

Knowledge Readiness for Nanorisk Governance

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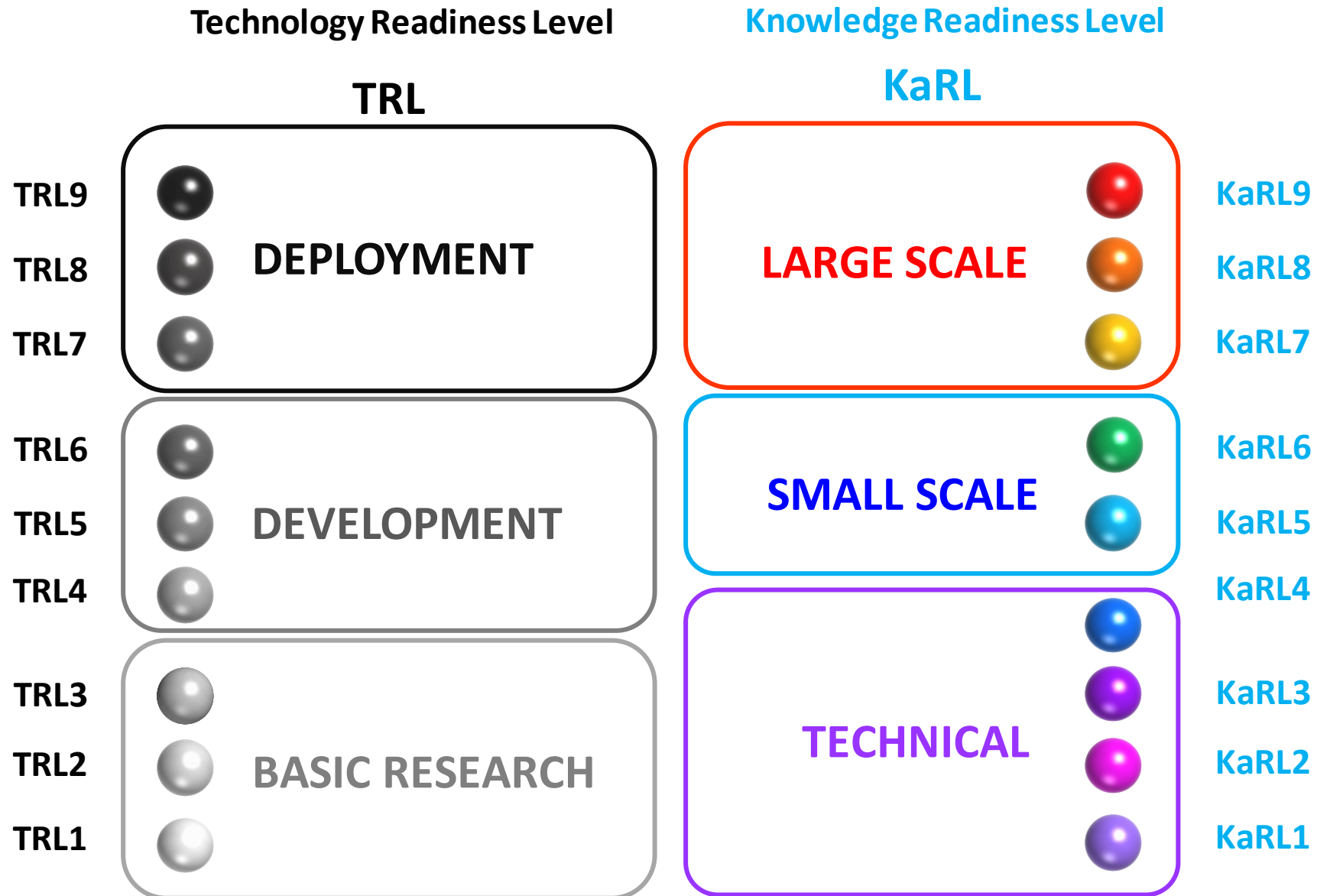


Contents

- Analogy with Technology Readiness Level (TRL)
- **K**nowledge, Information **a**nd Data **R**eadiness **L**evel (KaRL)
- Conclusions (How KaRL could improve Nanorisk Governance)



Analogy with Technology Readiness Levels (TRL)



KaRL1

ALL AVAILABLE DATA

ALL DATASOURCES

EXAMPLE

digital

text files



- Physical libraries
- Web of Science
- Google Scholar
- eNanoMapper
- NanoCommons
- CaLibrate
- E-Lab books

Publications on nanomaterials (TiO₂, ZnO, Au NP etc.)



KaRL2

DATA COMPLETED WITH METADATA

Metadata

reference, structural,
statistical, bibliographic,
or technical metadata

Minimum reporting standards

MINChar

MIAMETox

MIRIBEL

ARRIVE

MIAN

EXAMPLE

A study on NM carried according to
MINChar

- *Particle size/size distribution*
- *Agglomeration state*
- *Shape....*



DATA COMPLETED WITH TOXICOLOGICAL CONTEXT

CONCEPT



Adding Toxicological Context to Nanotoxicity Study Reporting Using the NanoTox Metadata List

Damjana Drobne

This paper proposes a list of specifications (NanoTox metadata list) to be reported about nanotoxicity experiments (metadata) together with resultant data to add toxicological context to reported studies. In areas involving nanomaterials (NMs), existing metadata reporting standards include the reporting of experimental conditions and protocols (MIRIBEL) and material characteristics (MINChar and MIAN), as well as reporting focused on specific experiments (MINBE). NanoCRED is a similarly transparent and structured framework, however, it is developed to guide risk assessors in evaluating the reliability and relevance of NM ecotoxicity studies. There is no reporting standard which would include interpretation of the aims and outcomes of nanotoxicity studies beyond regulatory purposes. The proposed NanoTox metadata reporting checklist is elaborated to extend reporting toward describing nanotoxicological context and thus is a logical complement to technology/material-assay focused reporting checklists. It is further designed to allow for NM toxicity data and knowledge integration, reuse, and communication. Its ultimate goal is to adhere to the basic rules of toxicology when taking a stand on the toxicity of NMs and to limit speculations on safety. As nanotoxicology becomes more interdisciplinary with the advent of new tools and new materials to be tested, reporting standards will contribute to cross-disciplinary communication.

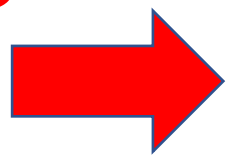
In medical research, reporting standards have a longer tradition.^[6] Here, the development of standards was also initiated by growing concerns about the inadequacy of method reporting in published journal articles to allow for the responsible communication of numerical results and research findings. Since the 1980s, suggested guidelines have been put forward as to what should be reported in medical papers. In the 1990s, serious international efforts began to promote better reporting, which led to the CONSORT (Consolidated Standards of Reporting Trials) guideline.^[7] The CONSORT reporting standard impacted not only the clinical trials but also influenced the development of other reporting guidelines on experimental study reporting in general, including, for example, ARRIVE reporting on in vivo experiments using animals^[8] and emergence of the EQUATOR network (Enhancing the QUALity and Transparency Of health Research).^[9] The in vitro reporting requirements are very well covered in Organisation for Economic Co-operation and Development (OECD) guidance document on Good In Vitro Method Practices (GIVIMP).^[10]

1. Introduction

The need to provide specifications about experiments (metadata) together with the resultant data via minimal information standards is driven by the increasing complexity of experiments in the biosciences and the large volumes of data generated. A wide range of reporting standards is enabling data to be used for "secondary use" of data, efficient data mining, and powerful analyses using diverse data sets to holistically study complex biological processes.^[1-4] An initial example of a reporting standard in the biosciences is MIAME (Minimum Information About a Microarray Experiment), which spurred the development of many similar standards.^[5]

The areas of nanomaterial (NM) research and applications have also generated their own approaches to reporting studies. Among the most comprehensive and widely applicable reporting standards in bio-NM studies is Minimum Information Reporting in Bio-Nano Experimental Literature (MIRIBEL), which covers the reporting of experimental details and tested material characteristics.^[11] More detailed material characterization reporting is recommended by Minimum Information of Nanoparticle Characterization (MINChar) working group, which includes a variety of physical and chemical parameters for characterizing NMs.^[12] The MINChar initiative influenced development of the minimal information about nanomaterials (MIAN) for physico-

NanoTox metadata checklist



- Study (assay) aim
- Toxicity/safety study
- Mode of action study
- Substance prioritization approach
- Substance persistence/body burden study
- Compliance with ARRIVE guidelines
- Material description by using other reporting standards
- MINChar or MIAN**
- MIRIBEL**
- nanoCRED**
- Minimum reporting details on study design
- Acute exposure (single dose/exposure)
- Chronic exposure
- Multiple dose/exposure
- Route of administration/exposure
- Body distribution
- In vitro (use ARRIVE reporting)
- Positive control (material, substance)
- Positive control (endpoint)
- Compliance with MIRIBEL guidelines
- Compliance with nanoCRED guidelines
- Type of toxicity data (values) produced
- Toxicity data /values: NO(A)EC(L), LO(A)EC, EC
- Benchmark dose (BMD)
- Benchmark concentration (BMC)
- Reference dose (RfD)
- Reference concentration (RfC)
- Body burden data
- Data on biokinetics
- Data on toxicokinetics
- ACDE
- ADME
- Endpoints measured/Endpoint selection principles
- Target endpoints
- Nontarget endpoints
- Critical (key) endpoints
- Secondary/comparative endpoints
- Integrated endpoints
- Hazard identification
- Decision points on hazard/safety
- Data on hazard

EXAMPLE

Toxicity, Hazard, Safety, Exposure



This project has received funding from The European Union's Horizon 2020 Research and Innovation Programme under Grant agreement 814530.

KaRL4

EXAMPLE

FITNESS-FOR-PURPOSE

A study fit for regulatory purposes according to Klimish Scoring system

Evaluation of a dataset or a study on **fitness-for purpose**

Purposes: scientific, regulatory, safe-by-design, exposure assessment

Quality scoring systems

nanoCred GuideNano

Klimish Scoring

DaNa

DaNa's Literature Criteria Checklist for toxicological publications

- *Physicochemical properties*
- *Sample preparation*
- *Testing parameters*
- *SOPs, OECD guidelines*

Score	Description
1	Reliable without restriction
2	Reliable with restriction
3	Not reliable
4	Not assignable



KaRL5

Co-Creation process

List of stakeholder-specific requirements

Stakeholder-specific additional requirements to solve a task (e.g. answer a risk-related question)



EXAMPLE

Task/Need/Question: *Is exposure to particles in the working environment affecting the worker's lungs?*

Stakeholder-specific requirements:

- Occupational exposure to NPs (Legal requirements for these NPs)
- *in vivo* data on the effects of NPs on lungs
- COmbined Dosimetry (CoDo) or other tools or models for additional information
- New experiments if necessary

What is an actionable document

An “**actionable document**” is a written instrument or **document** on which an **action** or defense is founded.



KaRL6

SMALL SCALE

FUNCTIONAL KNOWLEDGE in a form of
ACTIONABLE DOCUMENT

EXAMPLE

Report on toxicity of NPs for an industrial producer

Actionable documents

Proposals
Reports
Dossier
Opinions
Comments
Explanations

Such document represents the basis for Small-scale decisions on the level of individual stakeholder



KaRL7

LARGE SCALE

SOCIAL DISCOURSE

A specialized governance authority is suggested to integrate Scientific discourse and social discourse

Governance authority

Including knowledge into steps of NRGF



Social aspects

Organizational impact

Legal and ethical values

Requirements for Large scale (risk governance)

Needs of ALL stakeholders



Public Academia Industry Regulator

EXAMPLE

List of requirements

Public opinion

SEIN principles

Circular Economy principles

Safe-by-Design principles

Good governance principles

Impact assessment



KaRL9

**ACTIONABLE DOCUMENT READY for
RISK GOVERNANCE**

EXAMPLE

**Such document represents the
basis for
regulatory decisions**

**OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON
A DOSSIER PROPOSING HARMONISED CLASSIFICATION
AND LABELLING AT EU LEVEL**

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: Titanium dioxide
EC Number: 236-675-5
CAS Number: 13463-67-7

The proposal was submitted by France and received by RAC on **27 May 2016**.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at <http://echa.europa.eu/harmonised-classification-and-labelling-consultation/> on **31 May 2016**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **15 July 2016**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Normunds Kadikis
Co-Rapporteur, appointed by RAC: Norbert Rupprich

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **14 September 2017** by **consensus**.



Public opinion

SEIN principles

Circular Economy principles

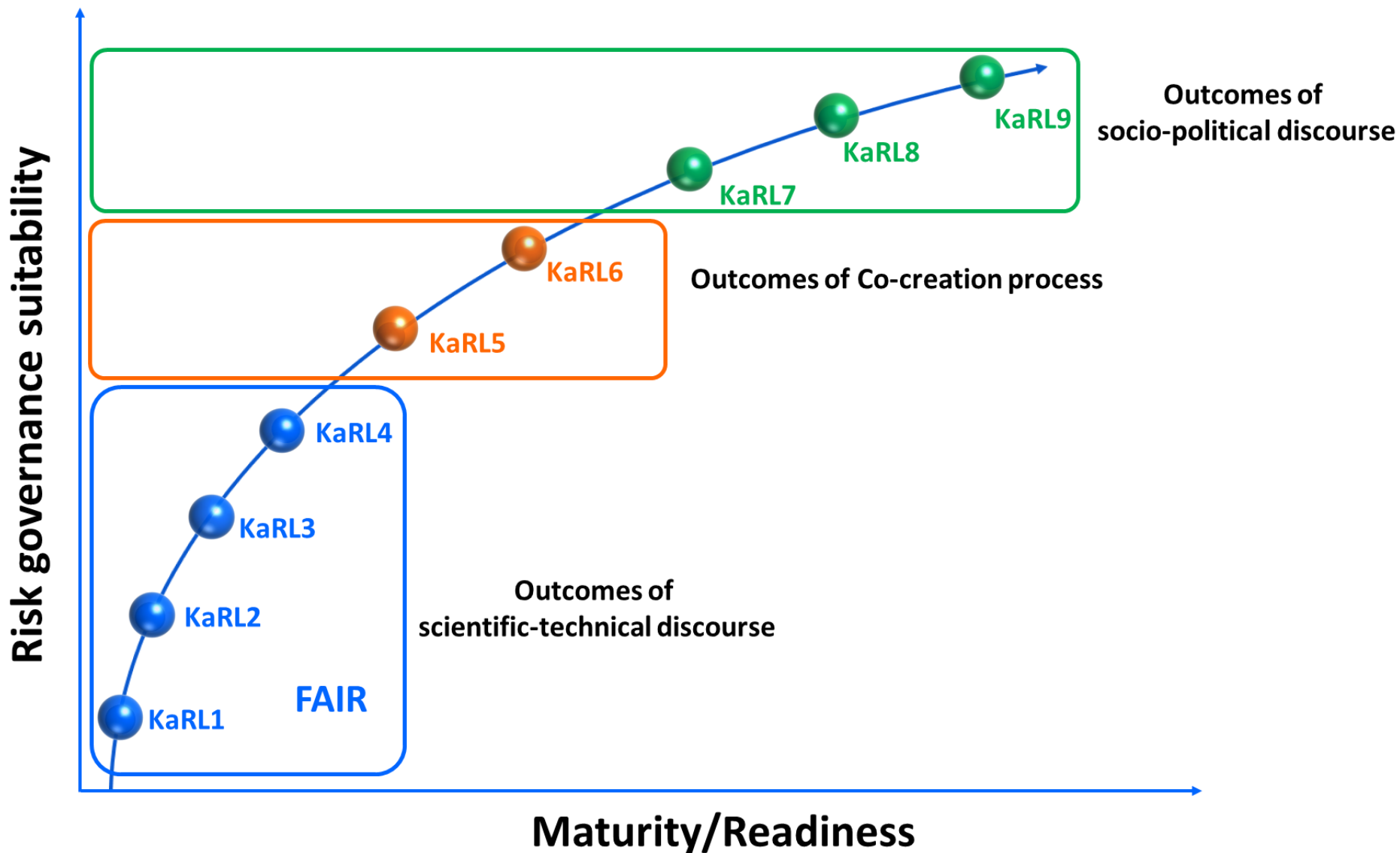
Safe-by-Design principles

Good governance principles

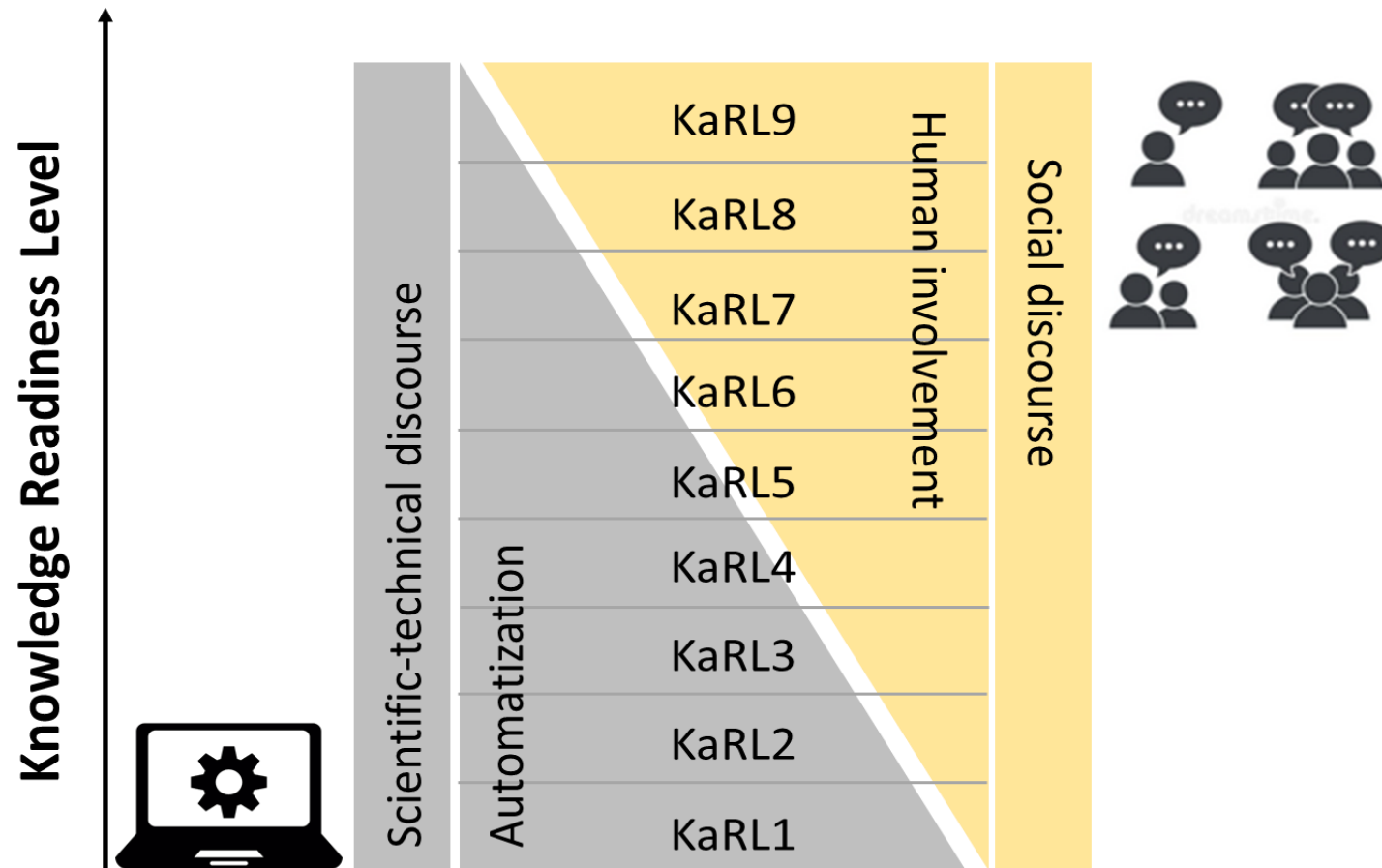
Impact assessment



Knowledge readiness



KaRL – involvement of both, human and automatization



KaRL Assignment

Requirements	KaRL 1	KaRL 2	KaRL 3	KaRL 4	KaRL 5	KaRL 6	KaRL 7	KaRL 8	KaRL 9
Data exist	✓	✓	✓	✓	✓	✓	✓	✓	✓
Accessibility		✓	✓	✓	✓	✓	✓	✓	✓
Metadata completeness (MINChar, MIAMETox)		✓	✓	✓	✓	✓	✓	✓	✓
Semantic metadata with toxicological context (NanoTox met.checkl.)			✓	✓	✓	✓	✓	✓	✓
OECD guidelines				✓	✓	✓	✓	✓	✓
SOPs				✓	✓	✓	✓	✓	✓
Fitness-for-Purpose criteria (Klimish, DaNa, NanoCred, GuideNano)				✓	✓	✓	✓	✓	✓
Legal requirements					✓	✓	✓	✓	✓
Can question be answered					✓	✓	✓	✓	✓
Is it an actionable document						✓	✓	✓	✓
Is an actionable document quality checked: fullfills requirements							✓	✓	✓
Actionable document is traceable							✓	✓	✓
Requiremets for broad context								✓	✓
SEIN								✓	✓
Circular Economy								✓	✓
Safer-by-Design								✓	✓
Good governance principles								✓	✓
Does an actionable document contain KaRL1-8									✓



How KaRL could improve Nanorisk Governance

- KaRL could support any stakeholder in providing a **guidance** on **how** and **where** to get **high-quality data (KaRL1-4)**
- KaRL helps to obtain **reliable knowledge** from data and a higher knowledge readiness for different purposes (**KaRL5-6**)
- Provides list of useful **nanoinformatical tools** to **fill knowledge gaps**
- KaRL enables involvement of all stakeholders and addresses ethical, social issues (SEIN), Safe-by-Design, Circular Economy and Sustainability (**KaRL7-9**)



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Thank you for your attention!

Are there any questions?

