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

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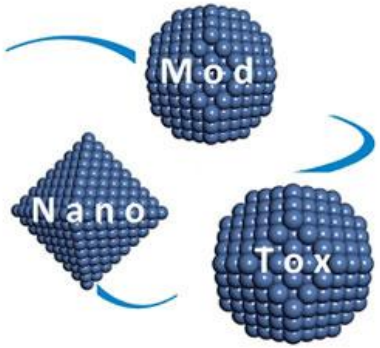

Risk assessment protection goals

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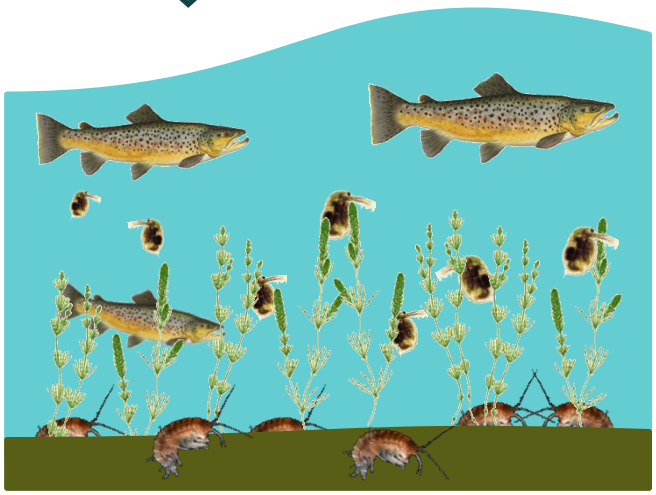
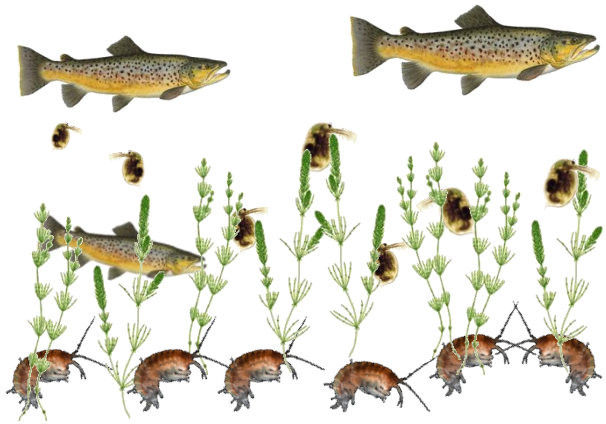
Example from legislation:
The aim of EU Waterframework directive is that member states ensure good (ecological) status for surface (and ground-) waters.
For the biotic part of the ecosystems ecological status has to do with 'composition and abundance of flora and fauna'

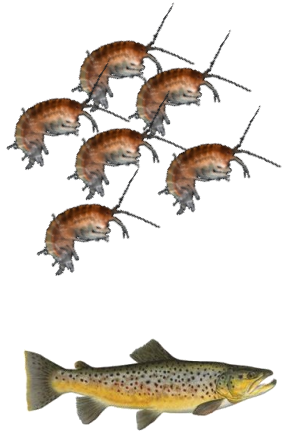
Described in Annex V of Directive 2000/60/EC



Ecosystems



Communities



Populations
(in some cases individuals)

How can mechanistic effect modeling help to address effects on protection goals

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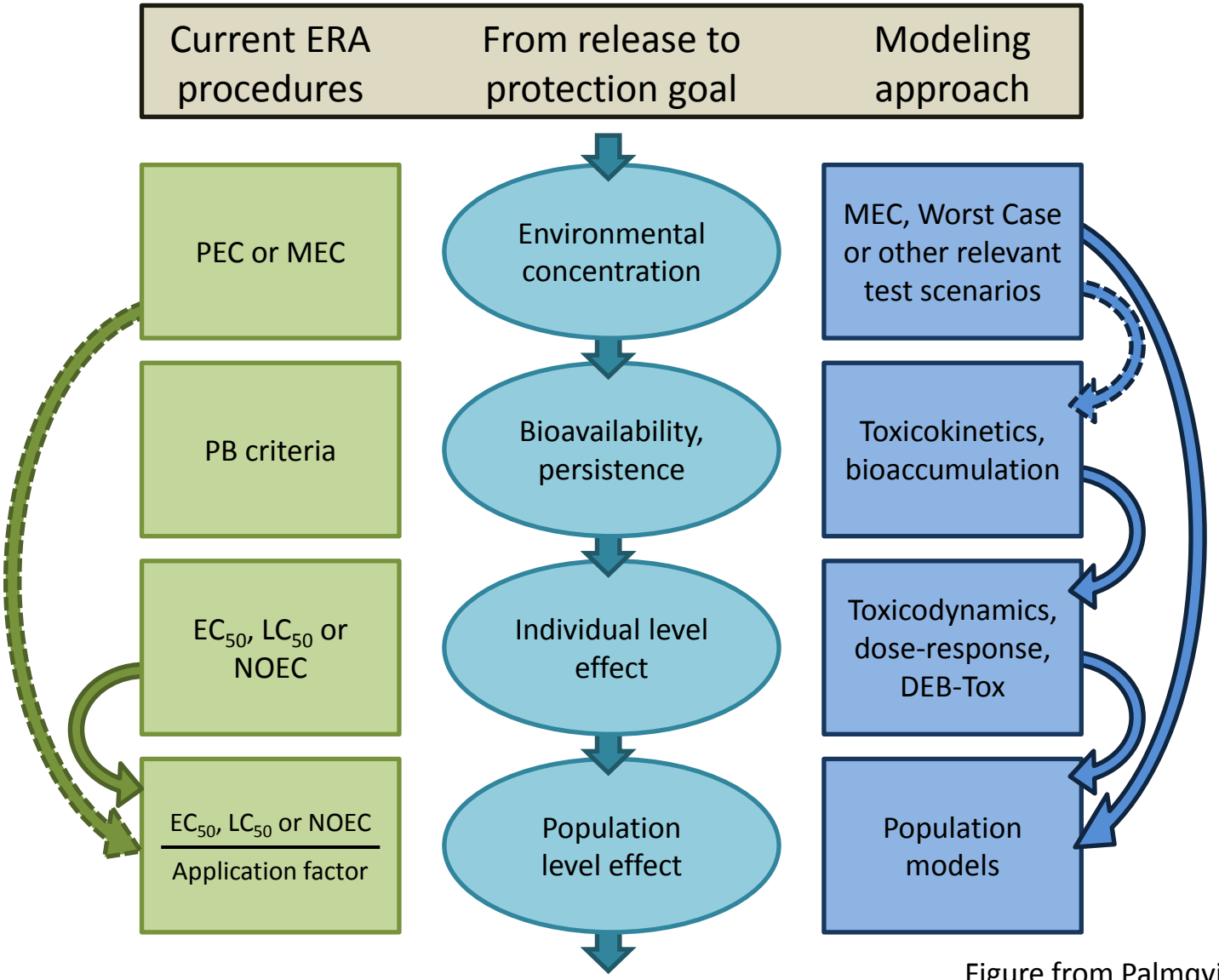

Figure from Palmqvist et al in prep

Modeling Nanoparticle Toxicity (ModNanoTox)

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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

Develop scientifically based risk assessment model

Model effects at population level

Perform physicochemical property assessment

University of Nebraska Lincoln

Universitas Roskildensis · In Tranquillo Mors · In Fluctu Vita ·

University of Birmingham

EMPA
Materials Science & Technology

eawag
aquatic research

in silico toxicology

Model nanoparticle exposure concentrations

Model toxicity at individual organism level (QSAR)

Model toxicity at individual organism level (TK-TD)

Data type needs for MEMs

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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

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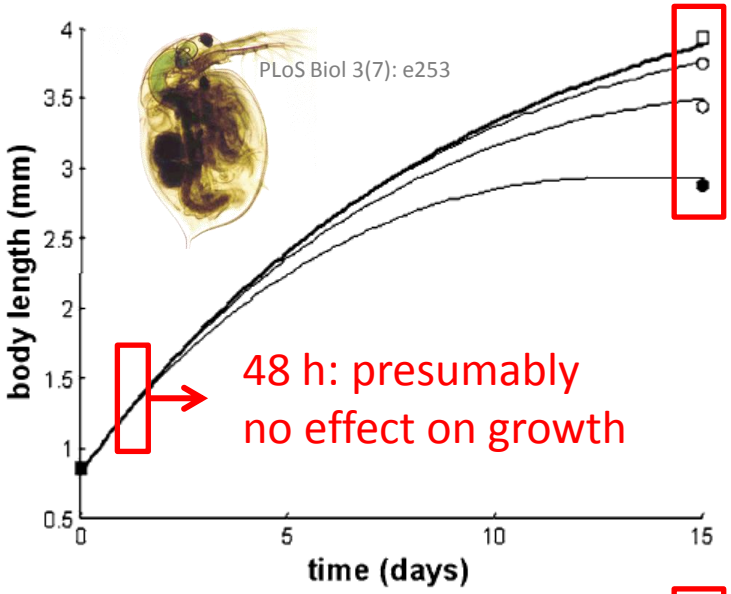
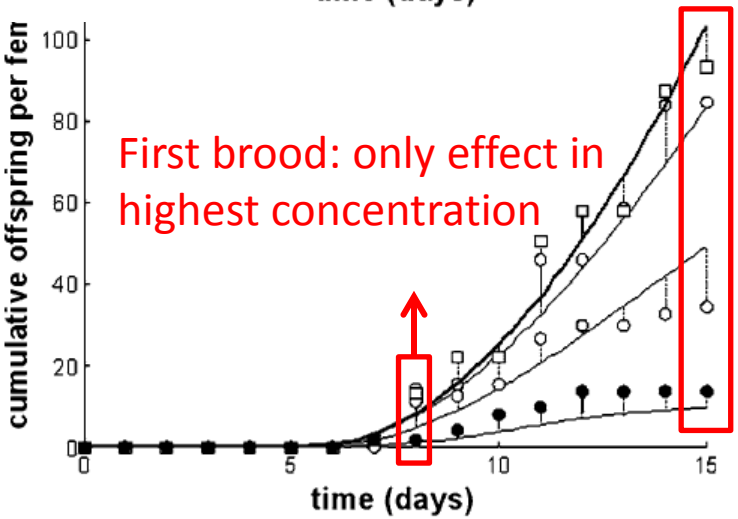
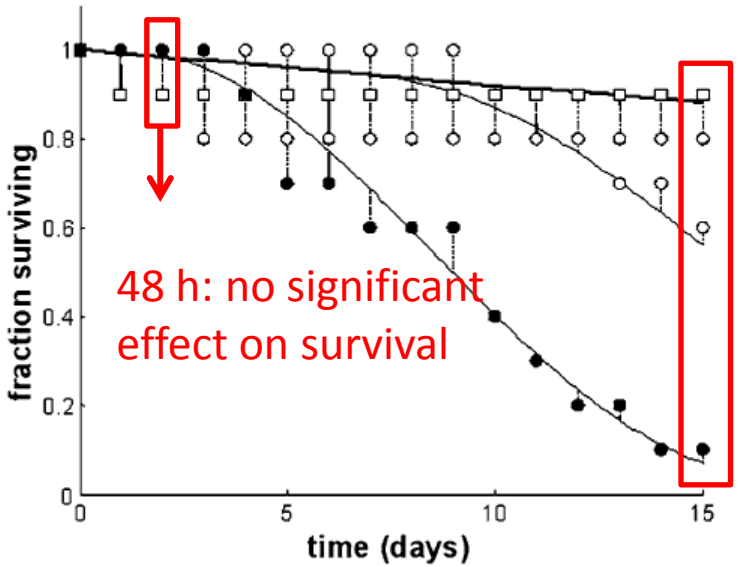




OECD 211:

- Measurements at the end of the test
- Cummulative reproductive output
- Additional endpoints e.g. growth, survival

→Effects detectable for
long term exposure



Figures from Jager et al (2006) Ecotoxicology 15: 305–314

Example: *Capitella teleta* exposed to Nonylphenol

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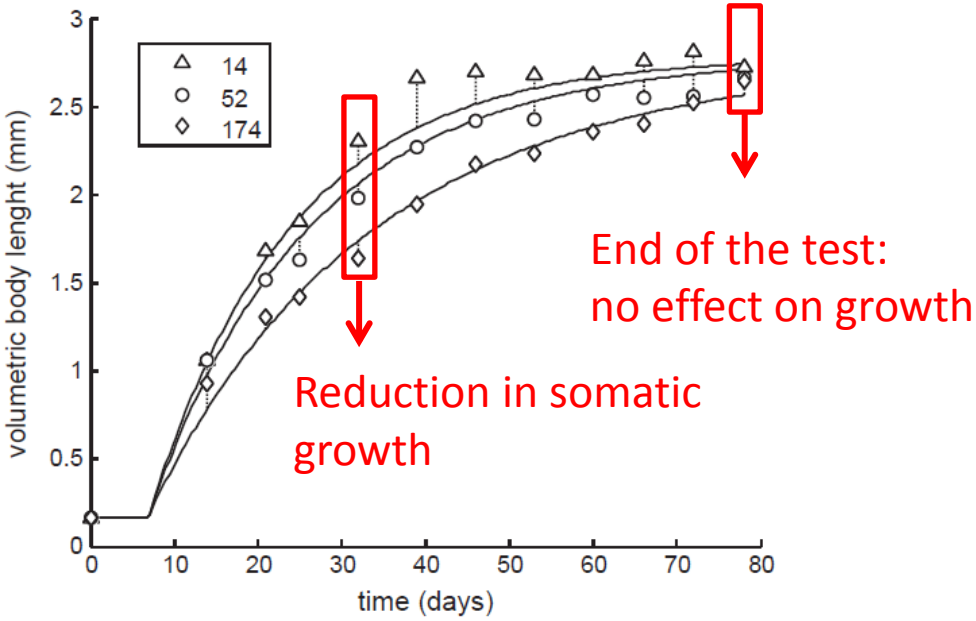
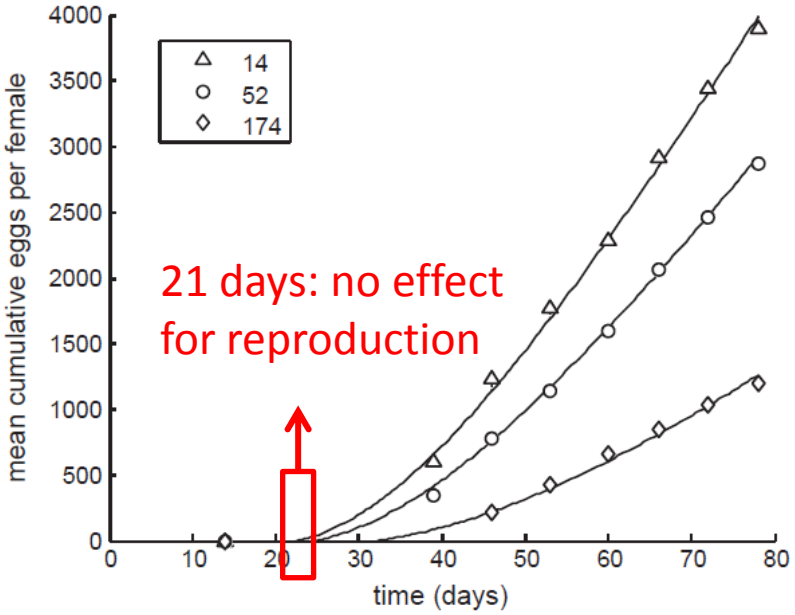
Why is OECD 211 not enough?

- Only surviving offspring included
- Effects on e.g. growth might go undetected
- Test duration might be not sufficent for other species





Figures from Jager and Selck (2011) Journal of Sea Research 66: 456–462

Major obstacles for obtaining NP data for MEMs

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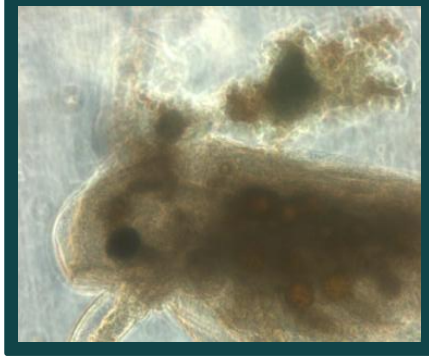
Major obstacles to producing and obtaining data required for MEMs:

- 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

VS

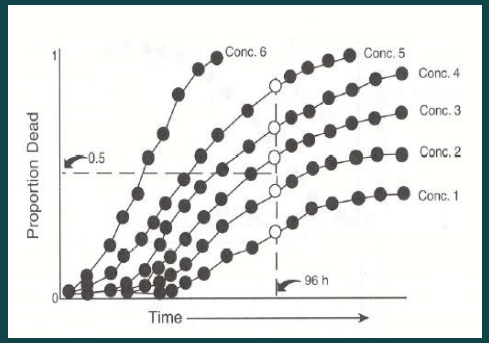


Figure From Fundamentals of ecotoxicology by Michael C Newman

Experience from other chemical groups
- In particular pesticides

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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

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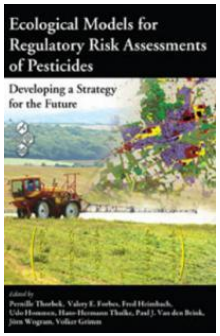

LEMTOX workshop (2007)
Was a turning point for the focus on potential use of Mechanistic Effect Models for Environmental Risk Assessment

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

RIFM

ecetoc

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

CREAM

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

SETAC

SETAC Europe advisory group for mechanistic effect models in ecological risk assessment (MeMoRisk)

How can we move forward?

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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 infomation may be obtained by a relatively small extra effort

Acknowledgement

Thanks to:
Amalie for letting us use her *D. magna* picture

Agnieszka for performing the stakeholder study and letting us present some of its key points today

ModNanoTox (and in particular coordinator Eva Valsami-Jones)