

Scientific basis for OECD TG on *in vivo* toxicokinetic study

NanoHarmony Webinar
December 16, 2020

Aims of this presentation

- Present highlights and updates based on feedback from NanoHarmony workshop and OECD Joint Expert Group
- Obtain additional feedback

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Outline

1. Approach of the draft gap analysis
2. Feedback from workshop and JEG
 - What will be taken into account and addressed in the TG?
 - What will be considered in developing the TG?
 - What has lower priority in developing the TG?
 - What needs to be addressed elsewhere (e.g. in GD)?
3. Questions and additional feed back

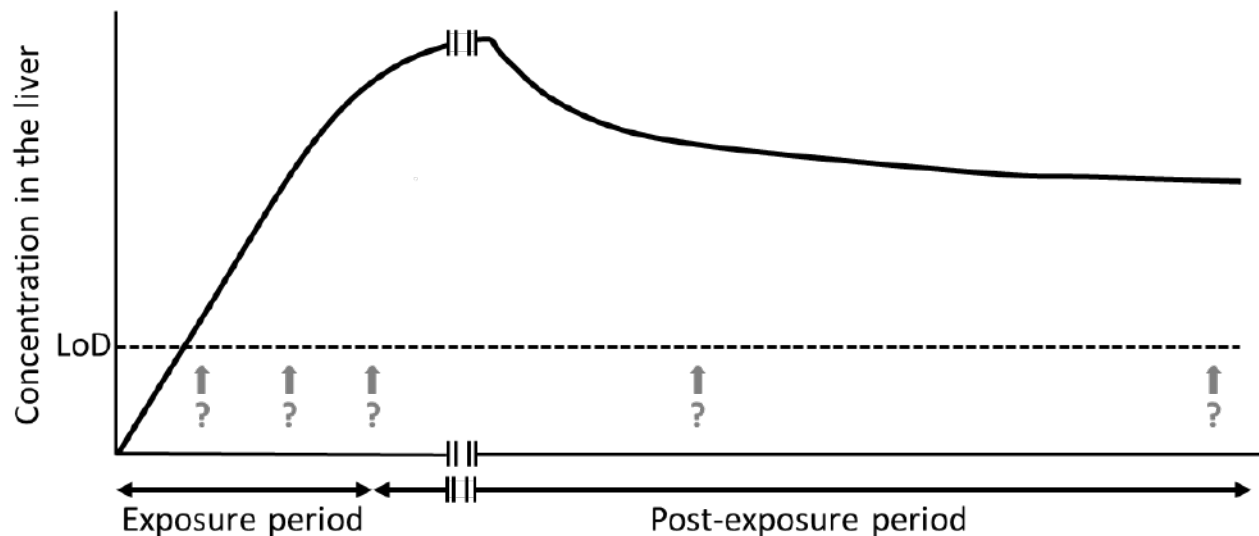




1. Approach Draft Gap Analysis

Is there sufficient data to roughly estimate:

- Exposure dose and duration
- Post-exposure period, and
- Number of time points to determine tissue kinetics (Figure 1)?



Using kinetic modelling and oral and inhalation toxicokinetic data with model NPs with slow (CeO_2 , TiO_2) and moderate (SiO_2) dissolution rates in relevant physiological media.

Figure 1: Hypothetical NP concentration in the liver during and after repeated inhalation exposure





2. Feedback from workshop and OECD JEG:

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

- Separate requirements for inhalation and oral exposure
- Clearly define very slowly, moderately quick and quickly dissolving NPs
- Exposure regimen and post-exposure period also depends on
 - analytics (LOD)
 - background concentration
 - administration mode
 - (agglomerated) particle size
 - dose at which toxicity is expected to occur





2. Feedback from workshop and OECD JEG:

What will be taken into account and addressed in the TG? (continued)

- Animal welfare
- Key organs and tissues, also depend on
 - Purpose of toxicokinetic study (e.g. reproductive)
 - Exposure route (olfactory bulb, Peyer's patches)
 - Physicochemical properties of NPs (expected toxicity of components)
- Number of animals per experimental group



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2. Feedback from workshop and OECD JEG:

What will be considered in developing the TG?

- Feasibility of including specific requirements with respect to
 - Mass balance
 - Urinary and fecal excretion
 - Blood kinetics (including blood volume and volume of distribution)
 - Transformation of NPs and secondary NP formation
 - Coating or surface modification





2. Feedback from workshop and OECD JEG:

What will be considered in developing the TG? (continued)

- Influence of
 - Retention of NPs in delivery systems
 - Volume of oral gavage (damaging epithelium)
- Use of the following data to determine requirements
 - IV data
 - Dose at absorption surface



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2. Feedback from workshop and OECD JEG:

What has lower priority in developing the TG?

- Broaden applicability (larger scale NPs and other types of ENMs)
- Quickly dissolving model NP (e.g. ZnO or Ag NPs) have lower priority (compared to slowly and moderately quick dissolving NPs)
- Localization of the NPs in the tissues and cells
- Sensitive populations



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2. Feedback from workshop and OECD JEG:

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

- Relation to other OECD TGs and GDs
 - TG412, TG 413, TG407 and TG 408 (28 and 90 day toxicity studies)
 - GD39, GD125 (guidance on inhalation and histopathology)
 - other TGs and GDs under development (other presentations today)
- Use of *in vitro* data on toxicokinetics
- Use of different analytical methods to follow NPs in the body
- Relevance of *in vivo* toxicokinetic data in rats for human risk assessment



Scientific basis for a new OECD TG on Toxicokinetics of ENMs



Are there any questions, remarks or suggestions?



Please, write your question, remark or suggestion in the chat



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Next steps

- a) Update of gap analysis
- b) Gather additional data, modelling and interpretation
- c) Deliver scientific basis for study requirements to OECD



Thank you very much for your input

If you have any additional suggestions please e-mail them to: Ilse.Gosens@rivm.nl.

