Do Mechanistic Effect Models have a place in ERA of engineered nanoparticles?

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Example from legislation:
The aim of EU Waterframework directive is that member states ensure good (ecological) status for surface (and ground-) waters. For the biotic part of the ecosystems ecological status has to do with 'composition and abundance of flora and fauna'

Described in Annex V of Directive 2000/60/EC
How can mechanistic effect modeling help to address effects on protection goals

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<th>Modeling approach</th>
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Figure from Palmqvist et al in prep
Overall objective is to assimilate data from major EU and US funded projects on nanotoxicity and generate models of the relationship between nanoparticle properties and toxicity.
Current data on nanoparticle toxicity primarily focus on short-term effects (often survival) and/or suborganismal effects.

For mechanistic effect models we need data like:

- Individual level effects under longer exposure periods with endpoints such as:
  - Somatic growth
  - Reproduction (output and timing)
  - Survival
  - Potentially some behavioral responses

- Uptake and elimination of chemicals (toxicokinetics)
  - Related to effects (toxicodynamics) under the same exposure conditions
Example: *Daphnia magna* exposed to Cadmium

**OECD 211:**
- Measurements at the end of the test
- Cumulative reproductive output
- Additional endpoints e.g. growth, survival

48 h: presumably no effect on growth

First brood: only effect in highest concentration

48 h: no significant effect on survival

Why is OECD 211 not enough?
- Only surviving offspring included
- Effects on e.g. growth might go undetected
- Test duration might be insufficient for other species

End of the test: no effect on growth
Reduction in somatic growth

21 days: no effect for reproduction

Major obstacles for obtaining NP data for MEMs

Major obstacles to producing and obtaining data required for MEMs:

• Keeping exposure concentrations constant over longer time periods
• Changes in NP size and properties over exposure time
• Characterizing NPs in complex media (such as sediment and soil)
• Distinguishing between adsorbed and absorbed particles in uptake and elimination.
• Data reported in a form that is not applicable for incorporation into models (e.g., LC$_{50}$ values) even if useful data are underlying the processed data
• Small changes in test design can produce applicable data, but lack of knowledge (communication) on what is needed may prevent these changes.

Picture by Amalie Thit Jensen: *Daphnia magna* exposed to CuO NPs (6nm; 1.2 mg Cu/L). Aggregated/agglomerated NPs stick to the outside of the carapace.

Single LC$_{50}$ or LT$_{50}$-value calculated based on dose- or time -response data

Figure From Fundamentals of ecotoxicology by Michael C Newman
Experience from other chemical groups
- In particular pesticides

Some experience from the evaluation of potential for implementation of mechanistic effect models in ERA has revealed the following challenges:

- Obtaining the right type of data for parameterization of models may be difficult (they are either not available or sometimes confidential)

- Stakeholder study by Hunka et al. (2012) showed high but often contradictory expectations to population models in pesticide ERA. Models should be:
  - Simple BUT able to answer complex questions,
  - Specific (i.e., precisely addressing explicit questions) BUT generic enough to be applied internationally (and represent average situations and generic species),
  - Provide different scenarios and ranges of probability estimates BUT give binary output (e.g., yes/no, below/above safety threshold)

- Population/effect models are seen as ‘black boxes’ (i.e., lack of necessary model documentation & lack of control over input parameters)

- Regulators request standard guidelines for models, and there is a general need for standardization of models
Examples of EU-US collaboration on MEMs

**LEMTOX workshop (2007)**
Was a turning point for the focus on potential use of Mechanistic Effect Models for Environmental Risk Assessment

**CREAM project (2009-13)**
Marie Curie ITN (EU FP7) involving 12 international partners

**RUC09 workshop (August 2009)**
On integrating population modeling in ERA

**ModeLink workshop (France this week)**
Guidance on use of MEMs in EU ERA

**SETAC Europe advisory group for mechanistic effect models in ecological risk assessment (MeMoRisk)**
How can we move forward?

We need:
• Better communication from modelers to experimentalists of the type of data needed (we are currently working on this)
• Better exchange of experience, knowledge and available data (e.g., at workshops such as this)
• Some general agreement on how to handle the problem with NP’s instability in exposure media (i.e., water) and the lack of ability to characterize NPs in complex media (e.g., sediment).

Why bother producing these data types?

See this as securing the data for future use, even if MEMs for NPs are not currently at a stage where it is realistic to include them in ERA

And even without MEMs more information may be obtained by a relatively small extra effort
Acknowledgement

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