NanoHarmony 2nd Project Workshop

Update task 1.3 Toxicokinetics of NPs
25th of November 2021

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 885931

Task 1.3 Scientific basis for a new TG on toxicokinetics of ENMs

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OECD Project 4.146: A new Test Guideline on toxicokinetic studies to accommodate testing of (nano)particles.
Lead the Netherlands and UK

Objective NH:

To provide the scientific basis for the minimum requirements of the study design of in vivo toxicokinetic studies, including:

a) dose levels/ranges,
b) duration of the exposure
c) duration of the post-exposure period,
d) time points for determining organ burdens, and
e) key organs, tissues and /or excreta to be analysed.

Approach:

Using kinetic modelling, available and newly generated toxicokinetic data of oral and inhalation toxicokinetic studies with nanoparticles with slowly and moderately quick dissolution rates in relevant physiological media.

Partners: RIVM, UKHSA, NRCWE, BASF
Associated partners: JRC, KIT, KRISS, Evonik

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Timeline: NH Task 1.3 and Associated OECD project

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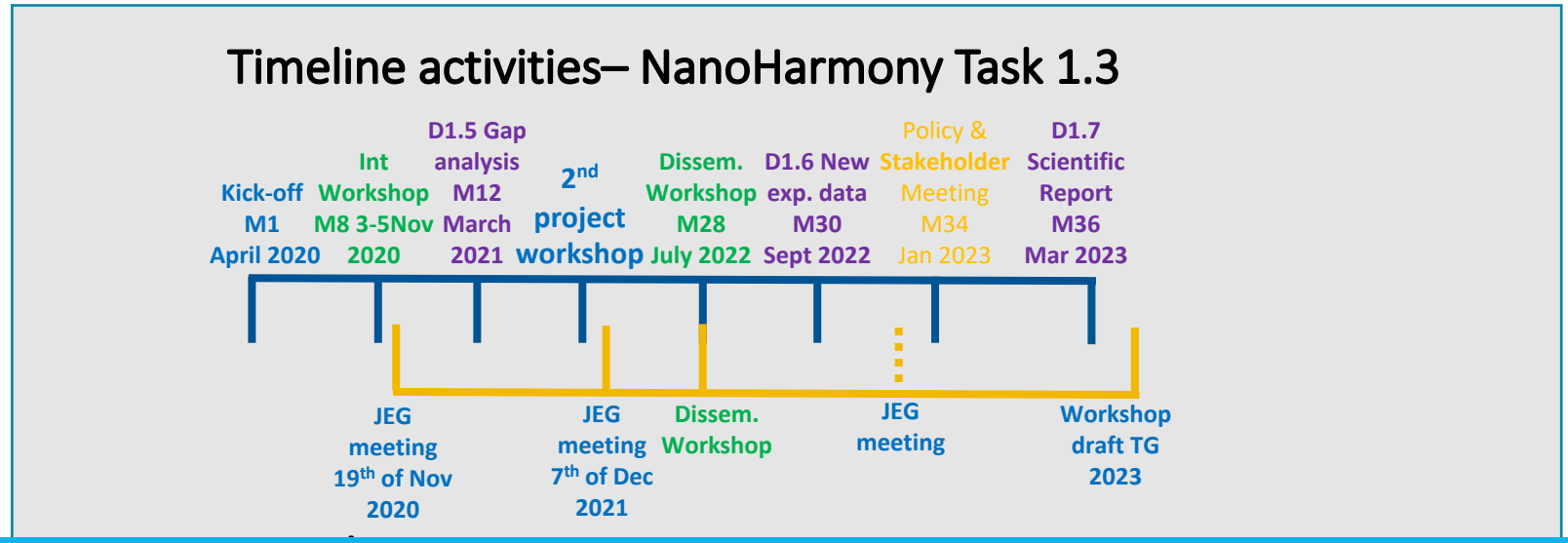

Next OECD event: Dec 7th 2021: Joint WNT/WPMN Expert Working Group by invitation: update on TG development and regulatory requirements/linked to purpose

Project Proposal APPROVED WPMN	**Submission SPSF at WNT**	**SPSF Commenting Round at WNT**	Formal approval at WNT	Project at WNT with 1 or more WNT Expert Group Meetings	Draft TG submitted to WNT	Potential OECD workshop/ Expert Group Meeting	1st Draft TG submitted to WNT	1st Commenting Round at WNT	2nd Draft TG submitted for comments to WNT	2nd Commenting Round at WNT	Final submission of TG to WNT	Approval by WNT

Proposed Timeline - OECD project to develop new TG on toxicokinetics to accommodate testing of nanoparticles

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Task 1.3 Meetings

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Monthly telco's with NH task 1.3 partners:

- discuss results gap analysis,
- regular updates on ongoing new studies,
- discuss study designs and new results,
- guest speakers from (future) associate partners or other tasks

Other

- eNanomapper - Prepare data template for inhalation biodistribution studies and if possible extend to oral distribution studies or different kinetic study designs.

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Task 1.3 Deliverables

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Deliverables:

D1.5 Report on the data gaps analysis on study design requirements for toxicokinetics of ENMs (M12 = 31rd of March 2021). Delivered in time

D1.6 Report on the new experimental data to complement existing studies on Toxicokinetics (M30 = Sept 2022)

D1.7 Scientific document to support OECD activities on the development of TG on toxicokinetics of ENMs (M36 = March 2023)

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Task 1.3 Deliverable 1.5 Gap analysis

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Goal:

Identify what existing information can be used for TG toxicokinetics development, if this is sufficient and what additional information is needed.

Model nanomaterials

Slow dissolution : nanosized CeO_2 and TiO_2

Moderately quick dissolution: nanosized SiO_2

Conclusion for model materials:

For inhalation, sufficient information from existing data + new data + PBK modelling to roughly estimate the minimum study design requirements to capture the toxicokinetics.

For oral, uncertain if combination of data is sufficient for minimum requirements.

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Task 1.3 Deliverable 1.5 Gap analysis

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Conclusions & recommendations workshop on 3rd and 4th of November 2020 and advise from OECD JEG meeting Dec 2020:

1. What will be taken into account and addressed in the TG?

General suggestions such as separate requirements for inhalation and oral exposure, clear definitions on dissolution kinetics, LoD of the analytical method used, the background concentration, additional parameters for dosing and # animals per group.

2. What will be considered in developing the TG?

Influence of retention in delivery system, volume oral gavage, IV data, dose at absorption surface, feasibility specific requirements such as mass balance.

3. What has lower priority in developing the TG?

Broaden applicability, NPs with fast dissolution rates, localization in cells/tissues, sensitive populations.

4. What needs to be addressed elsewhere (e.g. in GD)?

Relation to other TGs and GDs, use of in vitro data, use of different analytical methods to follow NPs in body, relevance of *in vivo* toxicokinetic data in rats for human risk assessment.

Please note that prioritization may be subject to change during the course of the project.

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New experimental data for D1.6

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	Available or planned in vivo studies	NM (Source)	Status
Inhalation	NanoHarmony (RIVM)	SiO_2 (NM203)	Exposure started January 2021, biochemistry and histopath done, organ burden pending
	German Initiative (NANoREG, etc.)	CeO_2 (NM212)	available, Tentschert et al. 2020
	BASF	polymer with fluorescent label	study starts beginning 2022
	PATROLS (RIVM)	CeO_2 (NM212)	available, PBK model parametrisation
	PATROLS (RIVM)	TiO_2 (NM105)	available, PBK model parametrisation

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New experimental data for D1.6

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	Available or planned in vivo studies	NM (Source)	Status
Oral	NanoHarmony (NFIDS)	Fumed SiO_2 (Aerosil 200F)	Finished, organ burdens and dissolution data in biological fluids
	NanoHarmony (NFIDS)	Precipitated SiO_2 (Sipernat 22S)	Finished, organ burdens and dissolution data in biological fluids
	PATROLS (NRCWE) (mostly toxicity, limited kinetics)	CeO_2 (NM212)	Finished, snack versus gavage
	PATROLS (KRISS) (mostly toxicity, limited kinetics)	TiO_2 (E171)	Finished, no TiO_2 above control levels
	NanoHarmony (ANSTO)	TiO_2 (radiolabeled)	Start delayed until Jan 2022 due to lockdown

Other inhalation or oral toxicokinetics ongoing relevant for toxicokinetic guideline development? Ilse.Gosens@rivm.nl

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D1.7 Scientific basis for *in vivo* toxicokinetic study

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The anticipated presence in tissues and the ability to detect the (nano)particles and determinants thereof in the target tissues likely depends on:

a) the dissolution kinetics of the particles in relevant physiological media (e.g. lung lining fluid, lysosomal fluids, gastrointestinal fluid, etc.) and

b) the limit of detection (LOD) and limit of quantification (LOQ) of the particles or determinants thereof in the target tissues.

NH 2nd workshop: 26th of November

- Small group discussion between NH partners 1.3 (toxicokinetics), 1.4 (detection) and 1.5 (dissolution testing in physiological media)

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Outlook NH task 1.3

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1. Update gap analysis existing studies on model materials:

- General insights on minimum requirements for intermediate soluble materials based on SiO_2 oral studies – from new and existing studies not yet in the gap analysis report.

- Closer look at contribution of ENM primary (and agglomerate?) particle size to bio-distribution and limit of detection considerations for the model ENMs - task 1.3 partners

2. Kinetic in silico modelling of ENMs

- Depending on purpose of toxicokinetic study, what potential in silico methods could inform toxicokinetic study design?
- What are the state-of-the art methods?

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