching in soil*** No. 342 Guidance Document on testing Nanomaterials using OECD TG No. 312 "Leaching in soil columns" *(DE)* TGP Project 3.10: New TG on dissolution rate of nanomaterials in aquatic environment ***(DE)*** TGP Project 3.12: New GD on assessing the apparent accumulation potential of nanomaterials ***(ES)*** …a tiered approach for reliable bioaccumulation assessment of MNs in environmental organisms minimising use of higher tier vertebrate tests ***(UK)*** ***Biodurability*** Series on the Safety of Manufactured Nanomaterials No. 86 Assessment of the durability of Nanomaterials and their Surface Ligands *(SA/Korea)*	**Inhalation tox. – 28d** TG 412: Subacute Inhalation Toxicity: 28-Day Study *(IN/US)* **Inhalation tox. – 90d** TG 413: Subchronic Inhalation Toxicity: 90-day Study *(US)* ***Inhalation toxicity*** No. 39 Second Edition - Guidance Document on Inhalation Toxicity Studies *(US)* ***Micronucleus assay*** No. 359: Study Report and Preliminary Guidance on the Adaptation of the In Vitro Micronucleus assay (OECD TG 487) for Testing of Manufactured Nanomaterials. *(EU)* ***Skin sensitisation*** TGP Project 4.133: Applicability of the key event based TG 442D …sk… …rials *(CH)* …etics to accommodate … TGP Project 4.158: Integrated *in vitro* approach for intestinal fate or orally ingested nanomaterials ***(IT)***

multiple other guidance documents published in OECD 'Series on the Safety of Manufactured Nanomaterials'

https://www.oecd.org/chemicalsafety/nanomet/

First prioritisation of identified needs

- Potential needs **specific to nanomaterials that are broadly relevant** (i.e. relevant for multiple regulatory areas) **– 22 topics**
- Information requirements for which the **need remains unclear** on whether further work is necessary **– 29 topics**
- Potential needs **specific to nanomaterials but not broadly relevant** (e.g. relevant to only one regulatory area or requirements not much relied upon in risk assessment) **– 11 topics**



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Nanospecific & broadly relevant - examples

Information requirements	Summary of expert opinions on nanospecific needs	Relevant OECD TGs/GDs*
Physico-chemical properties		
Dispersion stability in relevant media, required for: - All regulatory areas	This endpoint is addressed in TG 318 and GD 318 for environmental media but further action on standardisation for biological media used in toxicology studies relevant for human health is needed, including *in vitro* studies.	TG 318 GD 318
Stability (physical and chemical), required for: - All regulatory areas	This endpoint need is relevant for all (eco)toxicity and *in vitro* studies during exposure.	-

* Relevant OECD TGs/GDs are those referenced in one or more of the documents used in identifying the regulatory requirements or identified by experts. Listing them here should not be interpreted as a need to adapt each of these documents for nanomaterials but rather as an overview of relevant OECD documents for which the needs for adaptation requires investigation.

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Unclear - examples

Information requirements	Summary of expert opinions on nanospecific needs	Relevant OECD TGs/GDs*
Reproductive toxicity (includes four information requirements, see Table S2 for details), required for: - All regulatory areas	Nanomaterials may pass through the placenta. Thus, information on the reproduction toxicity, fertility/ developmental effects is considered relevant. As for other TGs clear guidance on dispersion is important, as well as measurement of nanomaterials in biological tissues (see also WNT Project 1.10).	TG 414 TG 415 TG 416 TG 421 TG 422 TG 443
Endocrine disruption, required for: - Cosmetics - Food and feed	Potential endocrine disruption properties of nanomaterials may potentially be related to the particle properties or to properties of (released) chemical components of a	TG 230 TG 231 TG 234

* Relevant OECD TGs/GDs are those referenced in one or more of the documents used in identifying the regulatory requirements or identified by experts. Listing them here should not be interpreted as a need to adapt each of these documents for nanomaterials but rather as an overview of relevant OECD documents for which the needs for adaptation requires investigation.

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Nanospecific, not broadly relevant - examples

Information requirements	Summary of expert opinions on nano specific needs	Relevant OECD TGs/GDs*
Dissociation constant, required for: - REACH - Cosmetics - Biocides - Medical products - Veterinary medicinal products	The dissociation constant may affect size. It is not clear how the results of OECD TG 112 might be impacted by the presence of a colloidal suspension (OECD, 2009), and also surface modification may play a role (Christensen & Larsen, 2013). As this endpoint is generally not relied upon in risk assessment, it is not considered a high priority.	TG 112
Stability in organic solvents, required for:	Stability in organic solvents may need further action, but this has no priority as it is not much relied upon in risk assessment	-

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Overarching needs for action on test methods[1]:

1. Resolving issues around nanomaterial **sample preparation, agglomeration, dispersion stability and dosing in toxicity testing**, especially for **human health endpoints**

2. Further development of tests or guidance on **degradation and transformation** of **organic nanomaterials** or nanomaterials with organic components to **better assess environmental fate** of this group of nanomaterials

3. Further development of tests and guidance to measure **(a)cellular reactivity** of nanomaterials
   - This will be critical, e.g. for the development of NAMs and in high-throughput systems needed for assessing the ever-increasing diversity of (newly) developed (advanced) nanomaterials

› Exact actions to take to be determined and responsible stakeholders to be identified

[1] Based on expert assessment (RIVM and EU experts)

Further recommendations

- **Monitor developments** of more complex 'advanced materials'
  - include in the applicability domain of any new/adapted test guideline

- **Set up a structural process** to identify information needs and generate knowledge
  - as part of risk governance
  - closely connected to technological innovation policy
    - Suitable guidance and test guidelines are a precondition for the successful implementation of adapted legislation
    - Uncertainty about regulatory validity could hamper to exploit the full economic potential of new technologies

More information

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