

Scientific basis for OECD TG on *in vivo* toxicokinetic study Session A & B

Closing plenary
November 5, 2020

Aims of these sessions

- Gather input on the draft gap analysis on study design requirements of *in vivo* toxicokinetic studies
- Identify additional data and prioritize most important remaining gaps

NanoHarmony



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

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Agenda Summary

1. Approach of the gap analysis
2. Identified data gaps
3. Identify additional data
4. Prioritization of most important data gaps



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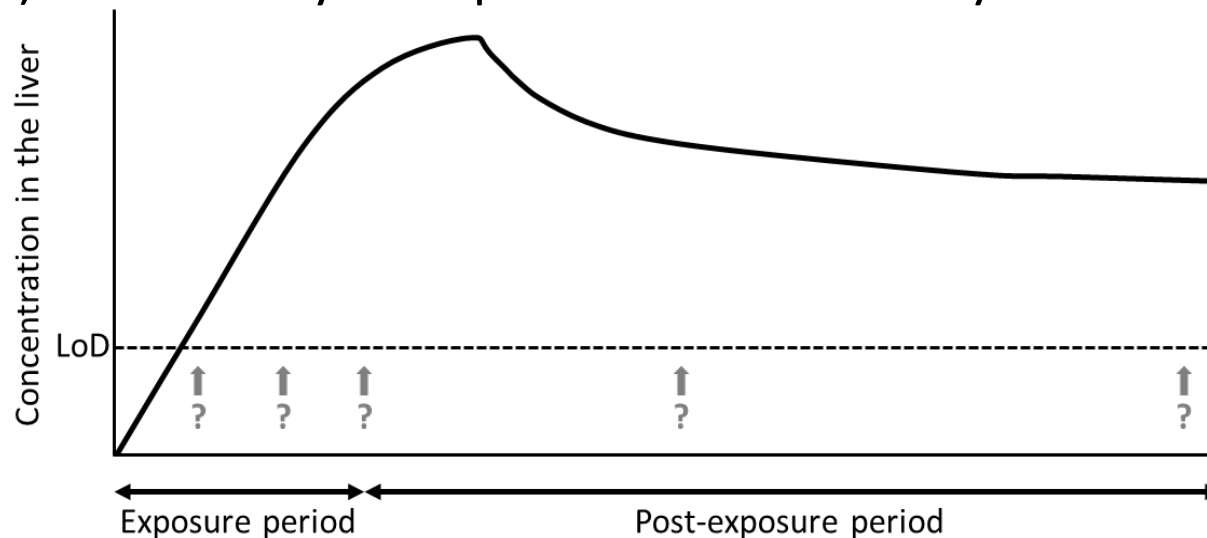
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1. Approach Draft Gap Analysis

Sufficient amount *in vivo* toxicokinetic studies available to roughly estimate:

- how high and long exposure
- how long post-exposure period, and
- how many time points for tissue analysis are needed to determine tissue kinetics (Figure 1)?



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

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



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Conclusions and recommendations: 1. Approach of gap analysis

General suggestions:

- Broaden applicability
- The hypothetical graph of liver burden
- Define very slowly, moderately quickly and quickly dissolving NPs
- Dosing and post-exposure also depends on analytics (LOD), background concentration, particle size, administration mode
- Also look at quickly dissolving NPs (e.g. Ag)
- Use of radiolabeled NPs as example

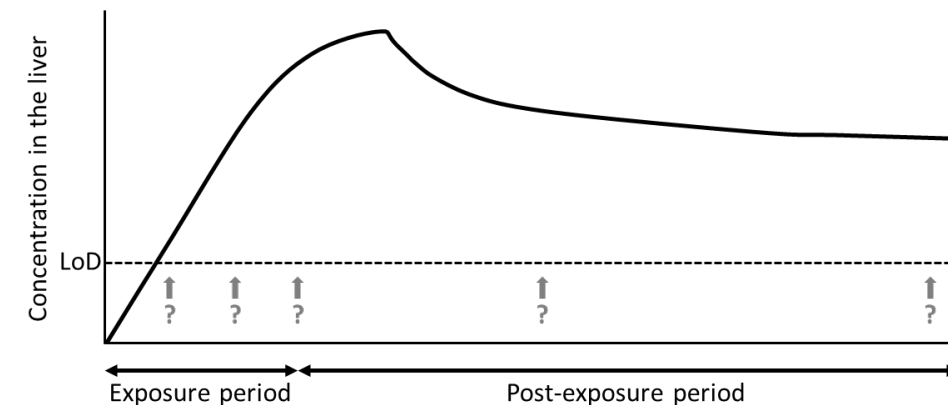


Figure 1: Hypothetical NP concentration in the liver during and after repeated inhalation exposure





Conclusions and recommendations: 1. Approach of the gap analysis

Other aspects identified in gap analysis

- toxicokinetic parameters
- dispersion and characteristics NPs within administration vehicle/matrix
- feeding status
- administration mode
- test species, strain, age and sex
- *in vitro* data

Additional aspects

- Animal welfare
- Blood kinetics
- Fecal and urinary excretion
- Additional organs
- Iv data
- Clearance from the body
- Number of animals per group
- Secondary particle formation
- Volume of gavage



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Conclusions and recommendations:

2. Identified data gaps

- PBK models oral exposure
- Toxicokinetic data SiO₂
- What is the worst-case situation?
 - dispersion and characteristics NPs in administration vehicle/matrix
 - feeding status
 - administration mode
 - test species, strain, age and sex

For some aspects, worst case situation is known:

- Oral exposure: fasted and juvenile animals
- Inhalation exposure: the most dispersed particles (less agglomeration or aggregation)

Additional data gaps

- Retention of NPs in delivery system
- Oral exposure: dose at absorption surface
- Blood volume and volume distribution
- Influence of size on absorption, urinary excretion, distribution and elimination





Conclusions and recommendations

3. Identification of additional data

- Unpublished data from EU projects and public REACH dossiers
- Several additional kinetic models
- Data indicating worst case oral is fasted state in juvenile animals
- Retention of NPs in delivery system

4. Prioritization of most important data gaps

- Prioritization of data gaps was not possible
- Many important issues were raised
- For regulation, insoluble nanomaterials would have priority



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Implications for the TG depend on:

- newly generated data
- kinetic modelling
- interpretation of all information
- prioritization of the various aspects

Next steps

- a) Update of gap analysis and discuss within the OECD JEG
- b) NanoHarmony Webinar on the 16th of December
- c) Generation additional data, modelling and interpretation
- d) Scientific basis for study requirements will be forwarded to OECD

Thank you very much for your input

If you have any additional suggestions please e-mail them to:
Susan.Dekkers@rivm.nl, preferably before the 18th of November

