PNEC – Predicted No Effect Concentration
PNEC – Potential Nanomaterial Enhanced Conflicts

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PNEC – Predicted No Effect Concentration
PNEC – Potential Nanomaterial Enhanced Conflicts

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Workshop: Addressing protection goals and adding realism to ERA of ENMs
SETAC, Vancouver 09NOV2014

The Danish EPA NanoDEN project

- The Danish EPA has issued a range of projects with the common title: "Better control of nanomaterials"

- The aim of the present work is to
  - Assess the current environmental risk assessment (ERA) framework with special focus on the applicability for nanomaterials (NMs) and suggest an alternative approach for the calculation of predicted no effect concentrations (PNECs)
  - Evaluate accessible ecotoxicological studies for their adequacy for PNEC estimation with the purpose of performing (ERA)
  - Derive PNEC values for the selected nine NMs (Ag, Fe, CuO, ZnO, TiO2, CeO2, carbon nanotubes, carbon black, quantum dots)

- Work is ongoing (deadline end of 2014)
- Results feed into an ERA of the selected NMs (spring 2015)

Established approach on PNEC estimation

- The Predicted No Effect Concentration is an approach to establish the contaminant level in the environment that should cause no harm
- NMs are considered similar to conventional chemicals in respect of ERA within REACH and EU
- The risk quotient is calculated from the PEC/PNEC relation: RQ=PEC/PNEC – the higher the RQ, the higher the likelihood for adverse effects
- REACH suggests PNEC (EC/AF) to be calculated either derived from the
  - assessment factor (AF) approach or
  - species sensitivity distribution (SSD)
  - Applying an AF to the lowest EC or the HC_5

1-5

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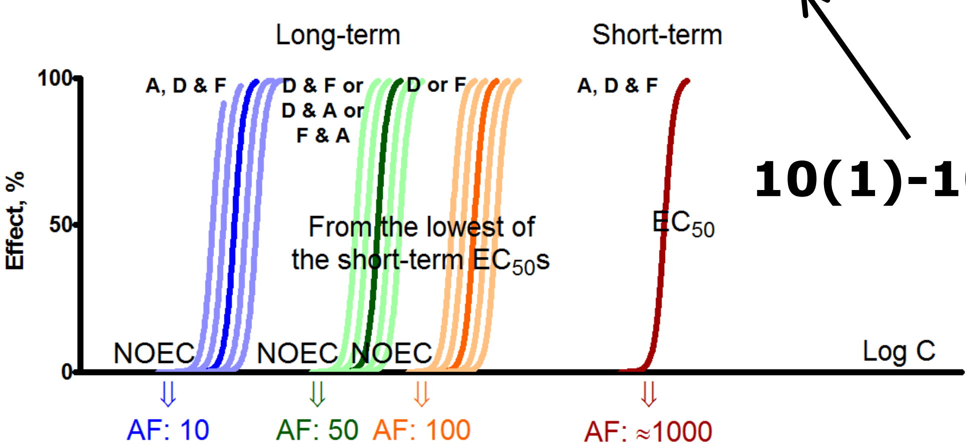

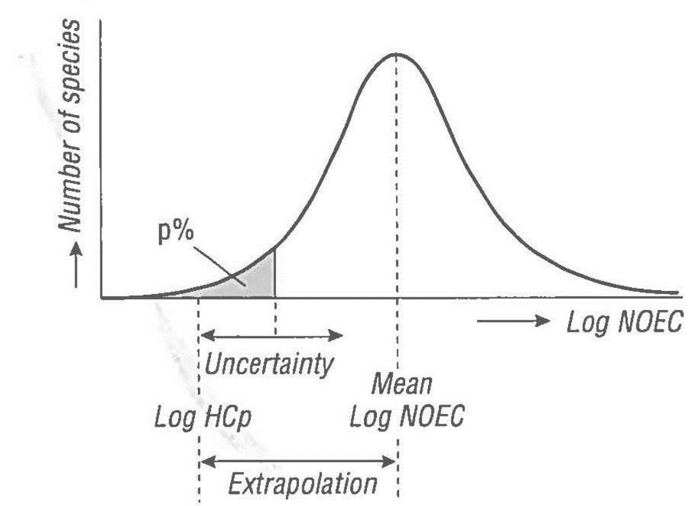

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- *IF NMs are similar to traditional chemicals, this seems to be straight forward and an approach that works – at least we believe it works for traditional chemicals*

Potential Nanomaterial Enhanced Conflicts

- However, we believe that NMs have properties that are distinctly different from traditional chemicals, e.g. aggregation, solubility, surface charge or even toxic mode of action, which will have significant influence on
  - NM quantification
  - NM behaviour in ecotoxicological tests
  - Dose-response relationships/mode of toxic action

- When blindly applying the traditional approach, there is thus a risk for **Potential Nanomaterial Enhanced Conflicts** when deriving PNEC values, **as PNEC estimation relies on the validity of the conducted ecotoxicological tests**

- Is the current regulatory validation of test results adequate for studies on NMs?
- Are our standard ecotoxicological test set-ups suitable for NMs?
- Is the current PNEC approach suitable for NMs (e.g. application of AFs)?

Current regulatory validation of ecotoxicological studies

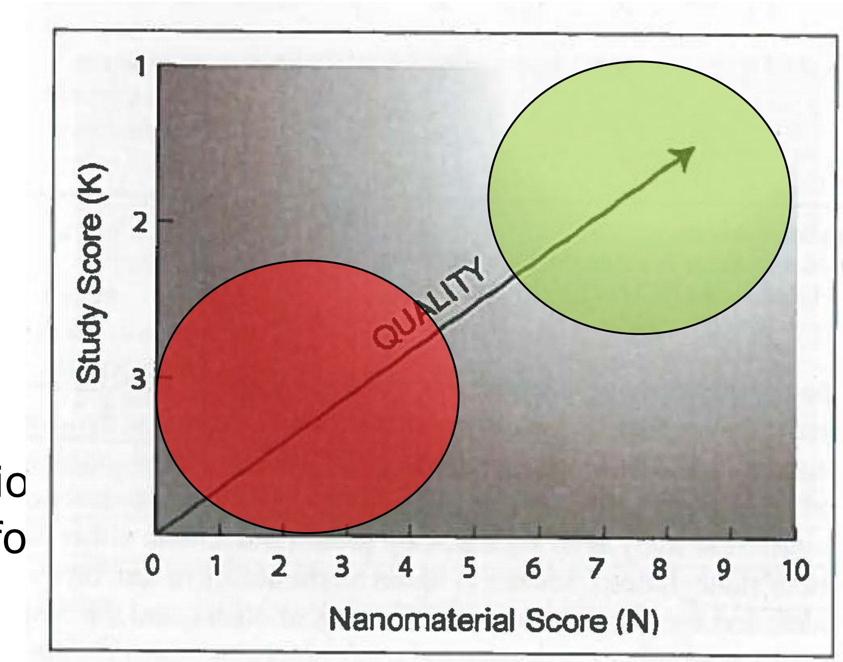
- Currently ECHA (the European Chemicals Agency) applies the Klimisch score to validate ecotoxicological studies
  - Studies performed (blindly) according to current guidelines, commonly accepted protocols (ISO/OECD) and GLP obtain scores of K1-2 and are thus valid for ERA
  - Studies NOT performed according to current guidelines and GLP, and maybe tailored to obey the tested substance's behaviour, obtain scores of K3-4 and are thus NOT valid for ERA

- Good to have proper test designs, but do established test set-ups consider the distinctly different nature of NMs in comparison to traditional chemicals?
- Guideline and GLP studies are thus favoured, despite their doubtful reliability for NMs

Klimisch et al., 1997

Literature validation of NM effect studies

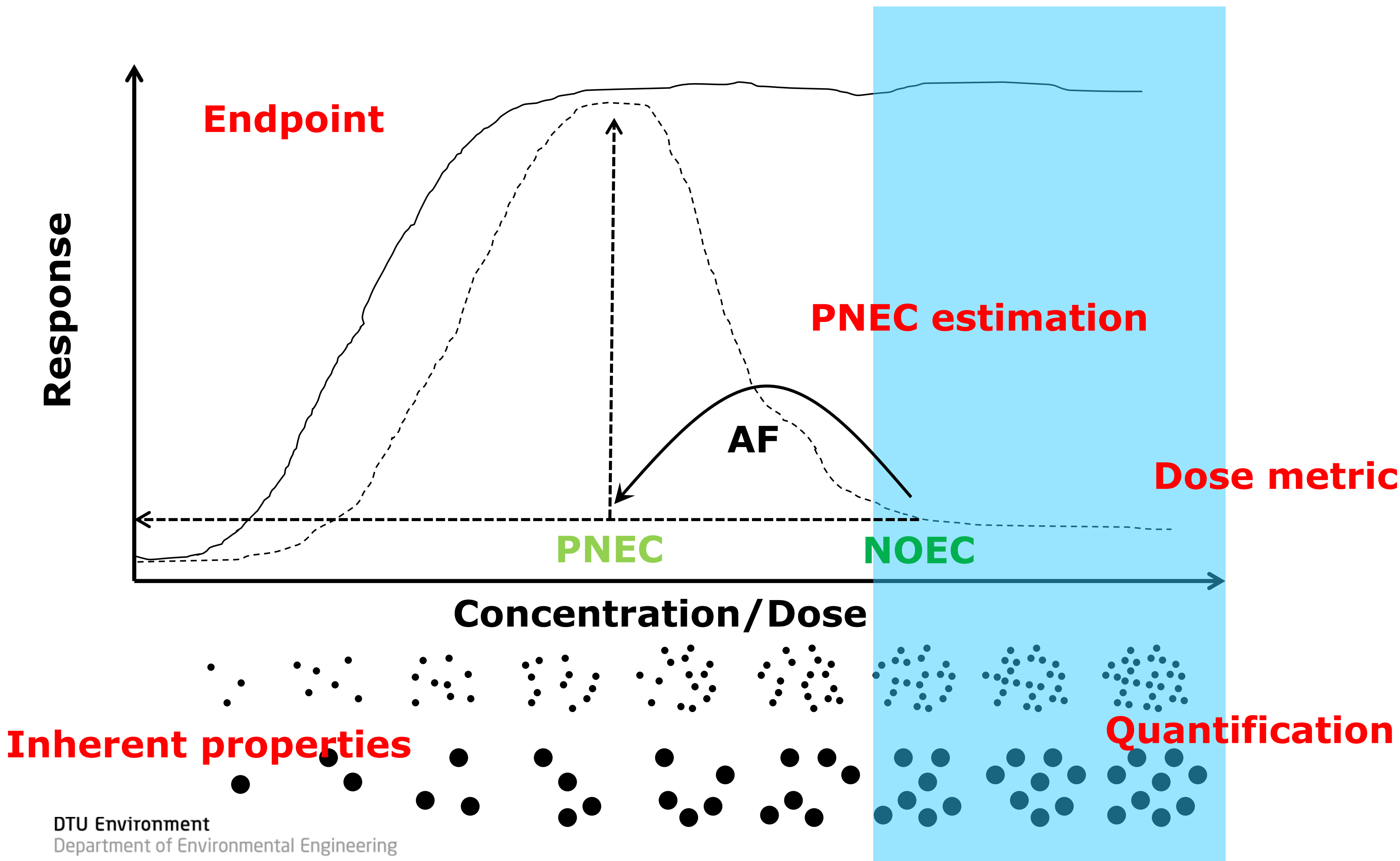
- It has been suggested to add a second dimension to the Klimisch score, by supplying information on the following characteristics of the NM:
  - Agglomeration and/or aggregation
  - Chemical composition
  - Crystal structure/crystalinity
  - Particle size/size distribution
  - Purity
  - Shape
  - Surface area
  - Surface charge
  - Surface chemistry (including compositio
  - Whether any characterisation was perfo
    media



- Toxicological studies of NMs should therefore be assessed according to the Klimisch score (K1-4) for test reliability AND the Nanomaterial score (N1-10) for characterisation
  - Good studies: **K1-N10**
  - Bad studies: **K4-N0**

Card and Magnuson, 2010

Hypothetical dose/response curve



Evaluation approach developed in collaboration with Stockholm University

- Conventional chemicals focusing on pharmaceuticals
- Four papers
  - Ring test
  - Evaluation of the ring test
  - Criteria for Reporting and Evaluating ecotoxicity Data. Part III. An improved method for **reliability** and **relevance** evaluation
  - Reporting

- Nanomaterials
  - Based on the same principles
  - Focusing on nanomaterials
  - Relevance of the study similar as for conventional chemicals
  - Reliability changed with a **strong focus on NM inherent properties, exposure and test conditions**

Ågerstrand et al., in prep; Hartmann et al., in prep

Relevance criteria

- Relevant organism in relation to the compartment
- Appropriate endpoints for regulatory purpose and studied effect
- Appropriate life stages
- Relevant set-up for the organism
- Tested substance relevant for assessed substance
- Significant magnitude of the effect and relevant for regulatory purpose
- Relevant exposure scenario

Re4/Re3/Re2/Re1

Reliability criteria

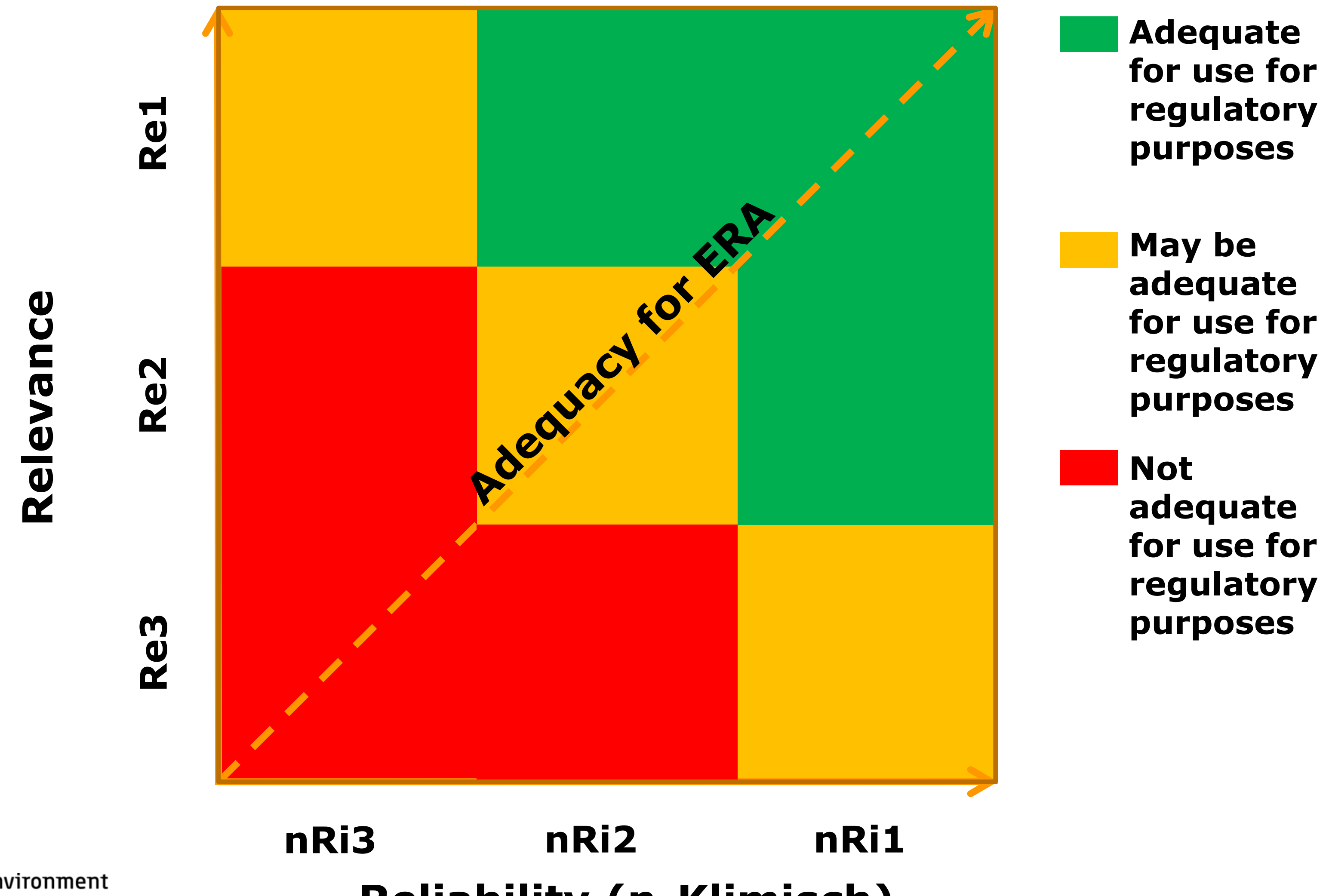
- Description of methodology, test organism and endpoint
- Validity criteria and proper controls
- Appropriate statistical methods and replicates
- Dose/response curve and raw data availability
- GLP/guidelines
- Identification and characterisation of the tested NM
- Appropriate exposure and test system
- Exposure quantification

nRi4/nRi3/nRi2/nRi1

Reliability criteria – NM characterisation and exposure quantification

- Core chemical composition
- Purity
- Measured size
- Shape and crystal structure
- Specific surface area
- Surface chemistry; coating, functionalization, stabilisation (if applicable)
- Agglomeration
- Ion release (solubility)
- Surface charge
- Agglomeration
- Size distribution
- Concentration
    - In stock suspension (prior to the ecotoxicological study)
    - In stock in test medium
    - In tested concentrations
    - In the tested organism as the body burden

Combined adequacy for ERA



Silver as an example

Organism	T, h	Endpoint	C, µg/L	RA adequacy
D. rerio embryos	72	Notochord/control ≠	0,010	nRi3/Re2
D. rerio embryos	72	Hatching/control ≠	0,010	nRi3/Re2
P. subcapitata	96	Growth/EC_{50}	190	nRi2/Re2
D. pulex adults	48	Death/LC_{50}	40	nRi2/Re2
D. rerio juveniles	48	Death/LC_{50}	7200	nRi2/Re2
Nitrifying cultures	0,5	ROS/control ≠	100	nRi3/Re2
D. rerio embryos	72	Mortality/LC_{50}	≈ 30000	nRi3/Re2
D. rerio embryos	72	Notochord/$EC_{60\text{-}90}$	50000	nRi3/Re2
C. reinhardtii	5	Photosynthesis/EC_{50}	89	nRi2/Re2
V. fischeri	0,5	Lum inh/EC_{50}	420	nRi2/Re1
D. subspicatus	72	Growth/EC_{50}	34	nRi2/Re1
D. magna	48	Immobilisation/EC_{50}	1,2	nRi2/Re1
D. magna	48	Survival/LC50	2,75	nRi3/Re2

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