Workshop on FAIRification

Towards improved regulatory readability of model validity

Dr. Martin Paparella
MUI Regulatory Science Group
Institute of Medical Biochemistry
Medical University Innsbruck

January 14, 2025, St. Gallen

1. FAIR model characterization

Current OECD templates for model characterization provide information on the 5 main validity criteria in **different order, different (sub)headers, different level of details**

1) FAIR model identity | 2) Purpose of the model | 3) Relevance | 4) Reliability | 5) Applicability domain (AD)

In vitro NAMs: ToxTemp (former OECD No 211)*

1. Overview
2. General information
3. Description of the general features of the test system source
4. Definition of the test system as used in the method
5. Test method exposure scheme & endpoints
6. Handling details of the test method
7. Data management
8. Prediction model and toxicological application
9. Publication/Validation status
10. Test method transferability
11. Safety, ethics and specific requirements

In silico NAMs: QMRF (OECD No 386, Annex 1)*

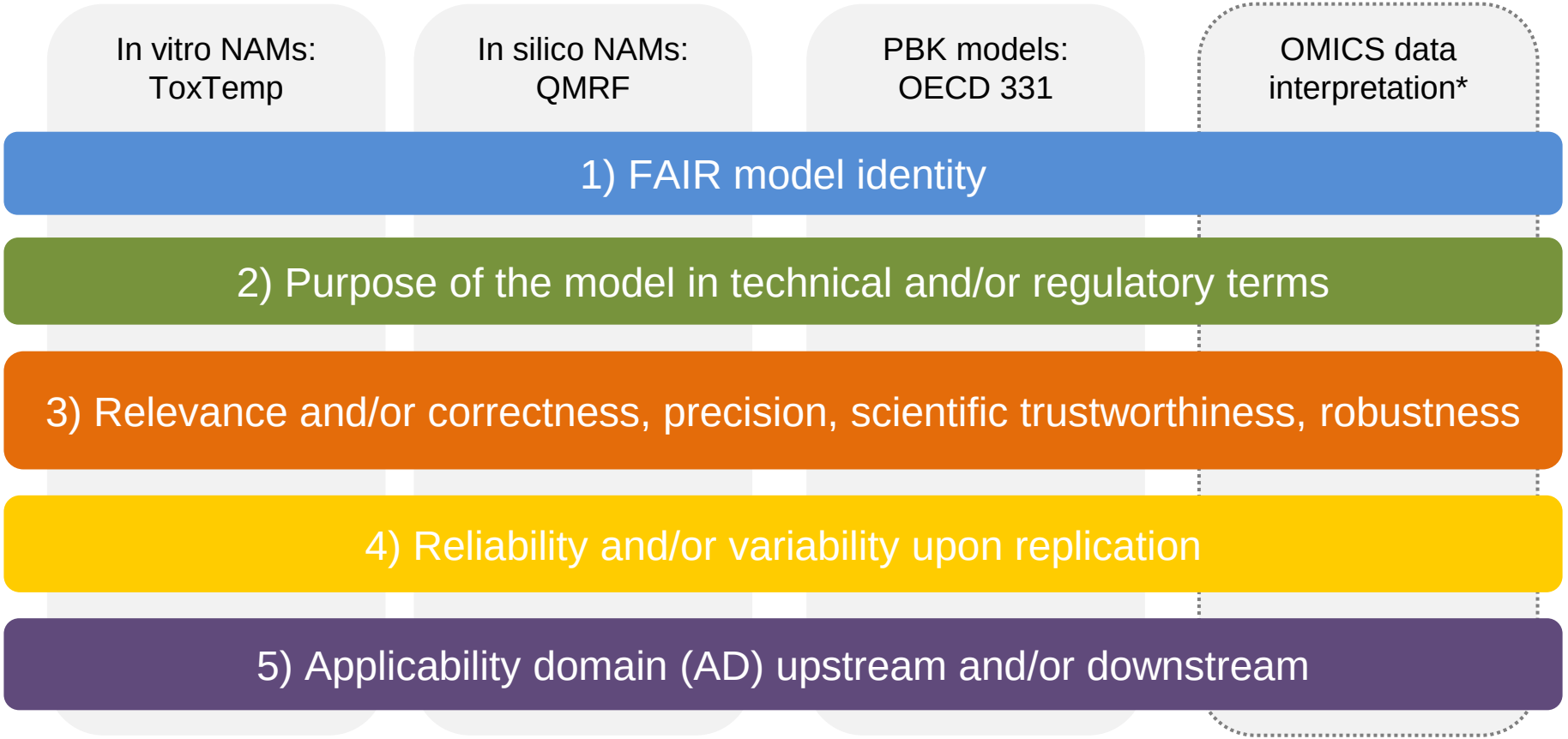
1. QSAR identifier
2. General information
3. Defining the endpoint
4. Defining the algorithm
5. Defining the applicability domain
6. Defining goodness-of-fit and robustness
7. Defining predictivity
8. Providing a mechanistic interpretation

PBK models: OECD No 331*

Table 3.1. A. Name of model
Table 3.1. B. Model developer and contact details
Table 3.1. C. Summary of model characterization, development, validation, and regulatory applicability
Table 3.1. D. Model characterization
Table 3.1. E. Identification of uncertainties
Table 3.1. F. Model implementation details
Table 3.1. G. Peer engagement (input/review)
Table 3.1. H. Parameter tables
Table 3.1. References and background information
Table 3.2. A. Context/Implementation
Table 3.2: B.1 Biological Basis
Table 3.2. B.2 Theoretical Basis of Model Equations
Table 3.2. B.5 Goodness-of-Fit and Predictivity
Fig. 3.4
Section 3.1. Context and implementation

* text color indicates which of the 5 validity information types can be found in which sections

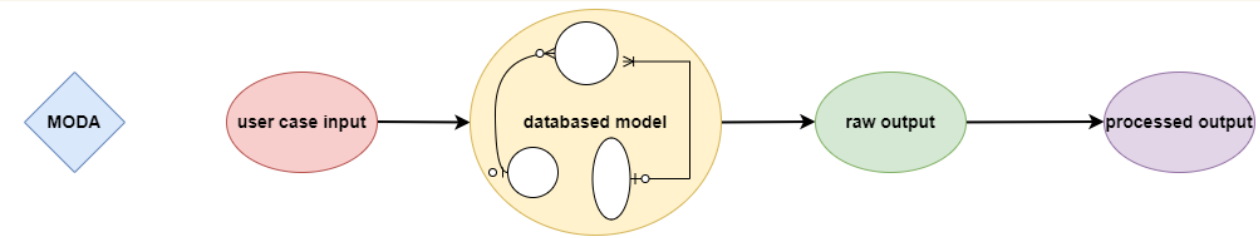
Using 5 common headers for the main validity criteria to resort the information within OECD templates could ease regulatory understanding of the models

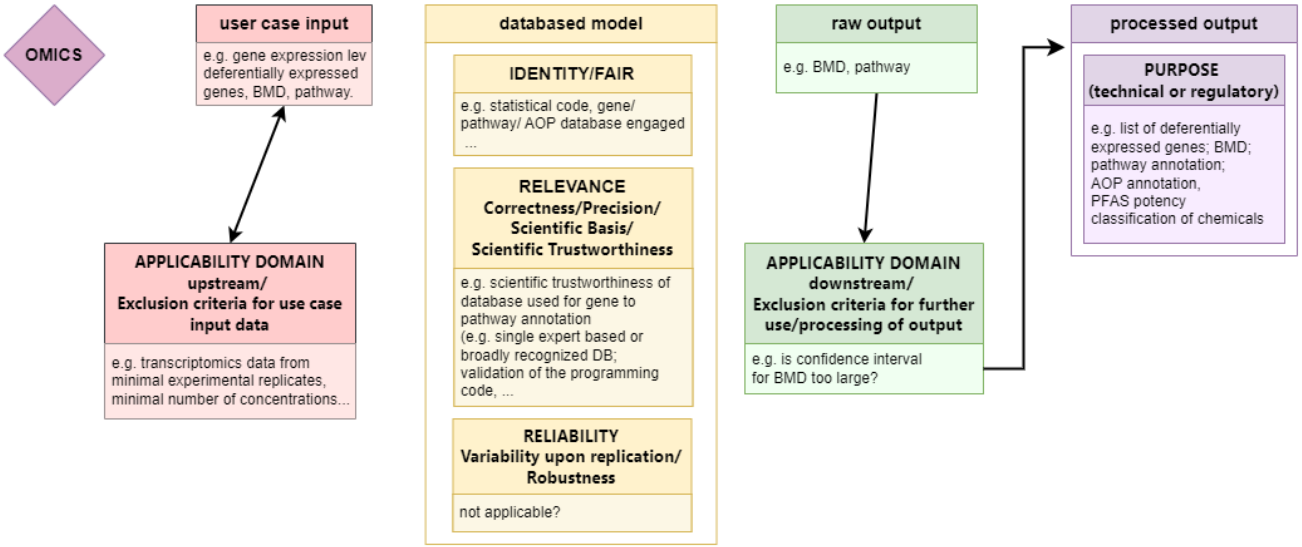


* still to be developed at OECD level

If useful, this could be applied to new omics data interpretation format and systematically linked to the MODA formatting,

as suggested in Kolokathis et al. 2024, http://dx.doi.org/10.1016/j.csbj.2024.10.018





2. FAIR model output

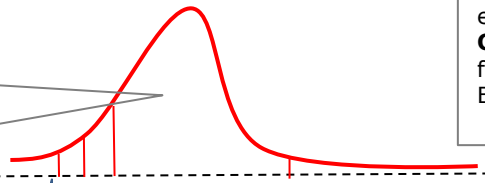
FAIR model output – should be transparent for uncertainty propagation

distribution for HD_M^I

is shifted to the left, if any of the Geometric Means of the assessment factor distributions is increased

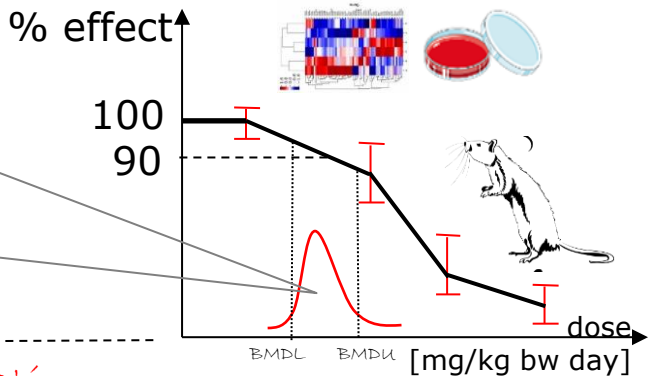
broadens, if any of the assessment factor distributions are broadened

human reference dose distribution



the protection goal for magnitude of effect (M) is defined by the BMR from experiment;

for continuous data e.g. by BMR = 5% erythrocyte decrease **OR** for quantal data by BMR = 50%



: extrapolation uncertainty

BMD

HD_M^I

HD = Human Dose, M= Magnitude, I = Incidence

e.g. HD_5^1=**Human Dose** causing

5% decreased erythrocyte count

for **≤ 1% of population**

with probability of e.g. 95%

A) probabilistic, quantify-able uncertainties

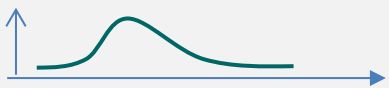
B) List of just qualitative uncertainties

HD_M^I which reaches the protection goals (e.g. M=-5% erythrocytes for I ≤1% population) with a coverage (= probability) of **99%.**

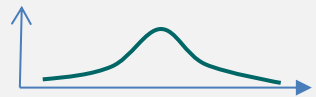
HD_M^I which reaches the same protection goals (e.g. M= -5% erythrocytes for I ≤1% population) but with a probability of just **1%**.

The range between the 99th and the 1st percentile of the HD_{05}^{01} is an estimate for the uncertainty of the HD_{05}^{01}.

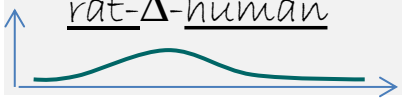
PBK in vitro->human



human-Δ-human



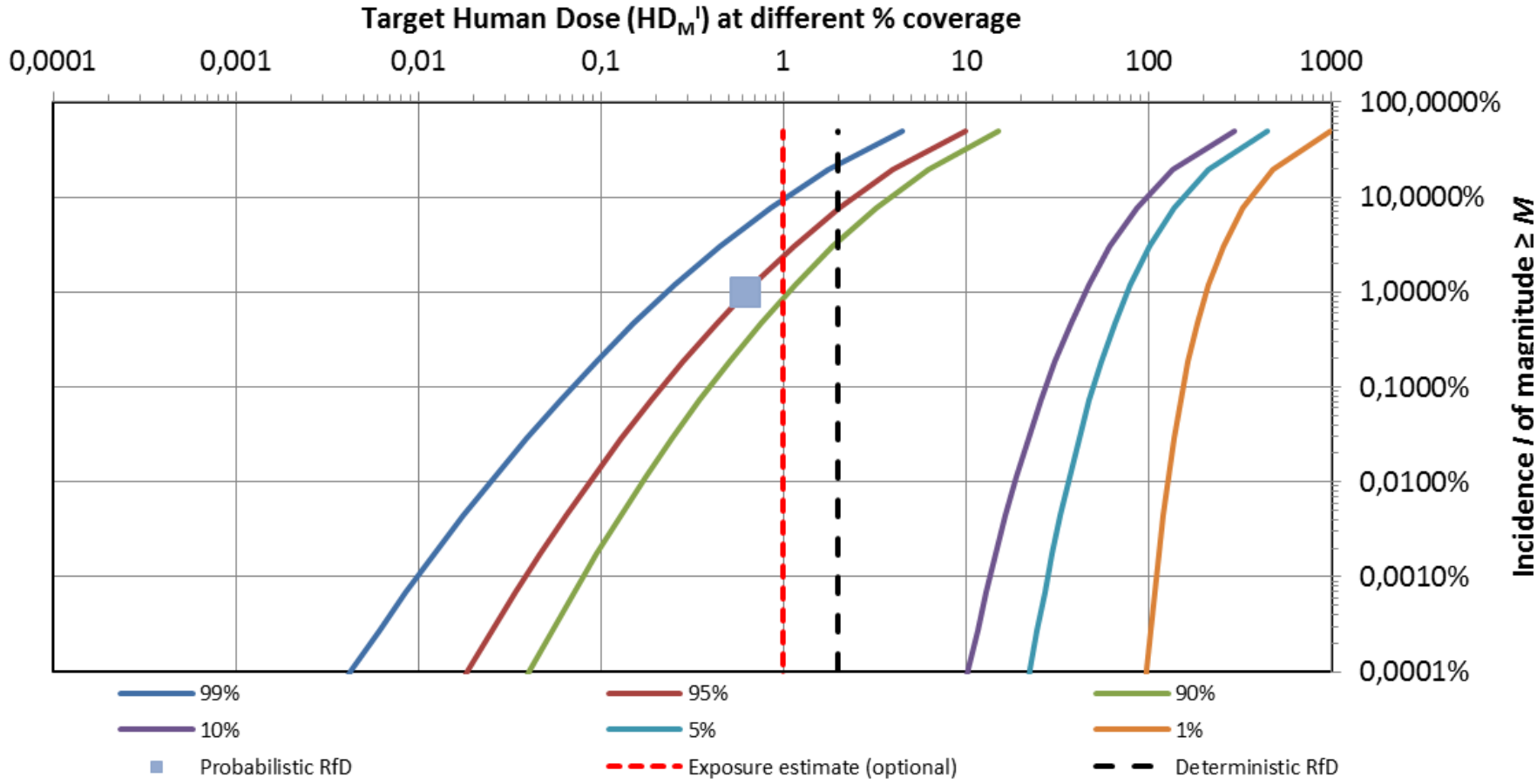
rat-Δ-human



the protection goal for the maximum incidence (I), is defined by the intra-species assessment factors distributions, specific for I

Incidence (%)	Lognormal approximation[a]	
	$P50_{approx}$	$P95/P50_{approx}$
10	3.49	2.24
5	4.98	2.82
1	9.69	4.32
0.50	12.36	5.06
0.10	20.42	6.99
0.05	24.82	7.93
0.01	37.71	10.39

HD_M^I depends on acceptable population incidence and acceptable probability (% coverage) to meet the protection goal and can be expressed relative to the exposure estimate and any traditional deterministic reference dose



One could compare the % contribution of uncertainty in the HD_M^I for different assessment approaches to ease regulators understanding of relative uncertainties and acceptance of NAM approaches

hypothetical example

ASPECT	**% contribution to overall uncertainty**	
	rat based	**human In vitro based**
PoD	10%	10%
Extrapolation NOAEL to BMD	--	--
Allometric Interspecies scaling	1%	--
Extrapolation rodent to human interspecies TK/TD	22%	--
Extrapolation exposure duration, experimental to real	--	--
PBK extrapolation in vitro to human	--	30%
Human intraspecies uncertainty	67%	60%
(Other aspect #1 ….)	--	
Greatest contributor to overall uncertainty on Target Human Dose (HD_M^I)	**Intraspecies**	**Intraspecies**

Summary

Improve regulatory readability of model validity by

- harmonizing model reporting templates by highlighting main regulatory validity criteria
- providing transparency for relative uncertainty contributions from (integrated) model outputs

Acknowledgement

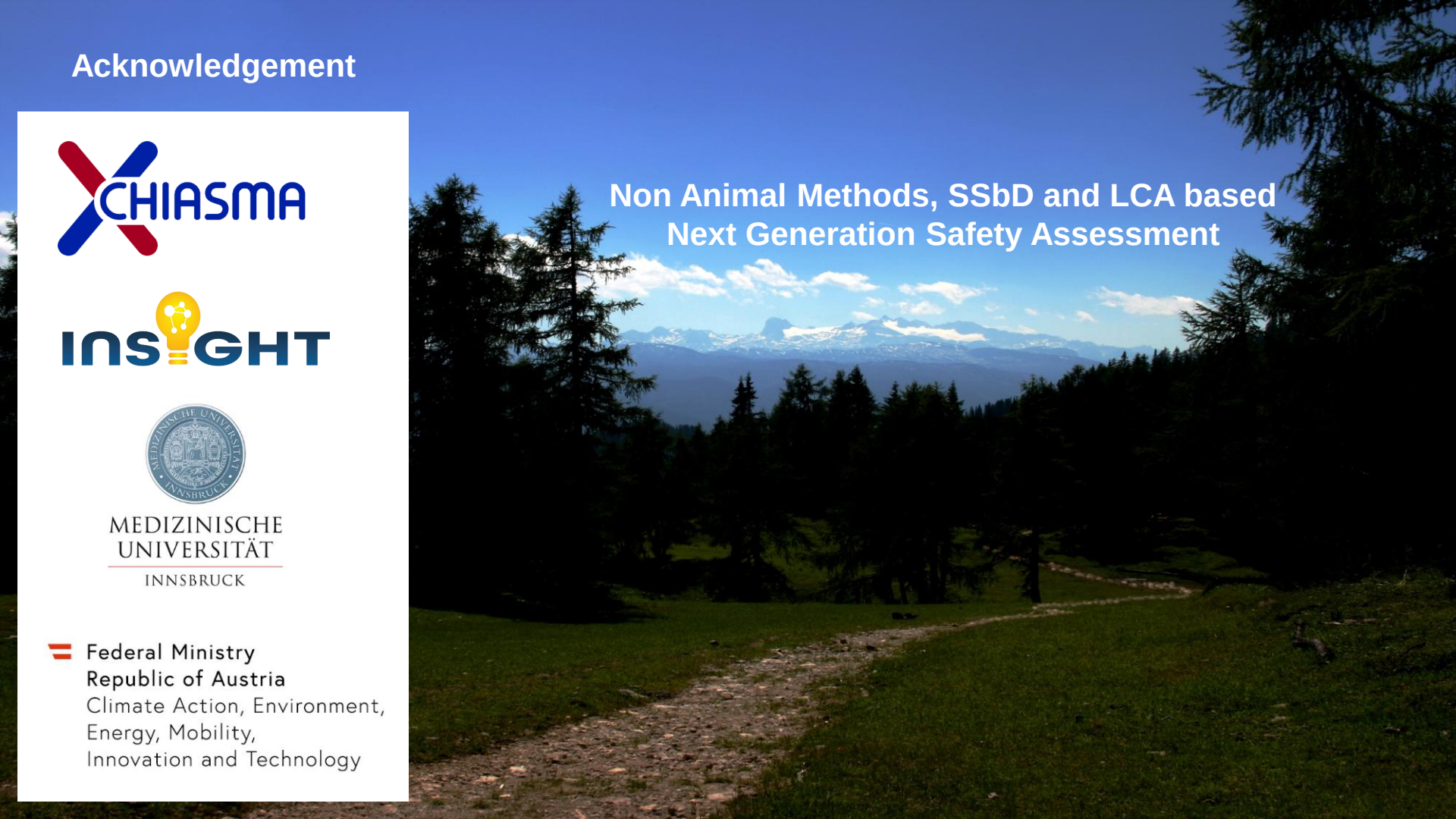
CHIASMA

INSIGHT

MEDIZINISCHE UNIVERSITÄT INNSBRUCK

Federal Ministry
Republic of Austria
Climate Action, Environment,
Energy, Mobility,
Innovation and Technology

Non Animal Methods, SSbD and LCA based Next Generation Safety Assessment



Backup slides

Evolution of

Traditional Safety Assessment

Next Generation Safety Assessment

safety assessment	data		Variable	extrapolation from model to assessment target	variability of assessment target	reference value	classification
traditional	human	rodent data (rarely dog or else)	usually NOAEL rarely BMD [+ BMDL/U]	interspecies extrapolation usually default factor 10 rarely data-based [+LCL/UCL], e.g. WHO 2017	human variability usually default factor 10 rarely data-based [+LCL/UCL], e.g. WHO 2017	usually human safe dose rarely human dose HD protective for x% of population [with y% probability]	effect type: irrit./corr., CMR effect potency: acute toxic, sensitizing, STOT SE & RE
	env	algae + daphnids + fish data	usually EC50 or EC10 or NOAEC rarely BMC [+ BMCL/U]	usually time extrapolation (factor 1 to 1000)	rarely: Interspecies Correlation Estimates & Species Sensitivity Distributions	usually environmental safe concentration rarely env. conc. protective for x% of species [with y% prob.]	effect potency: acute, chronic, PBM
Next Generation	human	human in vitro data, In silico data	bmc [+ bmdl/bmdu]	QIVIVE extrapolation [+ uncertainty from input data & model parameter]	human variability [+ uncertainty], e.g. from PBK and/or historical WHO data	human dose HD protective for x% of population [with y% probability]	effect potency: revised STOT SE & RE [+% prob. for category]
	env	algae + daphnids + fish cell data, In silico data	EC50 or bmc10 [+bmdl/bmdu]	time extrapolation?	Interspecies Correlation Estimates & Species Sensitivity Distributions	environmental concentration protective for x% of species [with y% probability]	effect potency: acute, chronic, PBM [+% prob. for category]

Integration with SSbD and LCA

NGSA
probably safe hazard & safe dose for toxic bioactivity in humans in environment

SSbD
probably safe hazard & safe MoE = safe dose / exposure for production, use, waste, recycling for human for environment

LCA
probably acceptable impact on environmental health biodiversity climate society socio-economy

visualizing uncertainty of risk metrics:

limit value versus exposure

to identify aspects of highest uncerainty

APROBA-plus - screenshot

https://www.rivm.nl/en/aproba-plus

Bokkers et al. 2017, doi:10.1016/j.fct.2017.10.038