Environmental Risk Assessment of Nanomedicines

Specific methodological issues and implications for risk assessment

Silvia Berkner, Petra Apel

Umweltbundesamt, Germany

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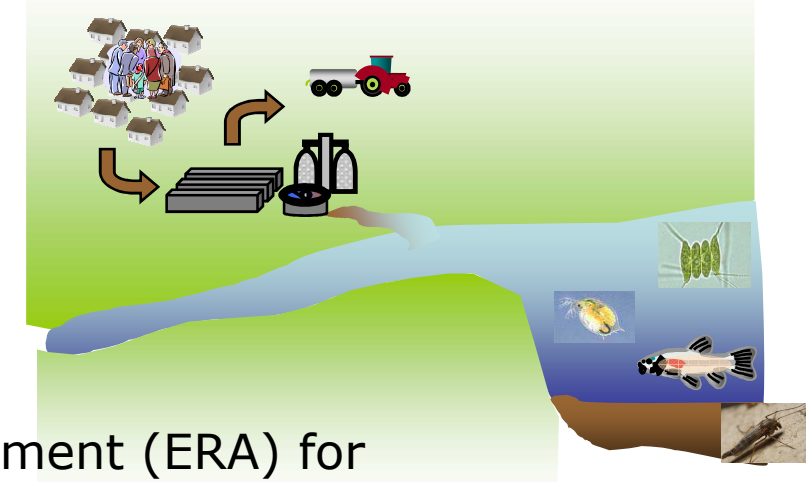
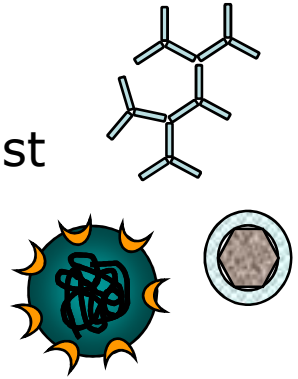
Outline



- Regulatory background
- Current Environmental Risk Assessment (ERA) for pharmaceuticals
- Necessary adaptations of the ERA approach relating to nano-pharmaceuticals
- Methodological issues - The OECD-Working Party on Manufactured Nanomaterials
- OECD Sponsorship Program - test substances of interest for the evaluation of nano-pharmaceuticals
- Conclusion and outlook



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Regulatory background

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Directive 2004/27/EC requires an ERA for

- all new marketing authorization applications
- type II variations, if an increase in environmental exposure is to be expected

The risk for the environment is not included in the Risk-Benefit-Analysis

-> Risk mitigation measures:
advice on correct disposal in PL and SPC

obtain information on compounds entering the environment that may pose a risk
-> e.g. include the compound in monitoring programs

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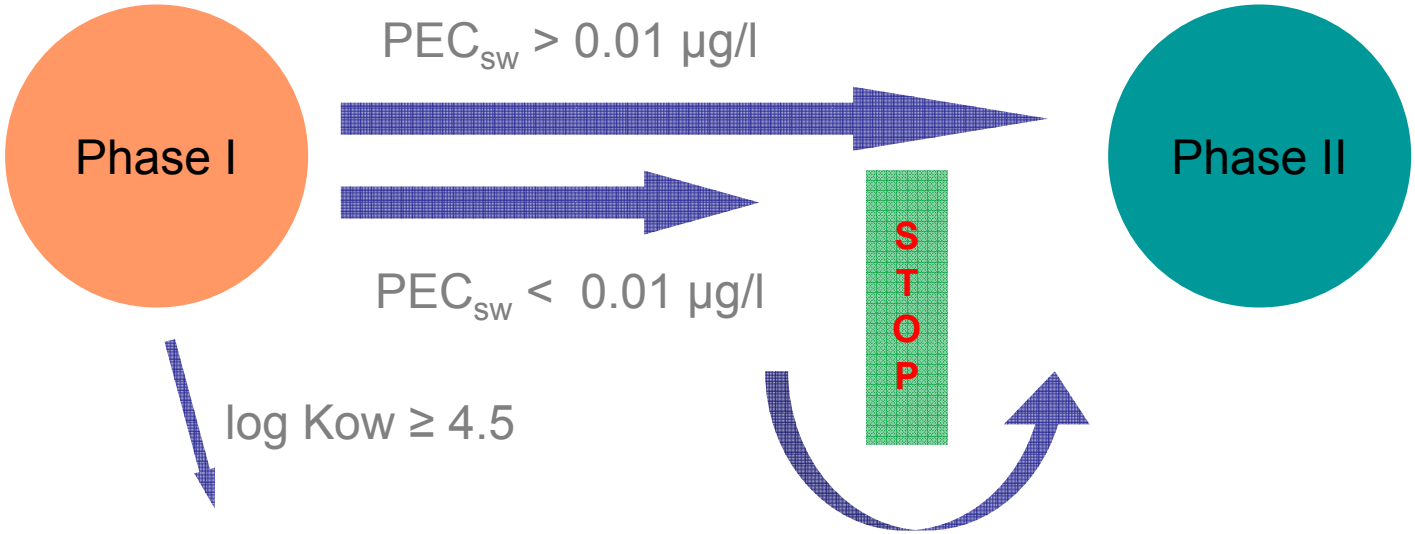
Environmental Risk Assessment

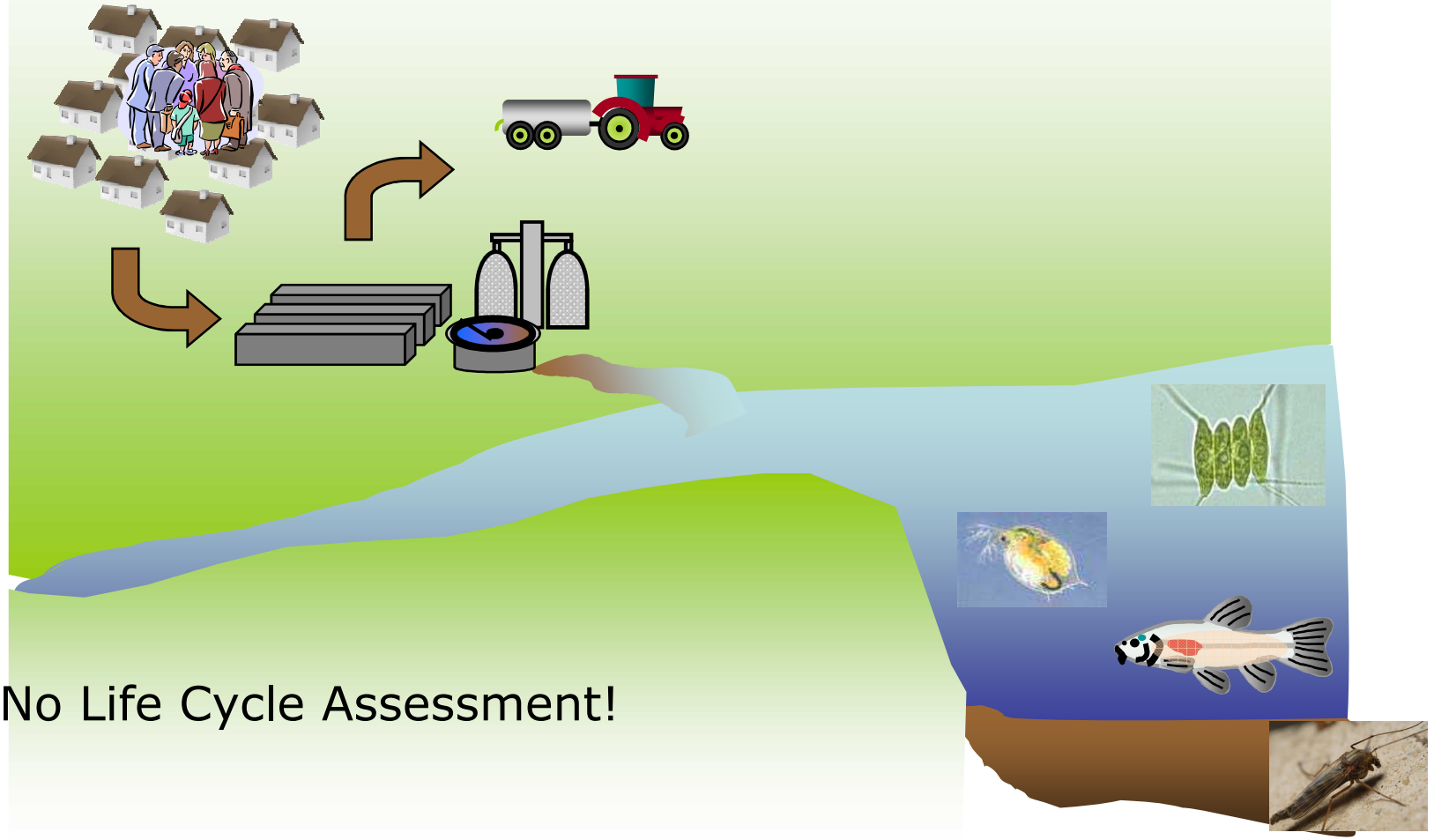
Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, came into effect in December 2006)

$$PEC_{surface\ water} = \frac{DOSEai \times Fpen}{WASTEWinhab * DILUTION}$$



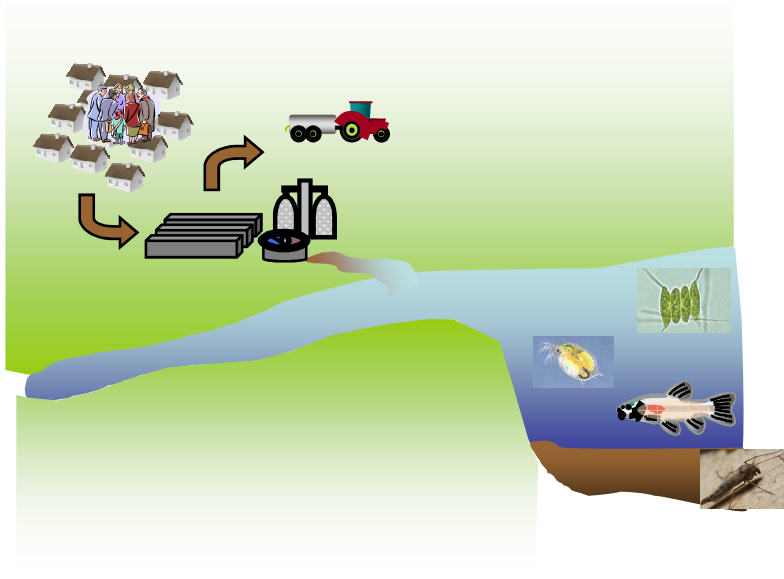
Data requirements

Phase II: data on fate and effects in the environment



No Life Cycle Assessment!

Data requirements



Phase II

Fate: log K_{ow} (OECD 107,…)

ready biodegradation (OECD 301)

-> if not readily biodegradable

-> water/sediment study (OECD 308)

-> if transfer to sediment -> sediment toxicity test

adsorption to sludge (OECD 106, 121)

-> if K_{oc} > 10000 the terrestrial compartment has to be considered

If log K_{ow} > 3 -> Bioaccumulation (OECD 305)

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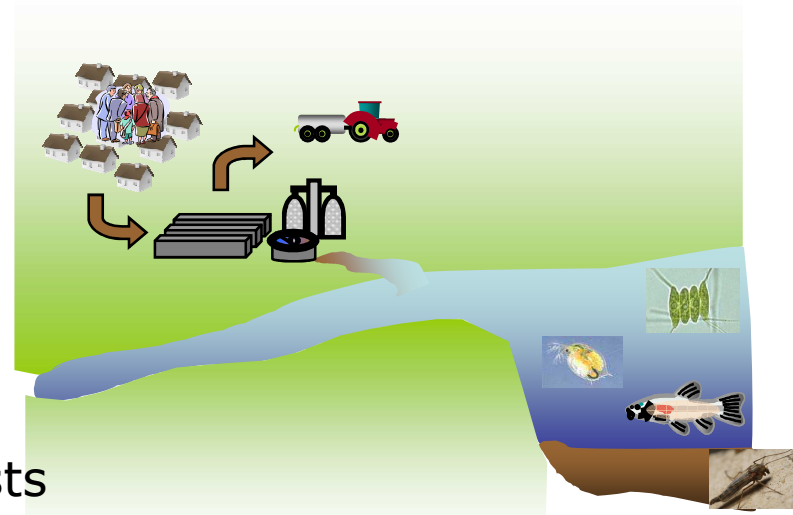
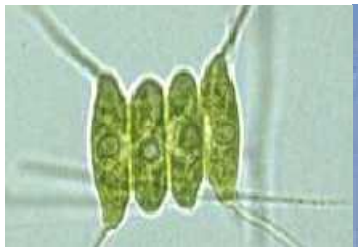
Data requirements

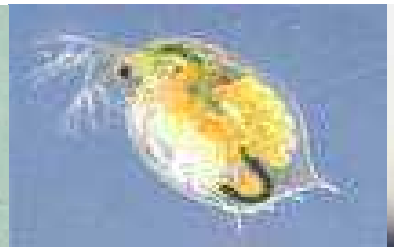


Phase II

Effects: aquatic base set long term tests

- activated sludge microorganisms (OECD 209)
- algae (OECD 201)
- Daphnia (OECD 211)
- fish (OECD 210)
- sediment organisms (OECD 219/218)





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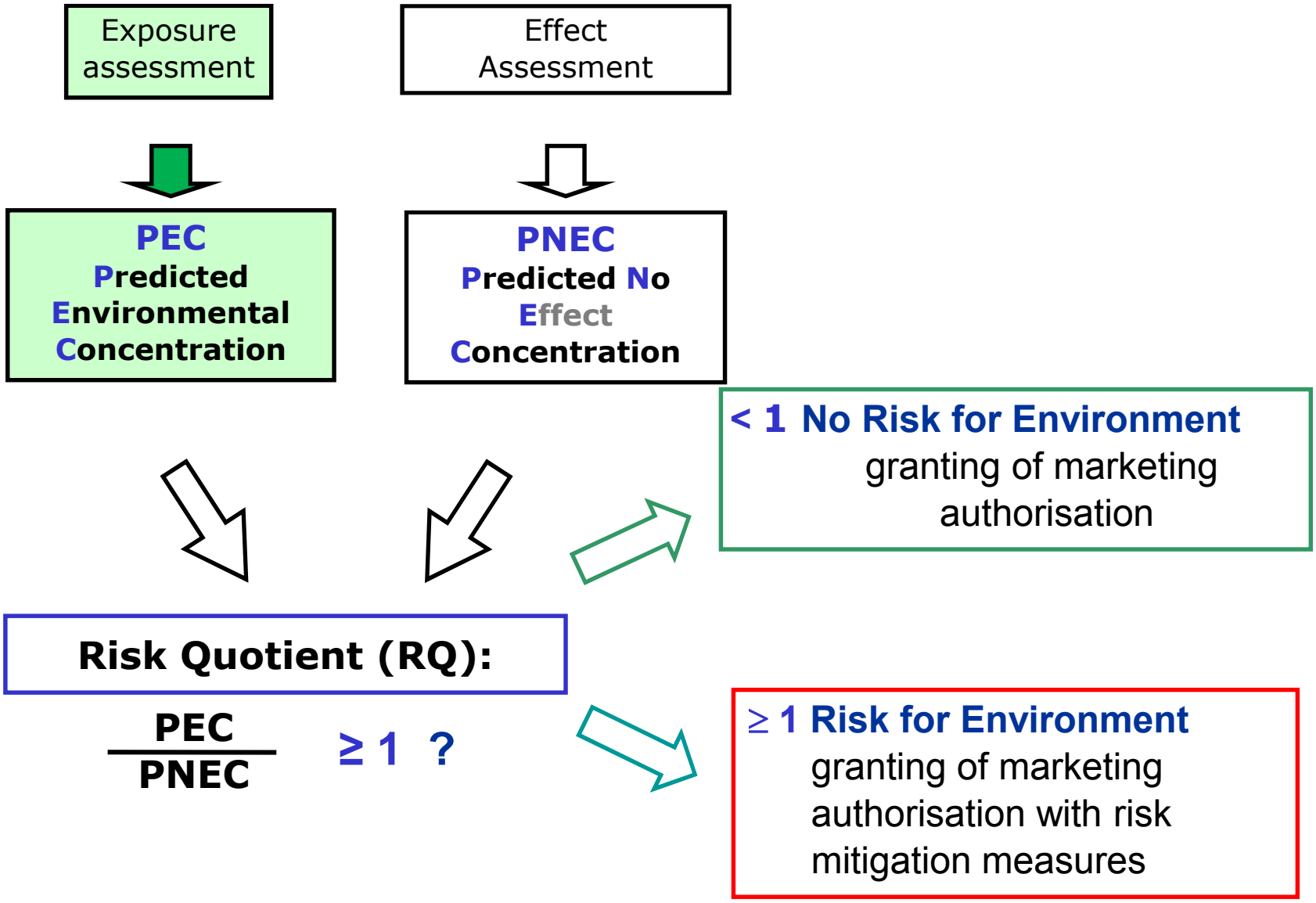
Environmental Risk Assessment



Adaptations for nanomedicines

Problem: PBT screening based on octanol/water partition coefficient (log K_{ow})

- log K_{ow} determination is only applicable for some nanomaterials
- mechanism of uptake into cells and organisms may be different from that of small molecules
- may vary for different nanoparticles

-> other descriptor(s) needed?

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Adaptations for nanomedicines

Problem: Phase I action limit

May nanoparticles show effects below 10 ng/L?

- only limited information available
- study results are often not comparable – no standardised procedures
- long term studies are missing although there are indications for sublethal effects (oxidative stress, histopathological effects)
- the role of nanoparticles as carrier for other molecules of concern and resulting effects need further clarification

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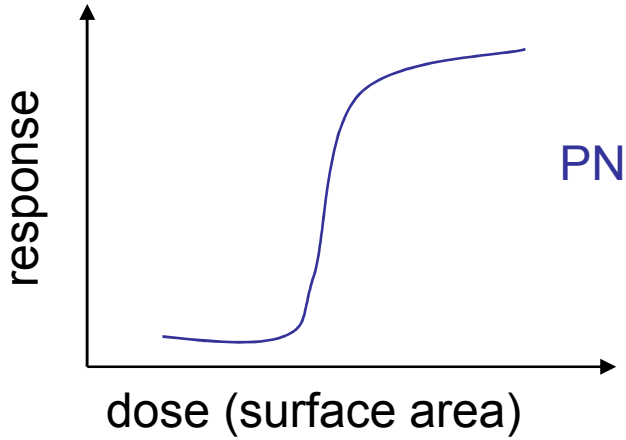
Adaptations for nanomedicines

Problem: mass based metrics in PEC/PNEC comparison

Better descriptors for observed dose-response relationship?

- number concentration
- size/size distribution
- crystalline phase
- specific surface area
- surface charge
- surface modification
- shape
- solubility
- aggregation/agglomeration state of the particles
- …



$$\frac{\text{PEC (µg/L)}}{\text{PNEC (surface area/L)}}$$

?

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Adaptations for nanomedicines

Problem: are nanoparticles excreted as nanosized compounds?
Can aggregated/agglomerated particles regain their nano character after excretion?

Importance of ADME studies, with special emphasis on

-> Metabolism

-> Excretion

However the aim of toxicokinetic/ADME studies is most often not to elucidate in which form the active ingredient is excreted

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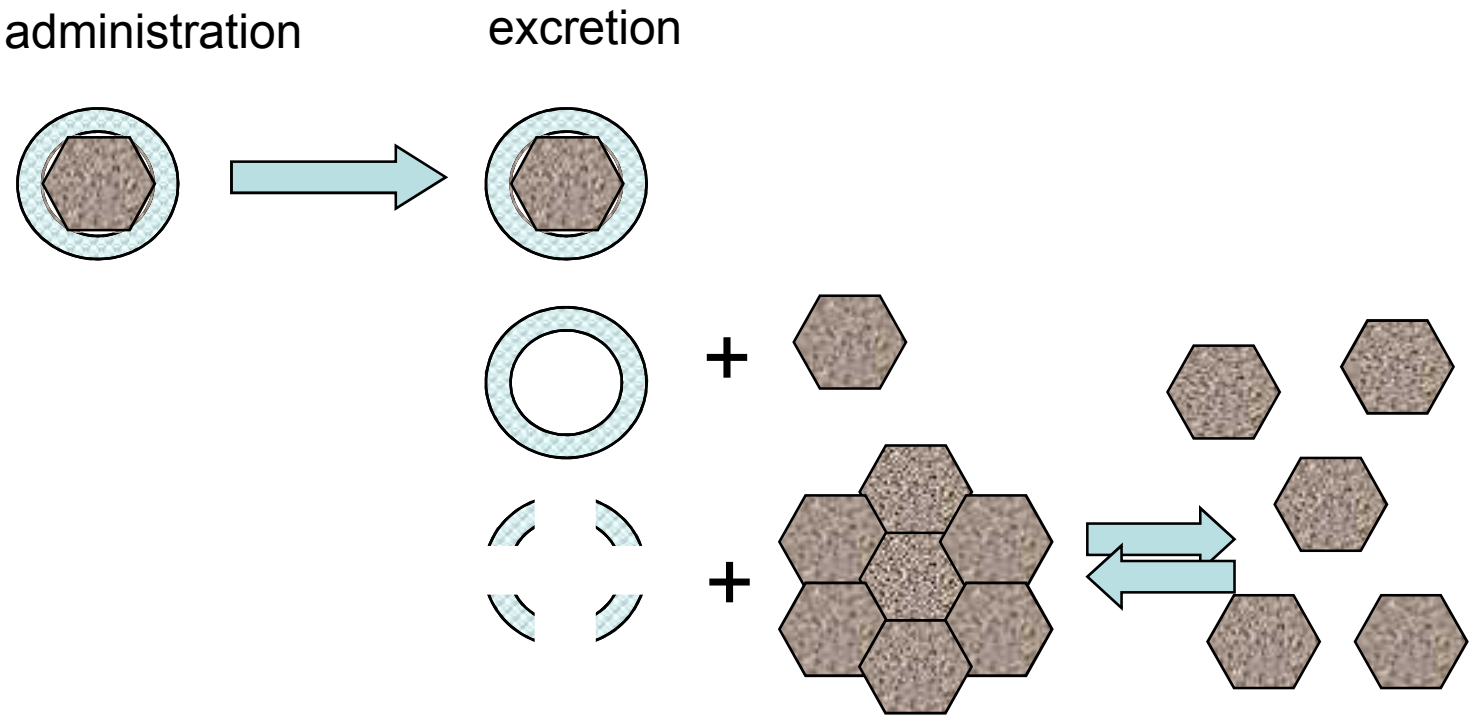
Adaptations for nanomedicines



Design of ADME studies is also important for ERA

-> Coating and core part of nanoparticle?

-> Dual labelling?

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Adaptations for nanomedicines

Problem: studies on fate and effects should be conducted according to OECD Guidelines for the testing of chemicals

- Several parts of the guidelines need adaptations
- Some tests may need completely different approaches

->OECD Working Party on Manufactured Nanomaterials

Established in 2006 to develop methods to ensure human health and environmental safety

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OECD Working Party on Manufactured Nanomaterials

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD

Areas of work

Development of a database on Human Health and Environmental Safety (EHS) research

EHS research strategies on Manufactured Nanomaterials

Review of OECD test guidelines for their applicability to Manufactured Nanomaterials

Safety testing of a representative set of Manufactured Nanomaterials (Sponsorship Programme)

International co-operation on voluntary schemes and regulatory programs

International co-operation on risk assessment

The role of alternative methods in nanotoxicology

Exposure measurement and exposure mitigation

Environmentally sustainable use of nanotechnology

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Review of OECD Guidelines

Preparation of test suspension/dispersion, test substance application and stability of test suspension/dispersion (all tests in general)

- Method of dispersion (stirring – sonication) and dilution influences the form/properties of suspended nanoparticles
- pH, ionic strength, an-/cations affect aggregation/agglomeration behaviour
- Presence of dissolved organic matter influences the properties of nanomaterials and the stability of the test suspension
- Stability during test
- Appropriate characterisation at appropriate intervals

Preliminary guidance document for sample preparation and dosimetry has been published (ENV/CHEM/NANO(2009)7/REV3)

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Review of OECD Test Guidelines (effects)

- testorganisms and endpoints generally suitable
- additional endpoints required?
- long term tests are important
- test substance characterisation and metrics are inadequate
  most predictive properties instead of mass based concentration to describe dose/response relationships
- appropriate control samples
  e.g. if stabilising agent is used to obtain stable dispersion

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Review of OECD Test Guidelines (fate)

Tests with only minor need for adaptations:

- ready biodegradation (OECD 301):

-> only for C-containing nanoparticles

not applicable for anorganic compounds

- adsorption/desorption to soil/sewage sludge (OECD 106, 121)

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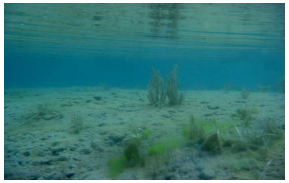
Review of OECD Test Guidelines (fate)



- Degradation in water/sediment systems (OECD 308)
- Bioaccumulation (OECD 305)

  Problematic because of more complex test systems and more complex analytical determinations

  e.g. analytical determination of nanoparticles in sediment without extraction?

  spiked food bioaccumulation tests might be more appropriate than exposure through the water phase

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OECD Sponsorship Programme

Aim of the program:

- systematic testing
- representative nanomaterials
- defined set of endpoints
- method adaptation and
- development of quality standards

Mainly OECD test methods are used, covering physico–chemical properties, environmental fate, ecotoxicology and toxicology

-> endpoints are relevant for ERA for human medicinal products

BUT: not all OECD tests that are relevant for the ERA might be covered by the programme

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OECD Sponsorship Programme

nanomaterials to be tested:

- Fullerenes (C60)
- Single-walled carbon nanotubes (SWCNTs)
- Multi-walled carbon nanotubes (MWCNTs)
- Silver nanoparticles
- Iron nanoparticles
- Gold nanoparticles
- Titanium dioxide
- Aluminium oxide
- Cerium oxide
- Zinc oxide
- Silicon dioxide
- Dendrimers
- Nanoclays

BUT: No lead sponsor ->
incomplete dossier is to be expected

Draft dossiers are scheduled for 2011

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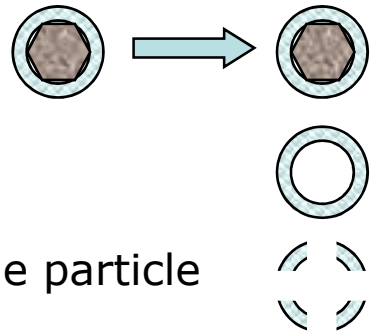
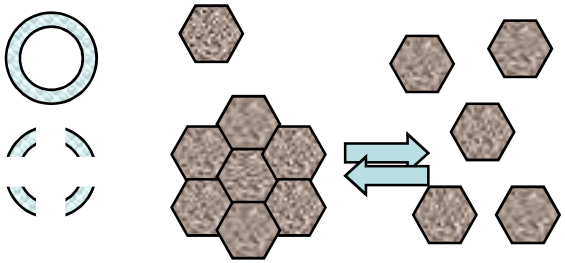
Medical nanoparticles





Inner core: nano sized metal oxide particle

Coating: polymer (carbohydrate)

Whole particle: nano scale, core: nano scale

Phase I: PEC calculation based on the whole particle

-> Phase II required

Information from ADME studies, stability studies

Information from scientific literature

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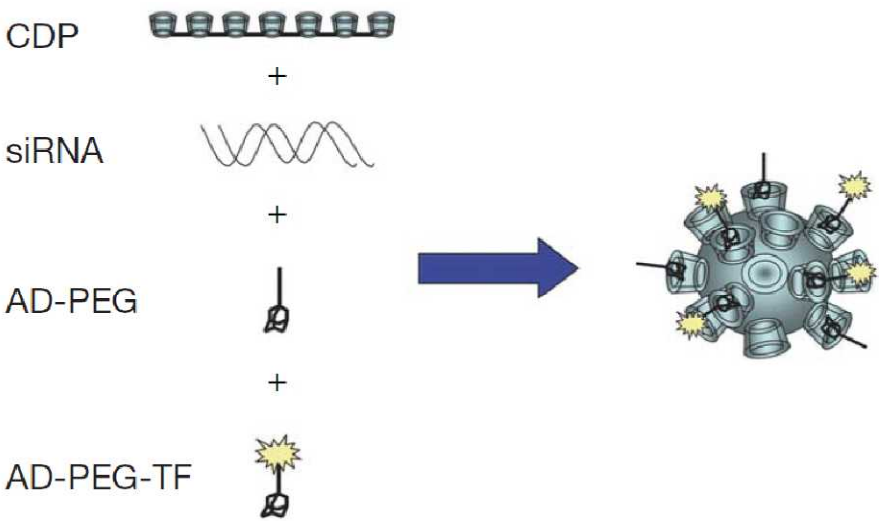
Medical nanoparticles

Nanoparticle for delivery of siRNA (Davis et al., 2010, Nature 464)

Complex particle:
Composed of siRNA,
Coating of cyclodextrin-polymer that forms an inclusion complex with adamantane that attaches PEG molecules to the particle that are partly functionalised with a protein

Whole particle: nano scale,
building blocks: nano scale?



Assessment will have to focus on the whole particle and on the building blocks

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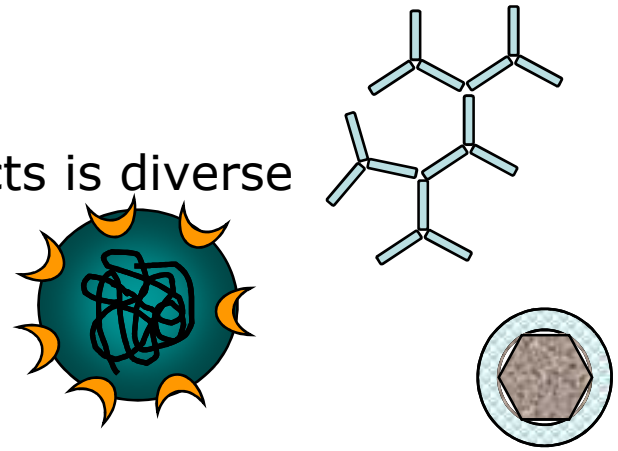
Medical nanoparticles

The spectrum of nanosized medicinal products is diverse



Different types of coatings/envelopes

- Liposomes
- Carbohydrate based coatings
- PEG based coatings
- Dendrimers
- combinations of different coatings
- no coating
- may be functionalised
- complex particles

May contain different core parts

- Small molecules
- Biopharmaceuticals/biologicals
- Anorganic particles

-> it may be difficult to find solutions that fit all particles equally well

-> consider whole particle
-> consider building blocks
-> consider "metabolites" from ADME studies
-> assessment case-by-case

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Conclusions and Outlook

- Nano pharmaceuticals need to undergo an ERA
- The current ERA approach needs adaptations
- Input and guidance is expected from the OECD Working Party on Manufactured Nanomaterials

BUT: Specific information for medicinal nanoparticles is missing

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Conclusions and Outlook

Applicants should submit **in the ERA part** of the application as much information as available on

- ADME studies
- fate and effects in the environment (e.g. scientific literature)
- Information from stability tests or other quality tests might also be helpful

Applicants are encouraged to seek regulatory advice

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