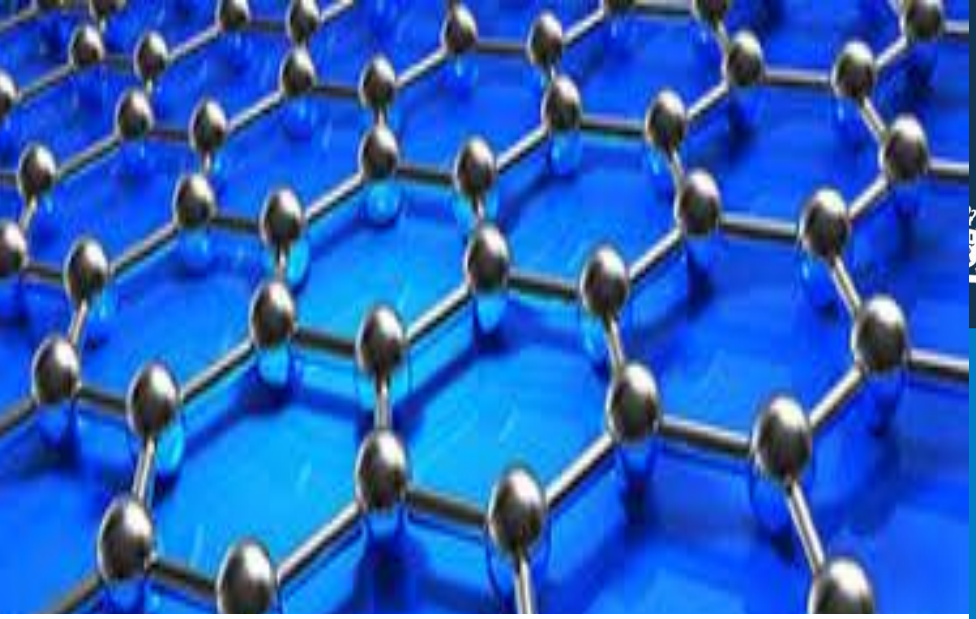
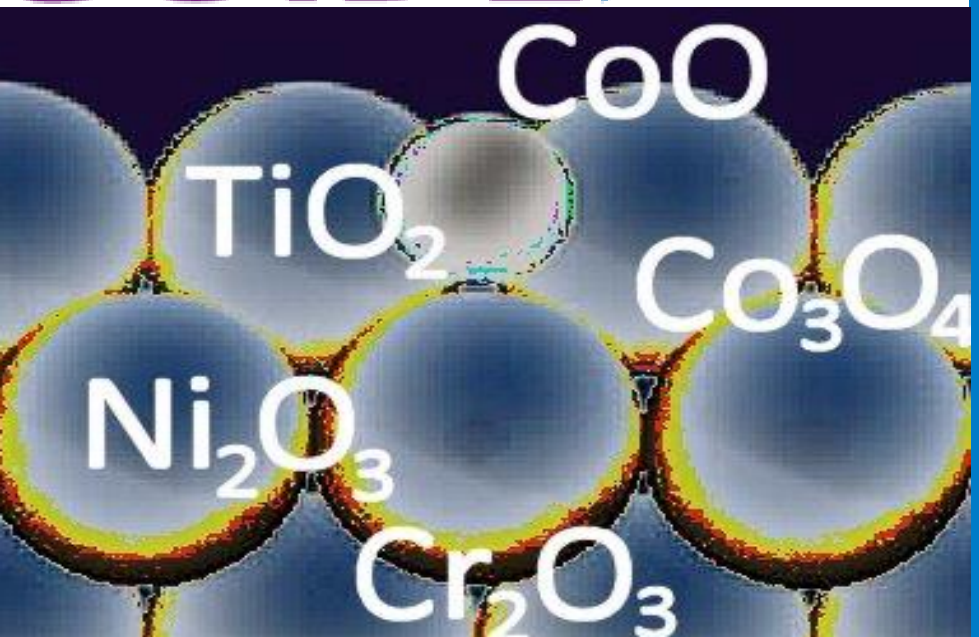


GUIDE nano



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Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Development of a risk assessment strategy for the GUIDEnano tool

Dr. Maria Luisa Fernandez-Cruz, INIA
Dr. Susan Wijnhoven, RIVM

NanoSafe, Grenoble 2016

Project Consortium

Universities & Research Centers

LEITAT Technological Center member of TECNIO
managing your technologies

VENEZIA RICERCHE

cea liten

UNIVERSITY OF GOTHENBURG

TÉCNICO LISBOA

IOM

TNO innovation for life

INSTITUTO TECNOLÓGICO DEL EMBALAJE, TRANSPORTE Y LOGÍSTICA
ITENE

ICN Institut Català de Nanotecnologia

UNIVERSITY OF EXETER

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Ministerie van Volksgezondheid, Welzijn en Sport

Finnish Institute of Occupational Health

UPPSALA UNIVERSITET

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Industry

CIB

PlasmaChem

LATI

inoTEX®

Servià Cantó

NanoServices

INNVENTIA

GEOCHEM RESEARCH

Honeywell

HEMPEL Estd 1915

Pinsent Masons

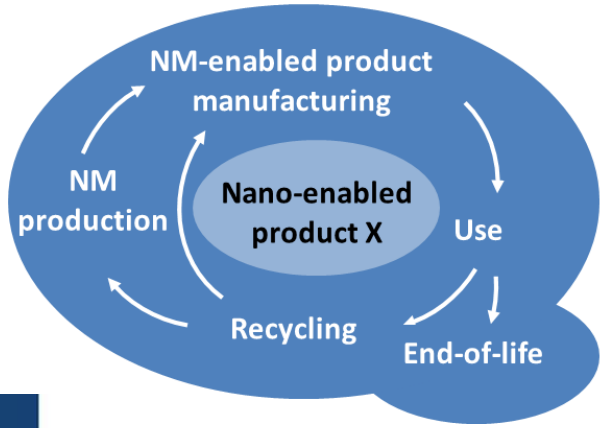
Project goal, target and scope

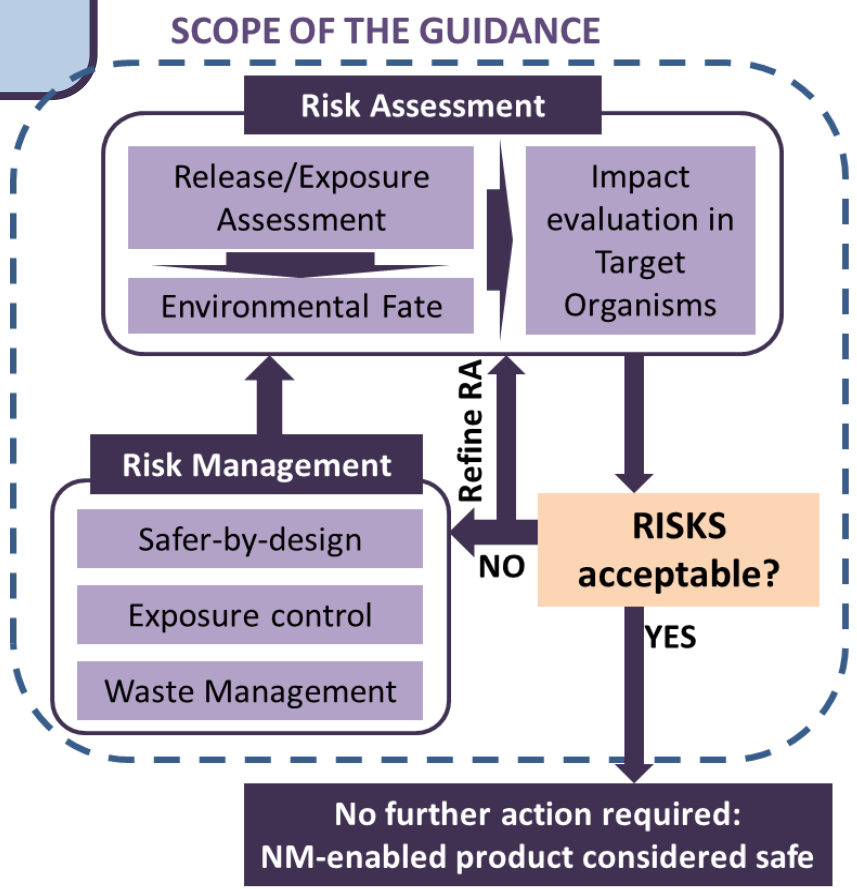
Develop innovative methodologies to **evaluate** and **manage** human and environmental health risks of NM-enabled products, considering the whole product life cycle

Interactive digital Guidance Tool

THE TARGET

NM-enabled product Life Cycle





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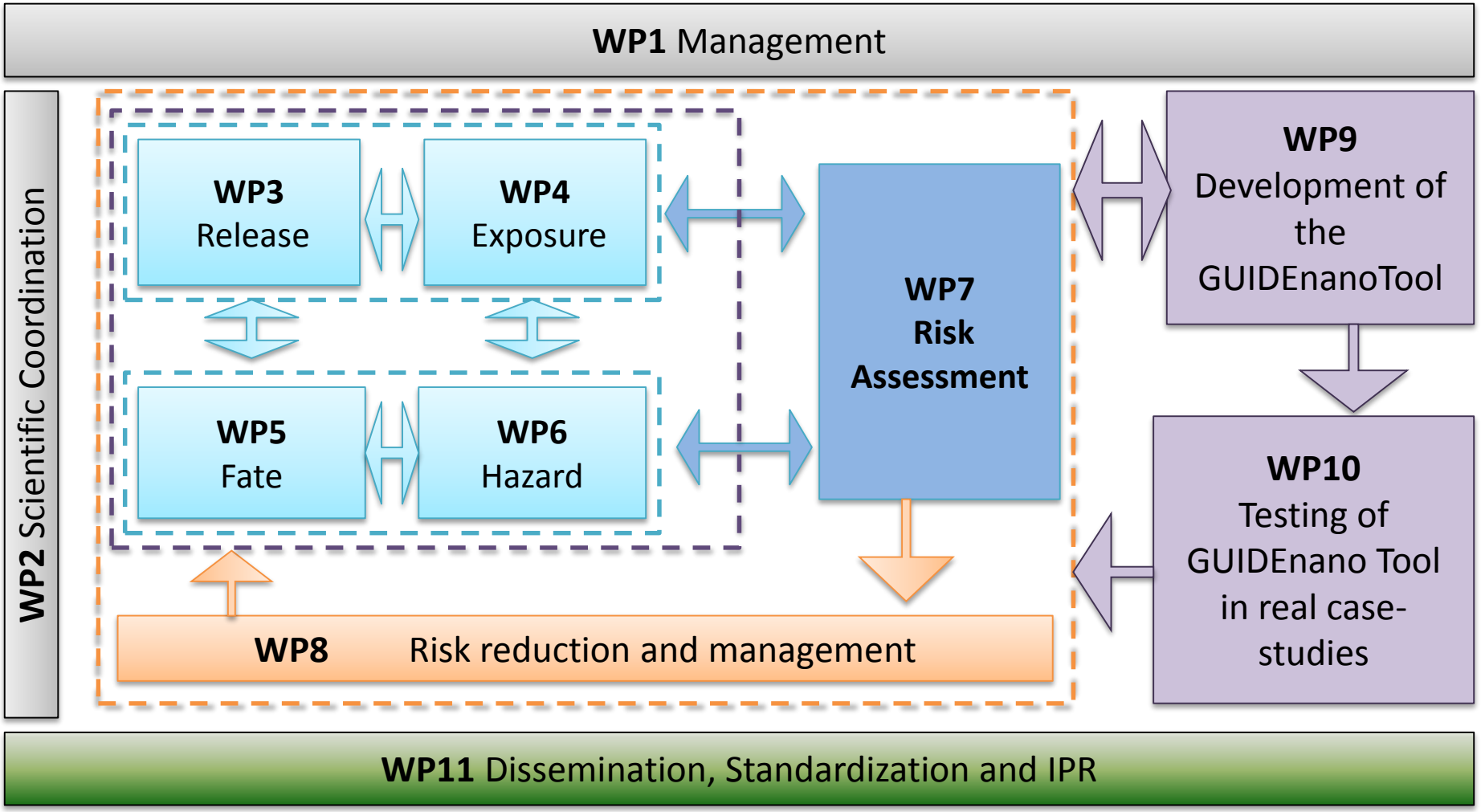
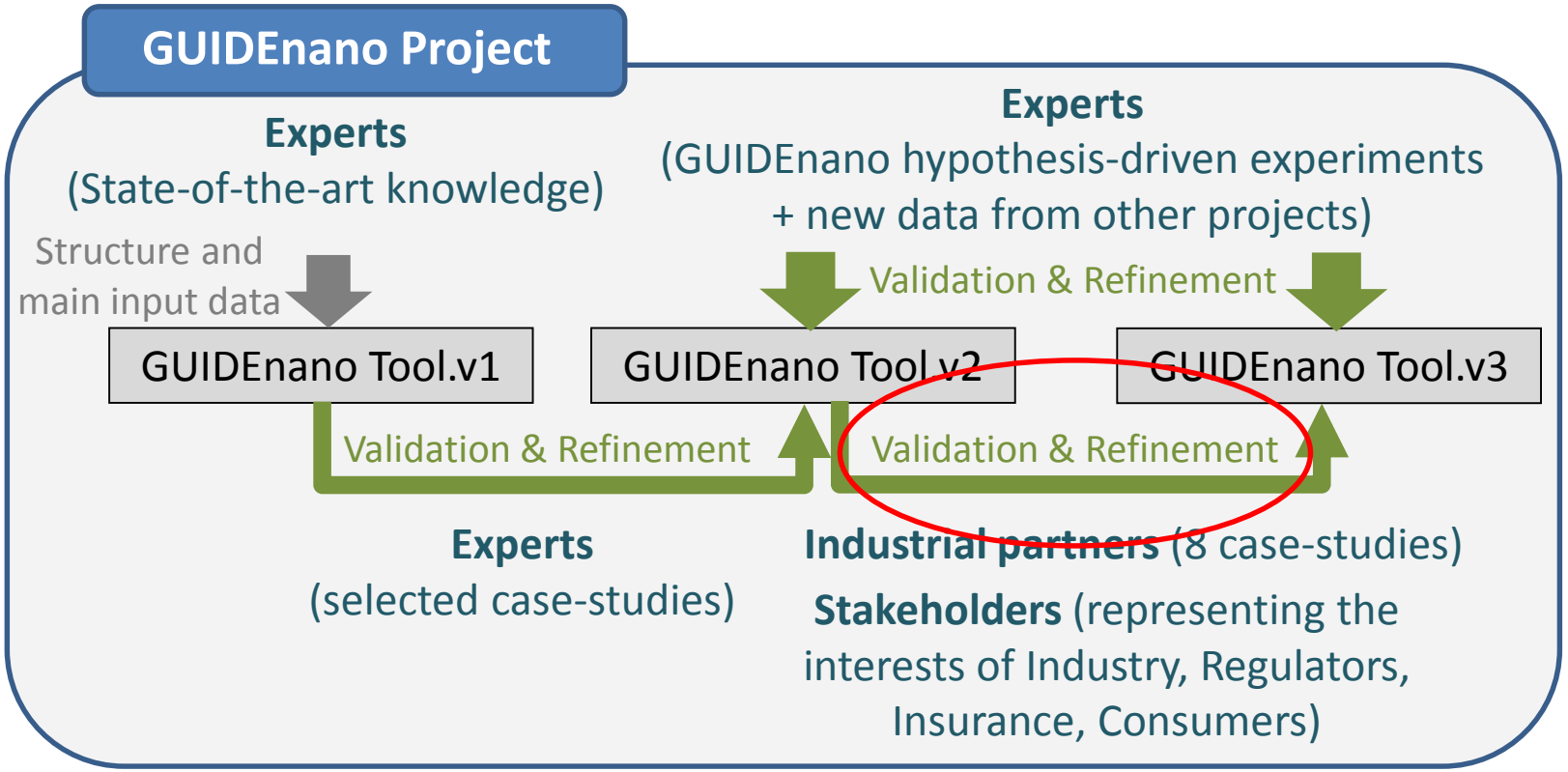
Organization in WPs



Project Timeline



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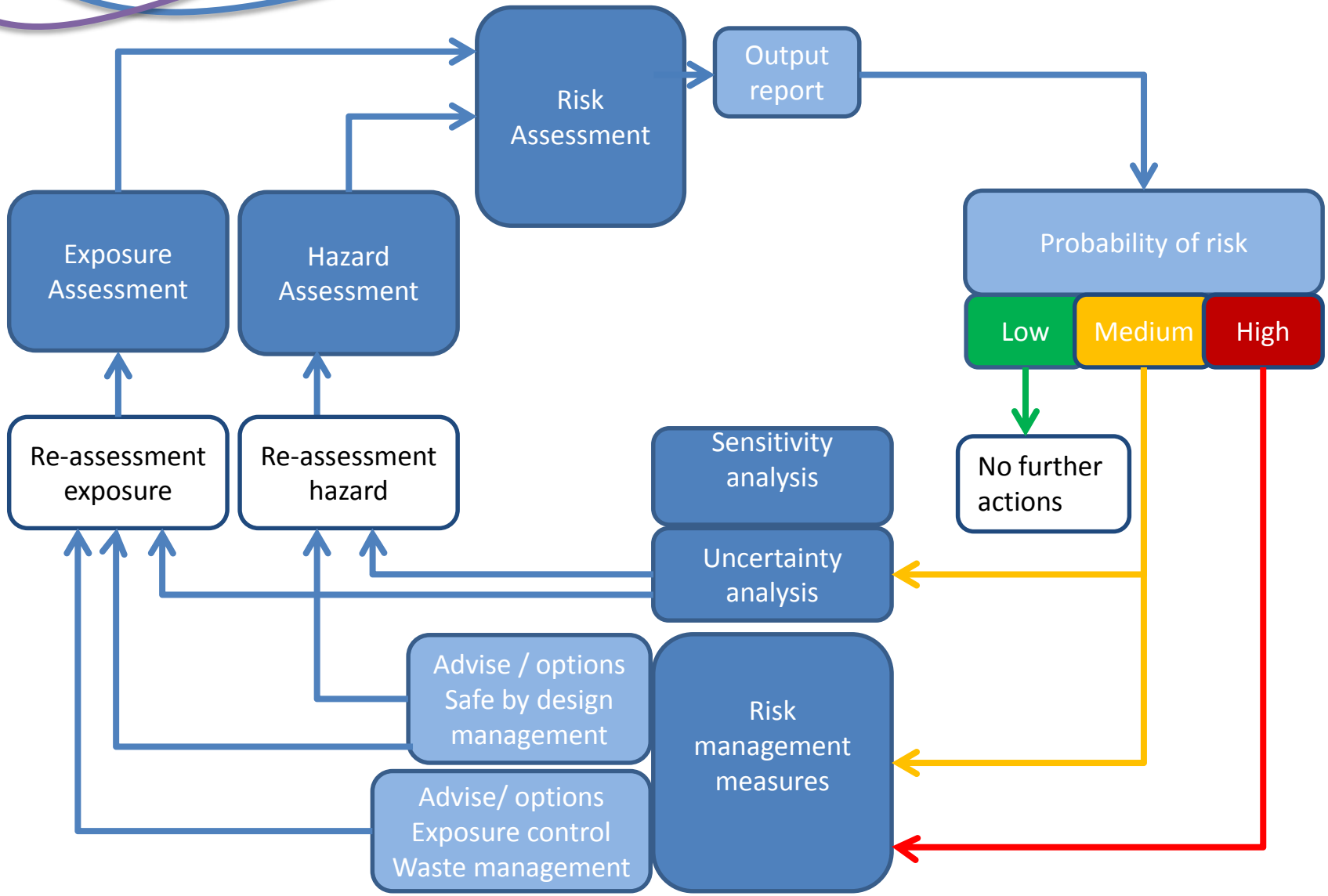
Risk assessment strategy



Derivation of safety limit value

- Stepwise approach for both hazard assessment and risk assessment
- Harmonisation between human and eco approach

Steps to derive a safety limit value human

1. Select toxicity studies
2. Derive effect level for each study (NOAEL, LOAEL, BMD, etc)
3. Determine uncertainty factor for each effect level
4. Determine modification factor for each effect level
5. Determine assessment factor for each effect level
6. Derive safety limit value: for example NOAEL/NOEC x modification x AFs
7. Derive overall safety limit value per endpoint
8. Risk assessment: compare safety limit value with corresponding exposure level

Hazard assessment

Risk assessment

Step 1: Select studies

Studies for the related endpoint are selected based on three scores

- **Similarity score**
  - Composition
  - Coating
  - Shape
  - Primary particle size, aspect ratio
  - Aggregated size
  - Etc…
- **Quality score:**
  - Klimisch score: reliability of the study
  - Nanomaterial score: completeness of the PC characterization of the nanomaterial/nanomaterials assessed within the study.
- **Relevance score**
  - OECD study y/n
  - Evaluation of relevant endpoints
  - Duration of exposure
  - Exposure method (e.g. inhalation: whole body, nose-only)
  - Species
  - Etc…

Derivation of safety limit value

- Stepwise approach for both hazard assessment and risk assessment
- Harmonisation between human and eco approach

Steps to derive a safety limit value human

1. Select toxicity studies
2. Derive effect level for each study (NOAEL, LOAEL, BMD, etc)
3. Determine uncertainty factor for each effect level
4. Determine modification factor for each effect level
5. Determine assessment factor for each effect level
6. Derive safety limit value: for example NOAEL/NOEC x modification x AFs
7. Derive overall safety limit value per endpoint
8. Risk assessment: compare safety limit value with corresponding exposure level

Hazard assessment

Risk assessment

Derivation of safety limit value

Steps to derive a safety limit value environment

1. Select toxicity studies per environmental compartment
2. Derive effect level for each study (NOEC, IC50, etc)
3. Determine uncertainty factor for each effect level
4. Determine modification factor for each effect level
5. Determine assessment factor
6. Derive safety limit value per compartment: i.e. NOEC x modification x AFs
7. Risk assessment: compare safety limit value with corresponding exposure level

Hazard assessment

Risk assessment

Step 2: Derive effect level for each study (NOAEL, LOAEL, BMD, etc)

Study type	Route	Effect level
Acute tox study	Oral	NOAEL/BMD/LOAEL/…
Acute tox study	Inhalation	NOAEL/BMD/LOAEL/…
Acute tox study	Dermal	NOAEL/BMD/LOAEL/…
Repeated dose tox study	Oral	NOAEL/BMD/LOAEL/…
Repeated dose tox study	Inhalation	NOAEL/BMD/LOAEL/…
Repeated dose tox study	Dermal	NOAEL/BMD/LOAEL/…
Carcinogenicity study	Oral	NOAEL/BMD/LOAEL/…
Carcinogenicity study	Inhalation	NOAEL/BMD/LOAEL/…
Carcinogenicity study	Dermal	NOAEL/BMD/LOAEL/…
Reproduction tox study	Oral	NOAEL/BMD/LOAEL/…
Reproduction tox study	Inhalation	NOAEL/BMD/LOAEL/…
Reproduction tox study	Dermal	NOAEL/BMD/LOAEL/…

- Each study will lead to at least one effect level, i.e. NOAEL, LOAEL, Benchmark Dose (BMD), etc.
- Multiple NOAELs are possible per study, for example a NOAEL for non-neoplastic effects and a NOAEL for neoplastic effects in a carcinogenicity study.

Step 3: Determine uncertainty factor

Available studies	Score		Overall score (multiplied value)[a]
Study 1	Similarity	0.7	0.56
	Quality	0.8	
	Relevance	1	
Study 2	Similarity	0.8	0.58
	Quality	0.9	
	Relevance	0.8	

- Translation of scores into uncertainty factor (WP6)
  - Relevance score: overlap with assessment factors (Step 5)

    → only elements not covered by AFs are taken into account
  - Further discussed and decided by WP6

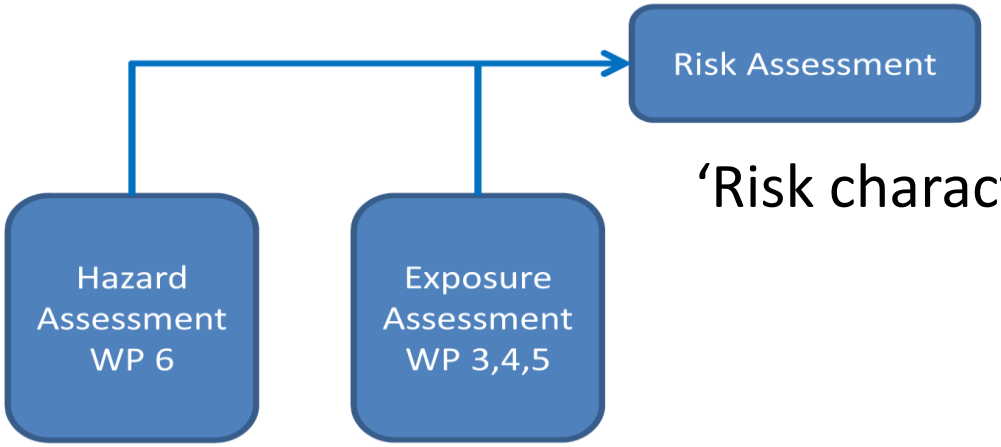
List of assessment factors for human RA- 1

Factor	Type of factor[a]	What does it address	Action on Safety Limit Value derivation	Possibilities of reducing uncertainty within the study
Exposure time per day (inhalation)	Modification	Differences in exposure time per day between exposure scenario and study considered i.e. if a 6h exposure study is used for a scenario involving 8h or 24h exposure for workers or consumers	Apply factor: - Worker, inhalation, 6h -> 8h: factor 1.33 - General population, inhalation, 6h -> 24h: factor 4	Reduction not possible
Correction activity workers (inhalation)	Modification	Differences in respiratory activity between experimental animals and workers (during 8 hours light activity at Work the respiratory rate becomes higher than standard).	Apply factor: Worker, inhalation, 6.7 m^3 →10 m^3: factor 1.49	Reduction not possible
Correction LOAEL – NOAEL	Uncertainty	For studies in which NOAEL cannot be derived, so safety limit value has to be based on LOAEL.	Apply factor: 3	Reduction of uncertainty by taking BMD approach
Interspecies differences - allometric scaling	Modification	Extrapolation of dose based on differences in bodyweight.	Apply factor: - Rat: 4 Rabbit: 2.4 - Mouse: 7 Monkey: 2 - Hamster: 5 Dog: 1.4 - Guinea pig: 3 Other: 4	Reduction not possible

List of assessment factors for human RA- 2

Factor	Type of factor[a]	What does it address	Action on Safety Limit Value derivation	Possibilities of reducing uncertainty within the study
Interspecies differences – remaining toxicokinetics and toxicodynamics	Uncertainty	Correction for interspecies differences (other than allometric scaling), i.e. toxicokinetic differences not related to metabolic rate (small part) and toxicodynamic differences (larger part).	Apply factor: 2.5	Reduction is possible, e.g. with information on toxicokinetics and toxicodynamics.
Intraspecies differences	Variability	Variability between humans (taking into account differences in sensitivity). Such variability is always present in a population.	Apply factor: - General population: 10 - Workers: 5	Reduction not possible
Study duration	Uncertainty	Determines whether study duration is long enough to even assess endpoint and if so, is used to correct for the differences in duration between study and exposure scenario, e.g. when a 28 day study is used for chronic exposure	Apply factor: - Sub-chronic to chronic: 2 - Sub-acute to chronic: 6	Reduction is possible based on evidence that increasing exposure does not increase the incidence or severity of adverse effects. e.g. for local dermal effects, local effects in the respiratory tract (considered concentration- rather than dose-dependent).

Information requirements

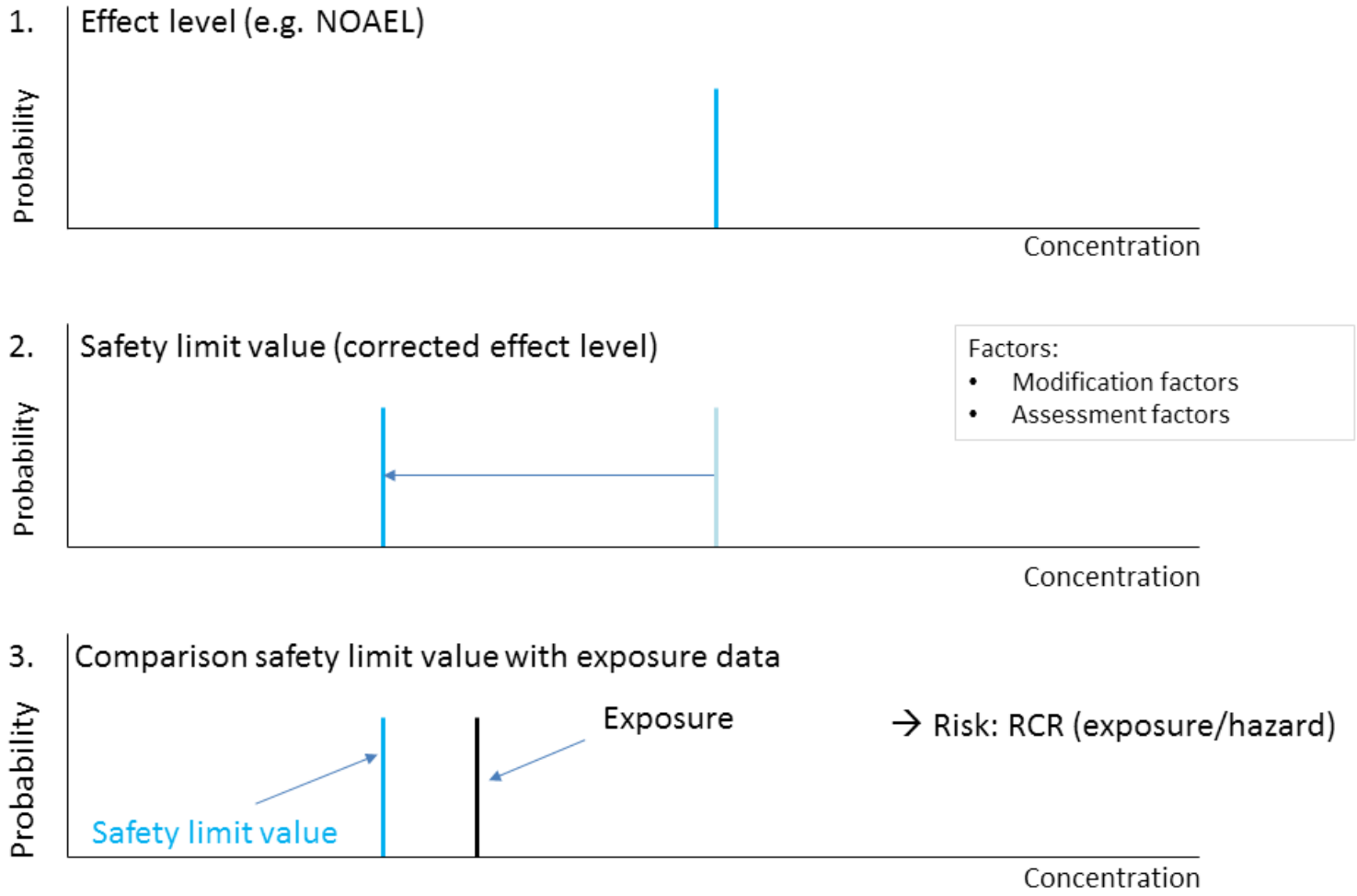


'Risk characterisation ratio' (RCR):

$$\frac{exposure}{hazard\ value}$$

- Exposure:
  - relevant exposure routes/ duration
  - model output, exposure libraries, direct measurement data
- Hazard:
  - relevant endpoints with (if possible) quantitative exposure estimate with uncertainty

Risk assessment



NB. Exposure data will, if available, be expressed in a distribution

Future work: risk assessment

- Continue with tool development
- Further development of output report of the tool
- Stakeholder analysis of tool
- Evaluation and validation with case studies
  - Hypothetical
  - Industry

Acknowlegdements

- GUIDEnano project consortium
  - All partners
    - Gemma Janer (LEITAT)
    - Socorro Vazquez (LEITAT)
    - Margriet Park (RIVM)
    - Ralph Vanhauten (TW)
    - Lion Traas (TW)
  - WP7
    - Petra van Kesteren (RIVM)
    - Maria Luisa Fernandez-Cruz (INIA)
    - Thies Oosterwijk (TNO)
    - Joost Westerhout (TNO)
    - Manoj Vaghela (Pinsent Masons)