Batch-to-batch reproducibility - a challenge for safety assessment and regulation

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For the safety assessment of nanoparticles reference materials of highest quality are required in sufficient quantities to the laboratories performing the tests. During physico- chemical and biochemical tests variability of the results for different batches is observed. The reasons for this variability are not yet clear. They may depend among other reasons on the variability of the physical properties and chemical composition of the tested particles, their dispersion in media and the exposure conditions. Without assuring the quality of reference materials the safety assessment and subsequent regulation of nanomaterials may face on-going discussion and legal challenge.

The identification of potential sources of variability of nanoparticles and their reduction is therefore an important task. As a first step towards this goal OECD proposed parameters for nanoparticle batches have been measured in the QualityNano project. These batches were prepared under carefully controlled conditions to relate the synthesis conditions with the measured results. The variability observed and the methods used will be discussed in more detail.

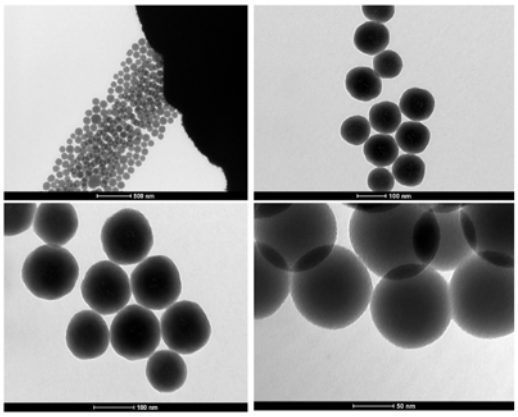

Figure 1. TEM images of silica nanoparticles SilNP003 produced by Stöber synthesis

Preliminary conclusions are drawn based on this work and on previous studies:

- Depending on the synthesis conditions the size distributions of the particle batches vary significantly.
- The size distributions of particles from liquid phase synthesis are narrow, however partial agglomeration is observed.
- Materials from flame synthesis are mostly aggregated and have broader size distributions.
- The batches produced by liquid phase synthesis are partly contaminated by low concentrations of metals (e.g. Cu).
- Particles from flame synthesis have a higher chemical purity, than the ones produced by Stöber synthesis.

With respect to the methods applied for measurement of the particle batches it is concluded:

- As the particles are frequently agglomerated or even aggregated the particle size distributions should be measured by several methods such as DLS and/or SMPS/electrospray and HR-TEM.
- The size distribution and crystallinity of the primary particles in agglomerates and aggregates should be characterized by HRTEM/SEM.
- ICP-MS is a valuable tool to identify variability of particle batches due to contamination by trace metals.
- The particle properties must be considered in the design and the interpretation of bioassays with respect to particle protein interaction, which may change the biological responses.
- The agglomeration of nanoparticles in culture media may lead to a partial sedimentation of the particles, which makes the dose determination difficult. To determine the applied dose the exposure at the air-liquid interface is the method of choice.

To reduce the variability of test results it is advised to set physico-chemical characterisation of all used particle batches by representative TEM images, DLS and ICP-MS. Only by identification and exclusion of particle batches of questionable quality this challenge for safety assessment and regulation will be met.

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