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Federal Department of Home Affairs FDHA
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Options for effect- and toxicology based legislation, the precautionary principle: Nanoscale chemicals as an example

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Effect- and toxicity-based assessment of exhausts
Empa, March 16, 2018

Precautionary Principle

«The general principle by which all that can reasonably be expected is done to prevent unnecessary risks»

C.J van Leeuwen, J.L.M. Hermens: Risk assessment of chemicals: An introduction, Kluvver Academic Publishers (1995), ISBN: 0-7923-3740-9

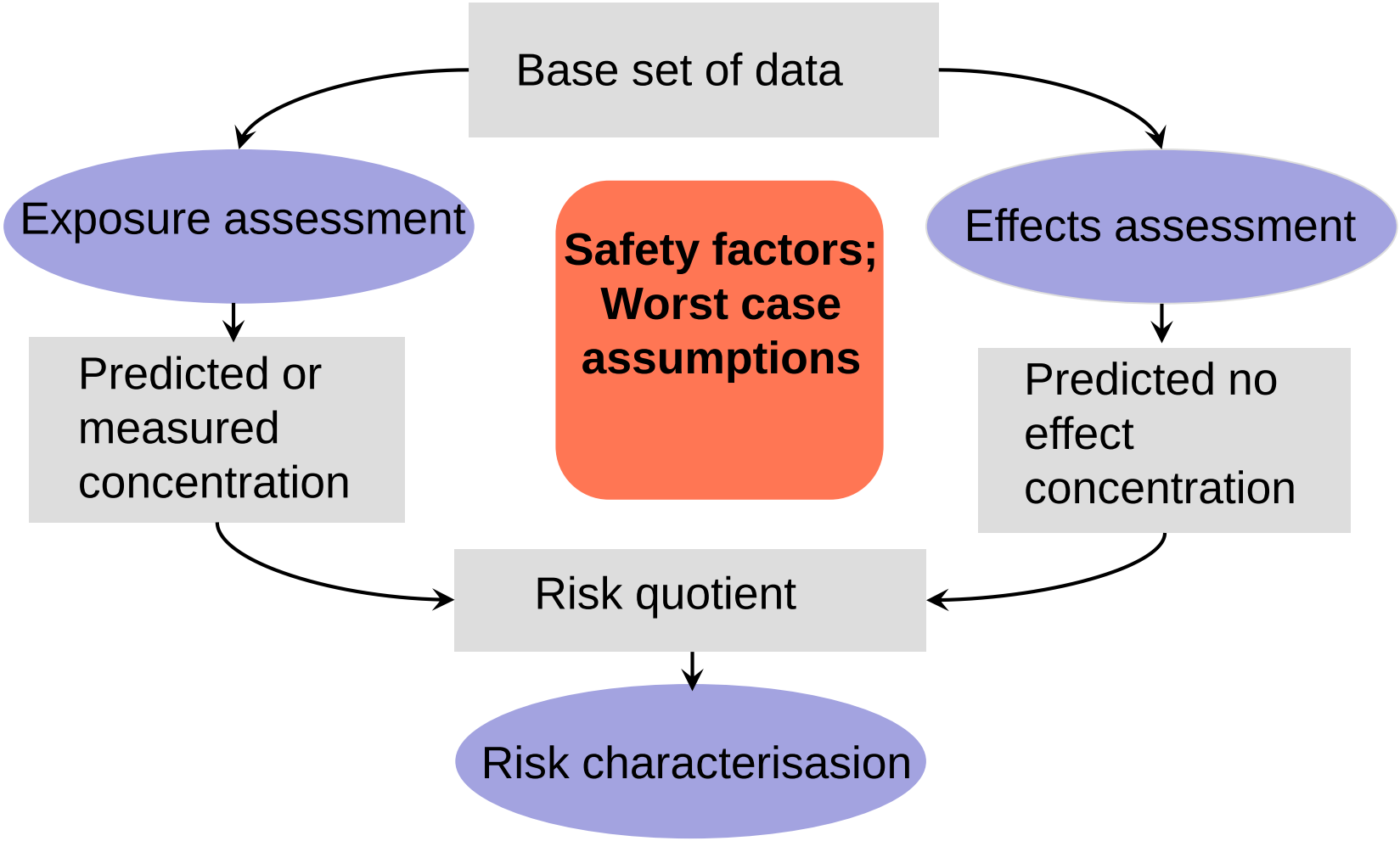
Precautionary principle in Swiss chemicals legislation

- Precautionary goal (Environmental Protection Act, Art. 1, 1983)

> [1] This Act is intended to protect people, animals and plants, their biological communities and habitats against harmful effects or nuisances and to preserve the natural foundations of life sustainably, in particular biological diversity and the fertility of the soil.[4]
>
> [2] Early preventive measures must be taken in order to limit effects which could become harmful or a nuisance.

- Obligation to generate data for risk assessment
- Obligation for adequate risk management measures
- Implementation of a market controle mechanisms
- **Development of a precautionary risk assessment methodology and testing strategies**

Risk assessment process for chemicals



REACH standard information requirements

The requirements below have to be adapted, waived or increased, according to the rules given in columns 1 and 2 of annexes VII to X and according to annexe XI.

≥ 1000 t/year (annexes VII + VIII + IX + X)

100-1000 t/year (annexes VII + VIII + IX)

10-100 t/year (annexes VII + VIII)

1-10 t/year (annexe VII)

Toxicological information

- Skin irritation or skin corrosion *(in vitro)*
- Eye irritation *(in vitro)*
- Skin sensitisation
- Mutagenicity (*in vitro*, gene mutation bacteria)
- Acute toxicity (oral route)

- Skin irritation (*in vivo*)
- Eye irritation (*in vivo*)
- Mutagenicity (*in vitro*, cytogenicity mammalian cells or micronucleus)
- Mutagenicity (*in vitro*, gene mutation mammalian cells)
- Acute toxicity (inhalation)
- Acute toxicity (dermal route)
- Repeated dose toxicity (28 days, one species)
- Reproductive toxicity (screening, one species)
- Toxicokinetics (assessment from available information)

- Repeated dose toxicity (28 days, one species)*
- Repeated dose toxicity (90 days, one species, rodent)
- Reproductive toxicity (pre-natal development, one species)
- Reproductive toxicity (two generations, one species)

- Reproductive toxicity (developmental, one species)
- Reproductive toxicity (two generations, one species)*
- Carcinogenicity study

** These studies have to be carried out if they have not been completed for the lower tonnage band because of waiving*

REACH registered substances by total tonnage band

Total Tonnage Band: This is calculated by summing the latest year values for actual tonnages in all full registrations (i.e. not including intermediates) for a given substance and converting it to a band

Tonnage Band	# Substances	
100 000 000 - 1 000 000 000 tonnes per annum	1	
10 000 000 - 100 000 000 tonnes per annum	24	
1 000 000 - 10 000 000 tonnes per annum	74	
100 000 - 1 000 000 tonnes per annum	165	1273
10 000 - 100 000 tonnes per annum	364	
1 000 - 10 000 tonnes per annum	645	
100 - 1 000 tonnes per annum	791	
10 - 100 tonnes per annum	947	
0 - 10 tonnes per annum	1,623	5857
Intermediate Use Only	2,496	
TOTAL	**7 130**	

ECHA 2018

Predictive Toxicology

Challenge:

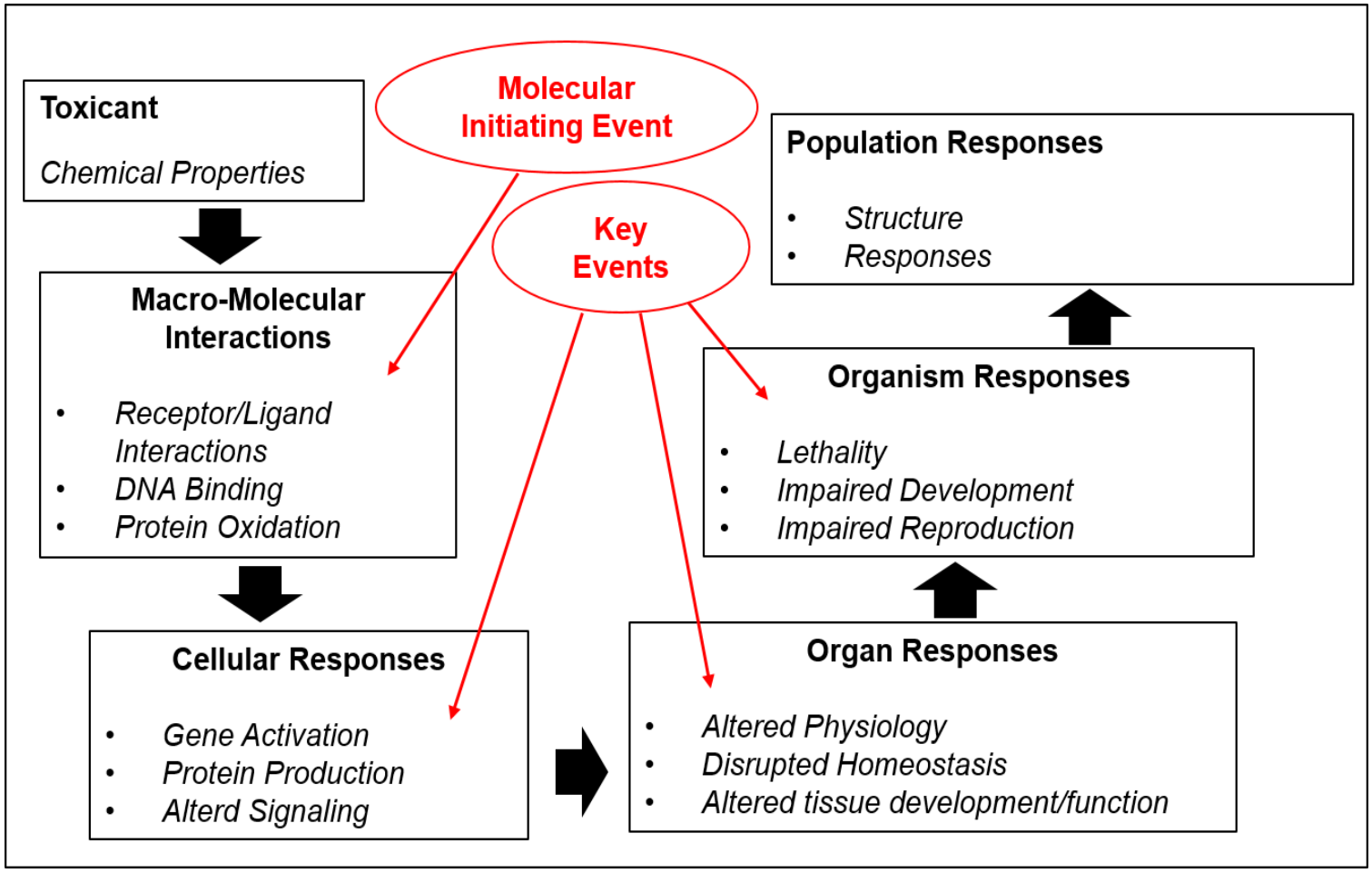
- Tests for chronic effects are necessary only at high production volumes
- How to prediced chronic effects without resource intensive animal testing?
- How to predict effects from multiple chemical exposure?

Predictive Toxicology (cont.)

Possibel solutions:

- Surch for cellular mechanisems resposible for chronic effects (endpoint specific)
- Development of Pathways of Toxicity and Adverse Outcome Pathways (AOP) and find key events
- Develop AOP based testing strategies in combination with in vitro methods for toxikological key events

Adverse Outcome Pathway



OECD, ENV/JM/MONO(2013)6

Lung fibrosis: Proposed AOP for MWCNT

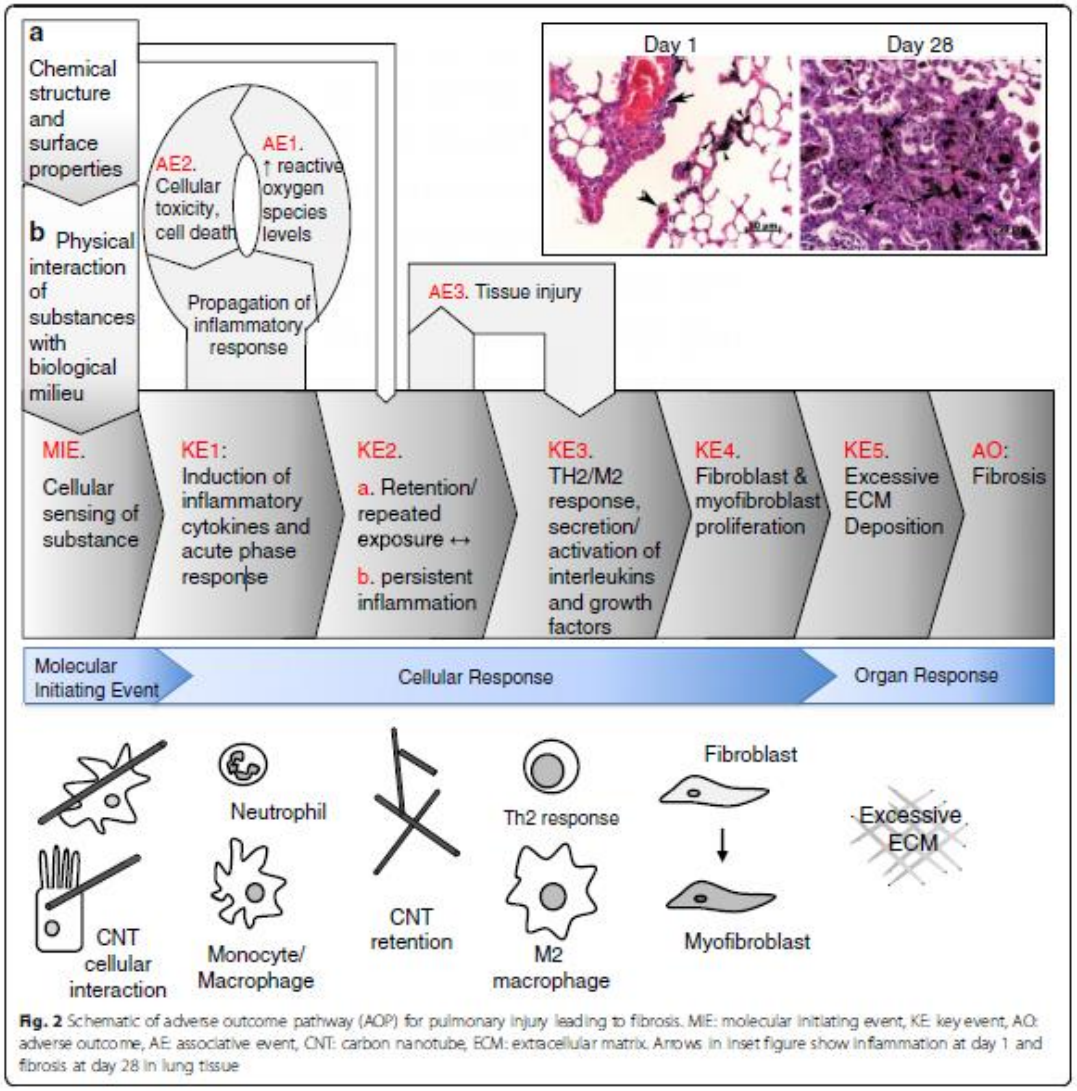


Fig. 2 Schematic of adverse outcome pathway (AOP) for pulmonary injury leading to fibrosis. MIE: molecular initiating event, KE: key event, AO: adverse outcome, AE: associative event, CNT: carbon nanotube, ECM: extracellular matrix. Arrows in inset figure show inflammation at day 1 and fibrosis at day 28 in lung tissue

Labib et al. Particle and Fibre Toxicology (2016) 13:15

Test Guidelines for *in vitro* skin sensitisation

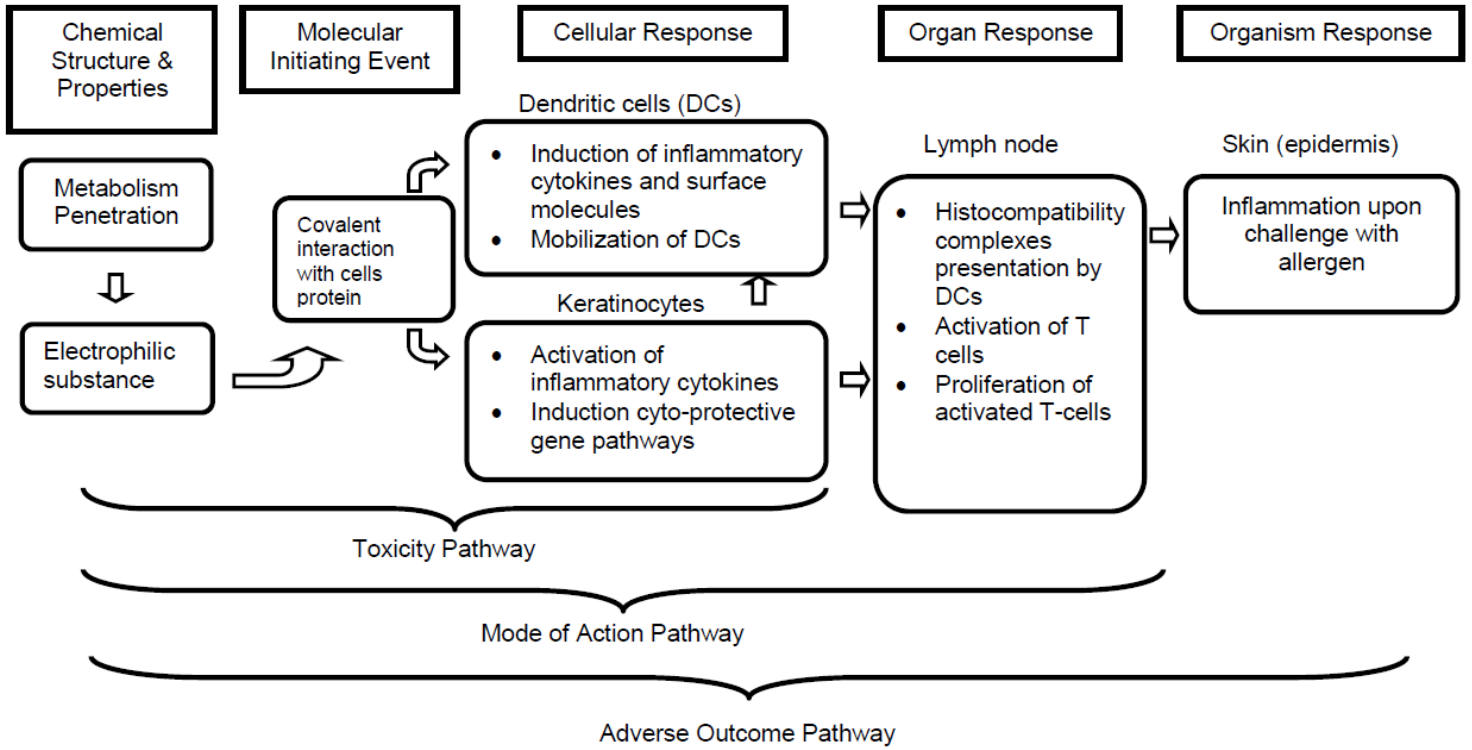


Figure 3. **Flow diagram of the pathways associated with skin sensitisation.**

ENV/JM/MONO(2012)10/PART1

The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins; Part 1: Scientific Evidence

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Safety assessment tool for Nanomaterials

Precautionary Matrix:

Guidance to support industry to comply with regulation (self-regulation, ChemO)

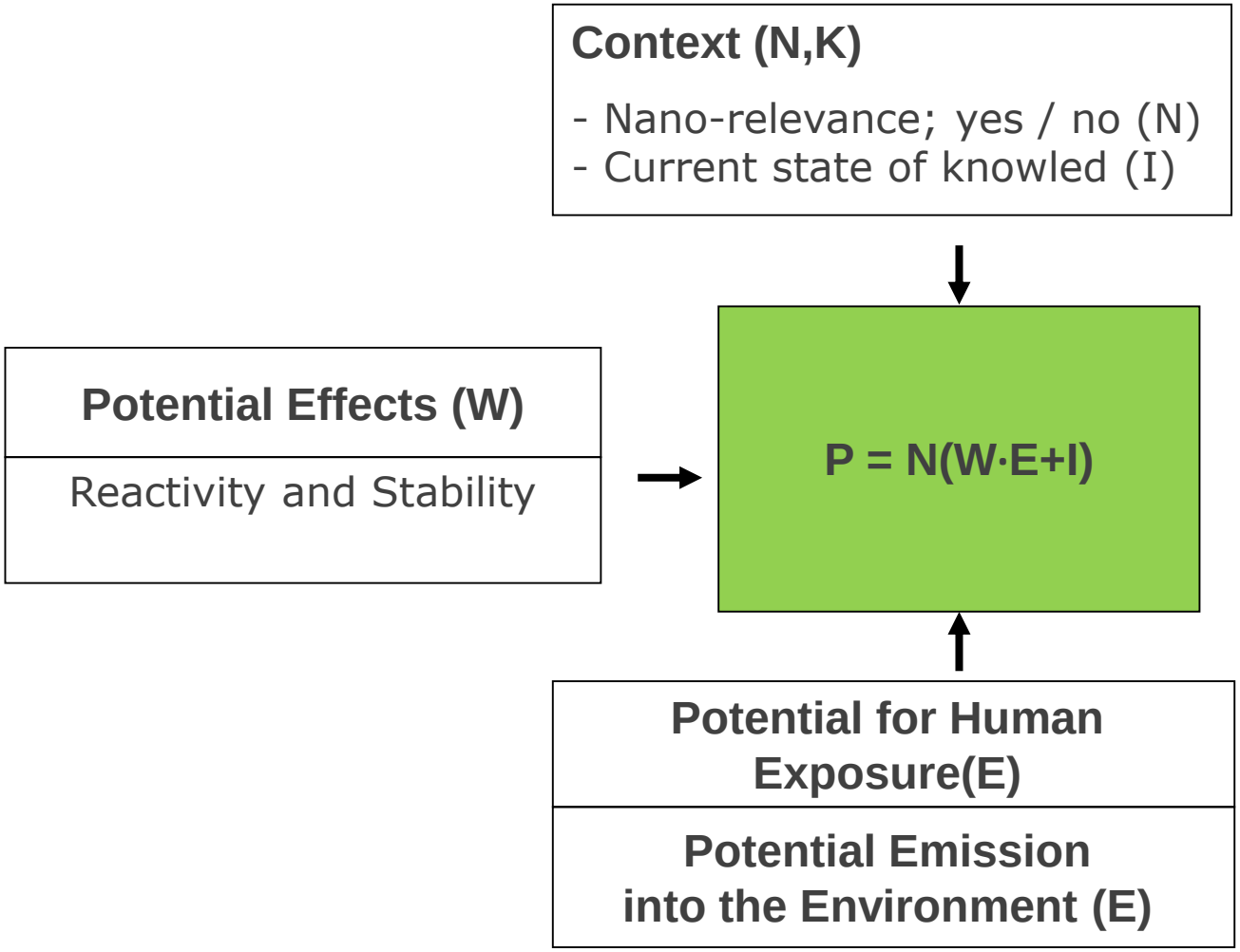
- Since 2008
- Last revision 2013

The Precaurionary Matrix:

- Is a controle banding tool based on a limited number of parameters
- Can be applied early in the safe-by-design process
- Is generally applicable
- Gives an indication of where a need for precautionary measures exisits
- Helps to detect knowledge gaps and risk potentials for workers, consumers and the environment

The Precautionary Matrix does not replace risk assessment

Set-up of the Precautionary Matrix:



P = Need for precautionary action

⇒ Result is a number, the higher the number the higher the need for a closer look

Potential effect and exposure of human beings / input into the environment

<table>
<tr><th>Potential effect (W)</th><th colspan="2">Potential exposure of human beings / input into the environment (E)</th></tr>
<tr><td rowspan="2">Reactivity: redox activity, fotocatalytic activity, oxidative stress, induction of proinflammatory cytokines
Stability of the nanomaterial in different media (Halflife)</td><td colspan="2">Physical Matrix in which the nanomaterial is embedded</td></tr>
<tr><td>Total amount handled / used by workers or consumers per day
Frequency of potential exposure</td><td>Emissions into the environment from production
Annual amount of nanomaterials marketed in consumer products</td></tr>
</table>

Reactivity parameters for the evaluation of nanomaterials

Draft revised version (March 2018)

low

medium

high

Nano-material (uncoated and unfunction-alized)	Calculated or Acellular Reactivity			Cellular Reactivity			
	Redox-activity (Band Gap)	Fotocatalytic activity	Biological oxidative damage, BOD	Induction of IL-8, IL-1b or TNFa	ROS induction	GSH depleation	Protein carbony-lation
Ag (0)			**c** (Ø: 35-60nm)	**d,** NM300 (Ø:8-47nm)	**d,** NM300	**d,** NM300	
CeO_2	**a** (Ø: 18.3nm)		**c** (Ø: 7-25nm)	**f, h** (Ø: 9.7nm)			
Co_3O_4	**a** (Ø: 10.0nm)		**c** (Ø: 20nm)	**f** (Ø: 18.4nm)			
CuO	**a** (Ø: 12.8nm)		**c** (Ø: 18-34nm)	**f** (Ø: 23.1nm)			
Fe_2O_3	**a** (Ø: 12.3nm)		**c** (Ø: 30nm)	**h** (Ø: 15nm)			
Fe_3O_4	**a** (Ø: 12.0nm)		**c** (Ø: 25nm)				
Mn_2O_3	**a** (Ø: 51.5nm)		**c** (Ø: 45nm)				
SiO_2 (amorph)	**a** (Ø: 13.5nm)		**c** (Ø: 15nm)	**h, i** (Ø: 14nm)	**g, i,** NM200, NM203 (Ø: ~15nm)		**g** (Ø: 15nm)
TiO_2 (anatase)	**a** (Ø: 12.4nm)	**b** (Ø: 10-100nm)	**c** (Ø: 10-25nm)	**h, i,** P25 Ø: 20-80nm)	**i,** P25	**d,** NM101 (Ø: 4-100nm)	**g,** NM105 (Ø: 21nm)
TiO_2 (rutil)		**b** (Ø: 100nm)	**c** (Ø: 5000nm)	**f** (Ø: 30nm)	**d** (Ø: 80-400nm)	**d** (Ø: 80-400nm)	
$BaSO_4$				h, NM 220 (Ø: 25nm)			g, NM 220 (Ø: 32nm)
MWCNT			**c** (Ø: 8nm, L: 20µm)	**d,** NM400 (Ø: ~14nm, L: ~850nm)	**d,** NM400	**d,** NM400	**g,** NM400
MWCNT			**c** (Ø: 15nm, L: 1-40µm)	**d,** NM402 (Ø: ~12nm, L: ~1370nm)	**d,** NM402	**d,** NM402	**g,** NM402

Predictive power of the callculated or acellular and the cellular assays for lung toxicity

Draft revised version (March 2018)

	Correct prediction	False positiv prediction	False negativ prediction	Evaluated datasets
Calculated and acellular (in vitro) reactivities ⇨ acute lung toxicity (in vivo)	9	1	3	13
Calculated and acellular (in vitro) reactivities ⇨ Subchronic inhalation toxicity (in vivo)	4	0	3	7
Cellular reactivities (in vitro) ⇨ acute lung toxicity (in vivo)	9	2	1	12
Cellular reactivities (in vitro) ⇨ Subchronic inhalation toxicity (in vivo)	8	0	0	8
Calculated and acellular (in vitro) **or** cellular reactivities (in vitro) ⇨ acute lung toxicity (in vivo)	10	2	0	12
Calculated and acellular (in vitro) **or** cellular reactivities (in vitro) ⇨ Subchronic inhalation toxicity (in vivo)	8	0	0	8

Work to do

- Foster research on AOPs and the development of AOP based testing strategies
- Test Guidelines: Development of test guidelines for key events of important AOPs
- Update and validation of the precautionary matrix for nanomaterials