PATROLS

Advanced Tools for NanoSafety Testing

Comprehensive testing of nano-material dissolution in biologically relevant media: Contributions to OECD guideline development

Background

The toxicity of manufactured nanomaterials (NMs) is controlled by several parameters among which material solubility and dissolution rate plays an important role. For regulatory use, an OECD test guideline (TG-105) for water solubility was previously used to assess solubility, but TG-105 is inadequate for testing of nanomaterials. Today, data on NM dissolution in relevant physiological media is required for grouping and read-across in the REACH regulation for chemical registration of nanomaterials (COMMISSION REGULATION (EU) 2018/1881 of 3 December 2018). Therefore, suitable standard methods or guidelines are highly warranted. A coordinated effort was initiated under the so-called Malta initiative to support development of OECD Test Guidelines and Guidance Documents needed to support different chemical regulations.

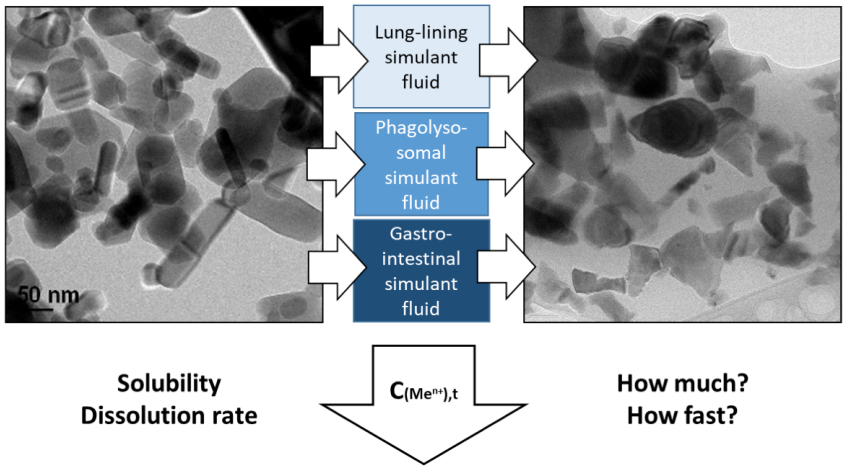

Illustration of the principal solubility and dissolution rate data generated in PATROLS. $C_{(Men+),t}$ indicates the concentration of elements in the solvent measured during testing.

Challenges

In PATROLS we tested and refined, as needed, three different approaches for determination of NMs solubility and dissolution kinetics in physiologically relevant media:

1. A continuous flow-through cell membrane system (CFS) tested for measuring the dissolution kinetics in lung-lining and lysosomal simulant fluid (Temperature and pH-control at liquid feeder) (inspired by ISO TR 19057:2017; Koltermann-Juelly et al., 2018)
2. A sequential batch reactor (SQBR) method tested using simulant fluids for the gastro-intestinal tract (Temperature and initial pH-control in media) (modified from DIN 19738:2017; Sieg et al., 2017).
3. An Atmosphere-Temperature-pH-controlled Stirred Batch Reactor (ATempH SBR) method for solubility and dissolution tested using lung-lining and lysosomal simulant fluid (test atmosphere, temperature and pH-control by titration in media) (Holmfred et al., In prep.)

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Studies were made to identify suitable physiological simulant test fluids (CFS), identify potential role of using different batch dispersion media for batch reactor testing (ATempH SBR) and document the established test protocols by dissolution testing of 12 to 15 different nano- and µm-size particles and fibres. These results are used as input for the OECD project developing a Guidance Document on the "Determination of solubility and dissolution rate of nanomaterials in water and relevant synthetic biological media".

Lessons learned

- Use of different simulant fluids for the same compartment can lead to significantly different results. Suitable test media for lung lining and phagolysomal fluid simulants were identified [results in preparation for publication]
- Use of different dispersion media can affect batch reactor dissolution data and selection may be needed considering biological relevance [results in preparation for publication]
- Relevant data on temporal solubility and dissolution rates can be achieved for each of the methods applied in PATROLS. Further evaluations will be made on comparability and toxicological relevance of data [results in preparation for publication].

References

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