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MEDIZINISCHE
UNIVERSITÄT
INNSBRUCK

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

Evolving Regulatory Frameworks through Uncertainty Analysis in Developmental Neurotoxicity Evaluation

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60TH

CONGRESS OF
THE EUROPEAN SOCIETIES
OF TOXICOLOGY

TOXICOLOGY
WITHOUT BORDERS WWW.EUROTOX2026.COM

Biology modifiers

(epi)genetic background, diet, life-style, socio-economic background,...

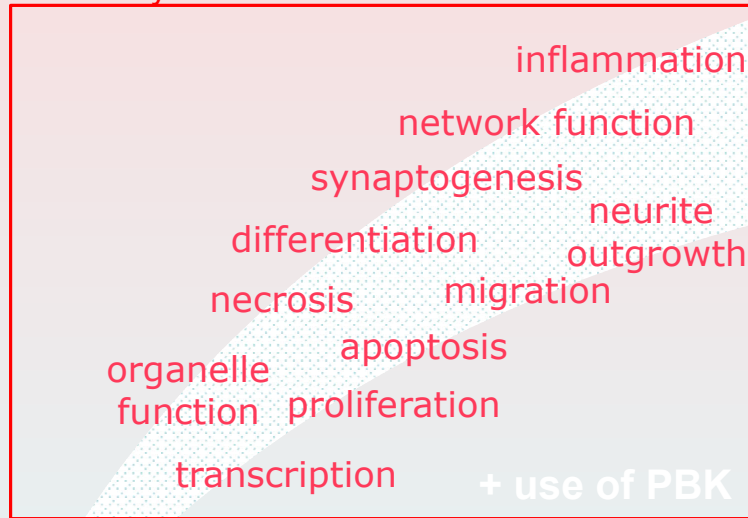
molecular

cellular

tissue/organ

organism

molecular/cellular effects as risk factors
for toxicity and disease



receptor binding

reproduction

motor & sensory

behavior

learning & memory

malformation

mortality

complex
problem
solving

sportive or
artistic
activity

planning
reading

adverse

Methods
limits AO
recognition
variability,
sample
number,
endpoint
definition,
bias,
statistics,
...

non
adverse

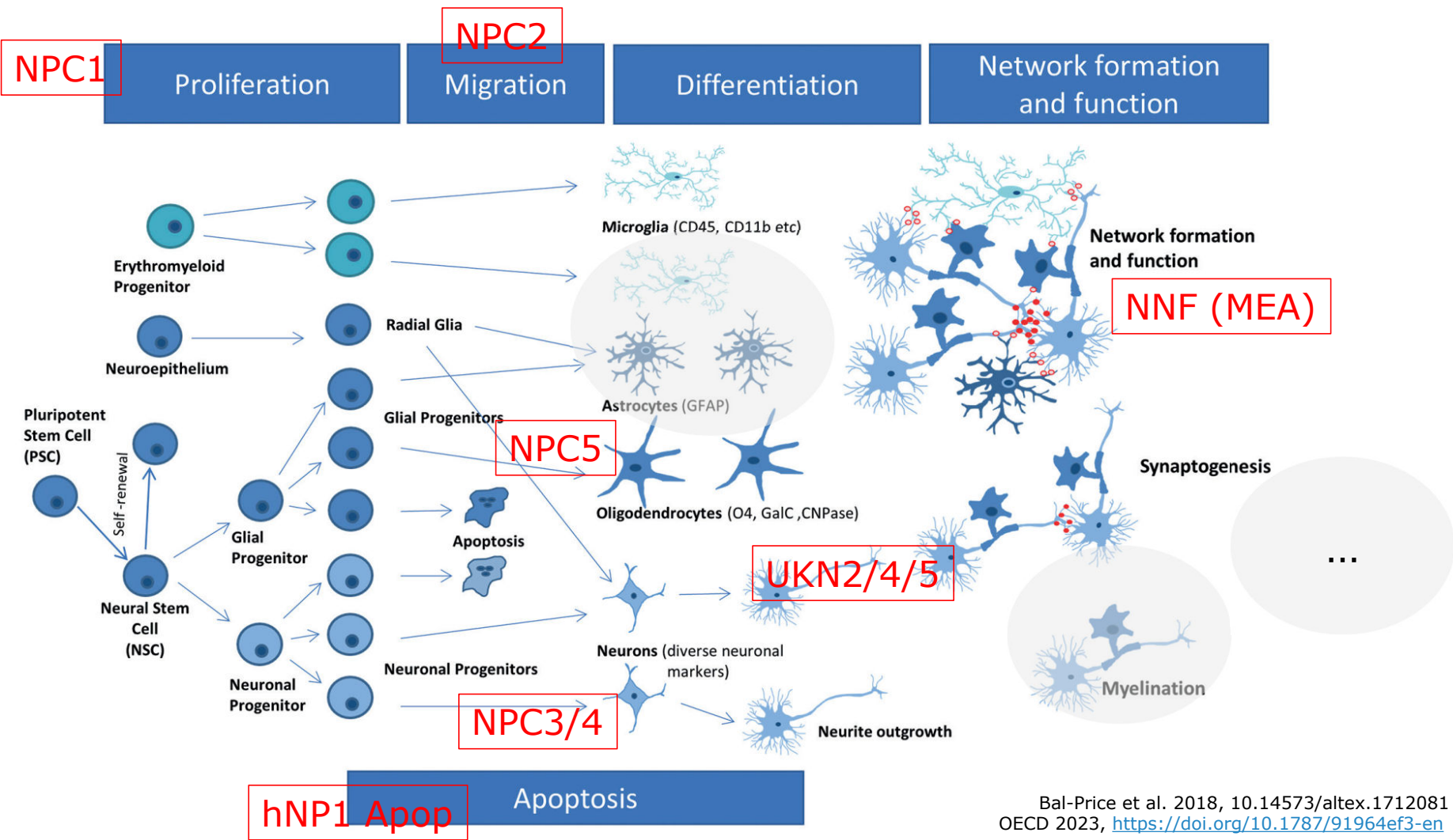
exposure

Biological modifiers

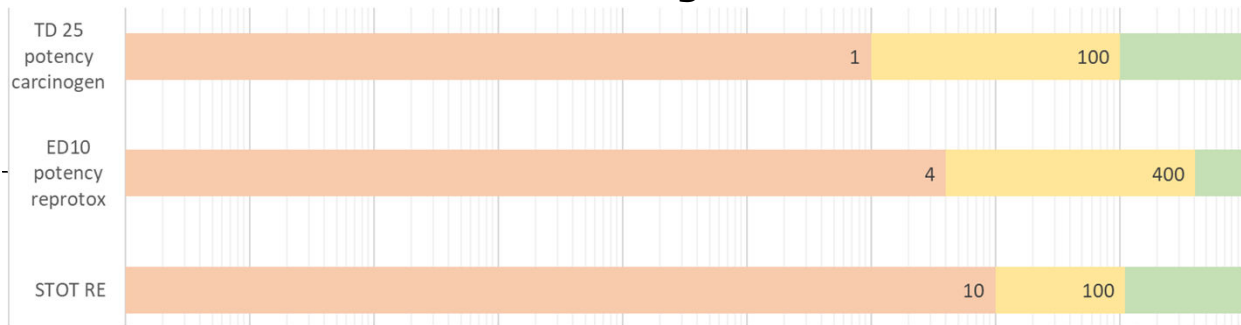
(epi)genetic background, diet, life-style, socio-economic background, stress, infections, co-exposure,...

figure from Paparella et al. 2020
<https://doi.org/10.1016/j.reprotox.2020.08.002>

The OECD Developmental Neurotoxicity In Vitro Battery (DNT-IVB): biological, mechanistic plausibility



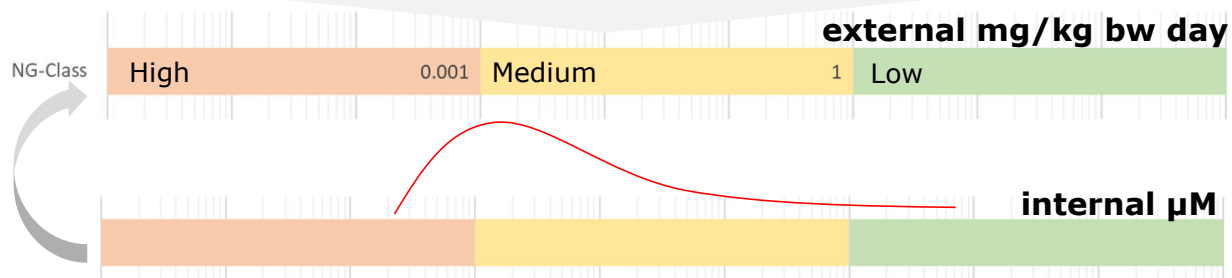
Next Generation Classification aligned with Next Generation Risk Assessment (NGRA)



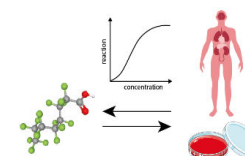
: 100 for animal -> human -> human variability
stretch medium class to 1000x for usual uncertainty

effect doses in rodent repeated dose studies [mg/kg bw day]

new classification,
similar to current GHS potency categories
but
boundaries lowered & stretched



PBPK modelling



- match probabilistically with exposure categories



- select lowest, reliable BMC from 17 DNT-IVB assays

depend on
maximum
incidence
accepted
[WHO 2018](#)

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





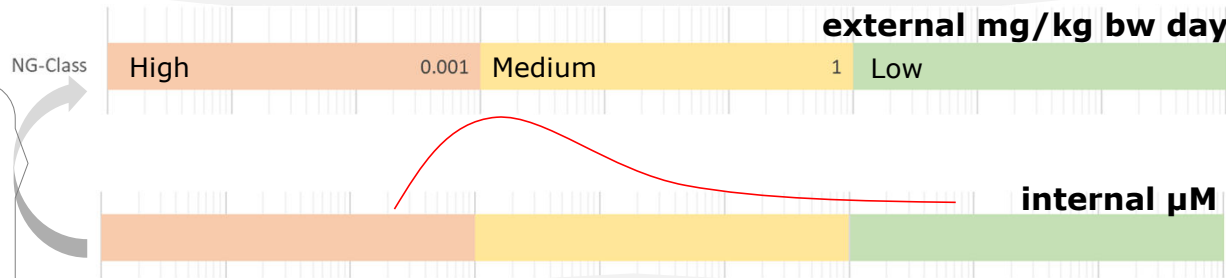
for demonstrating the principle, chemical specific

high-throughput -PBK

esqlabs
WE EMPOWER HEALTH CARE



: 100 for animal -> human -> human variability
stretch medium class to 1000x considering usual uncertainty

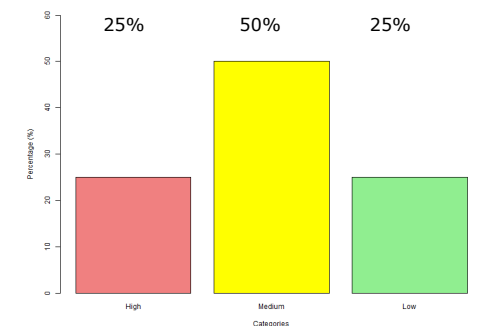


- match probabilistically with exposure categories

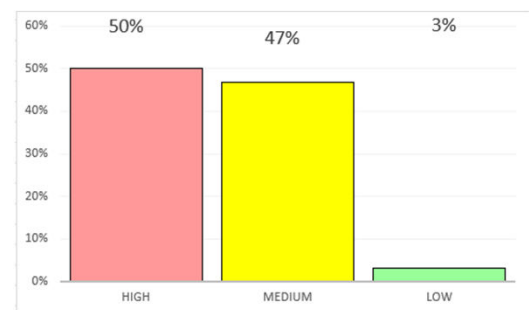


163 compounds with all 17 IVB and PBK model outputs
=> lowest, reliable BMC from 17 DNT-IVB assays

EU potency boundaries are pragmatically stratifying compounds into three groups



Next Gen Classification may also pragmatically stratify for DNT IVB potency



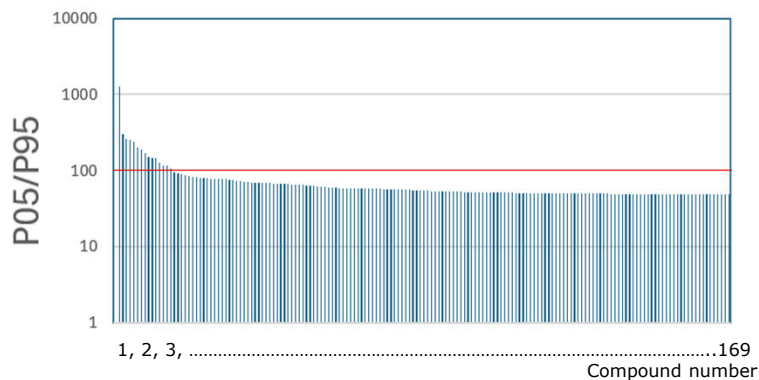
169 compounds active in at least one of the 17 IVB assays => select lowest, reliable BMC per compound
=> probabilistic extrapolation to human protective concentration

Uncertainty for human protective concentration increases with decreasing "acceptable % population under risk"

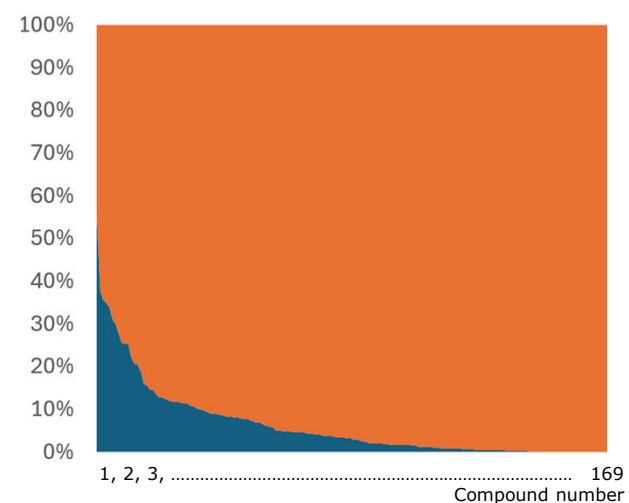
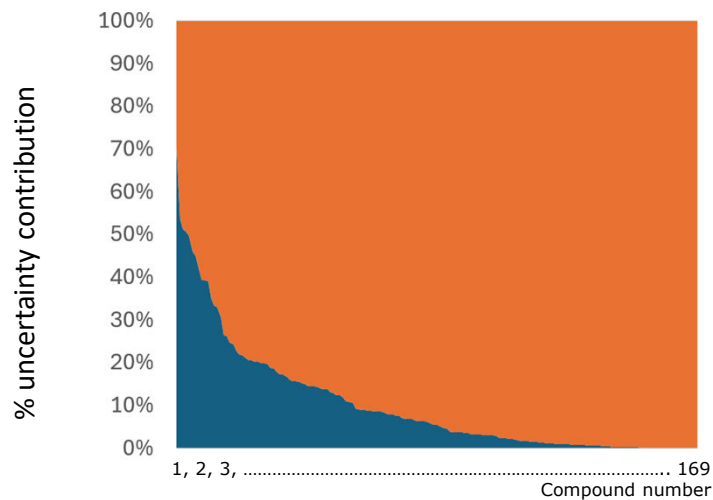
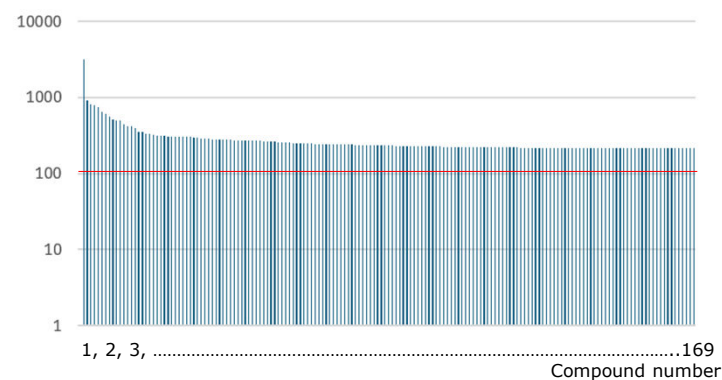
% uncertainty from BMC vs. human variability modelling is dominated by human variability

■ bmc ■ human variability

population under risk $\leq 0.1\%$



population under risk $\leq 0.001\%$



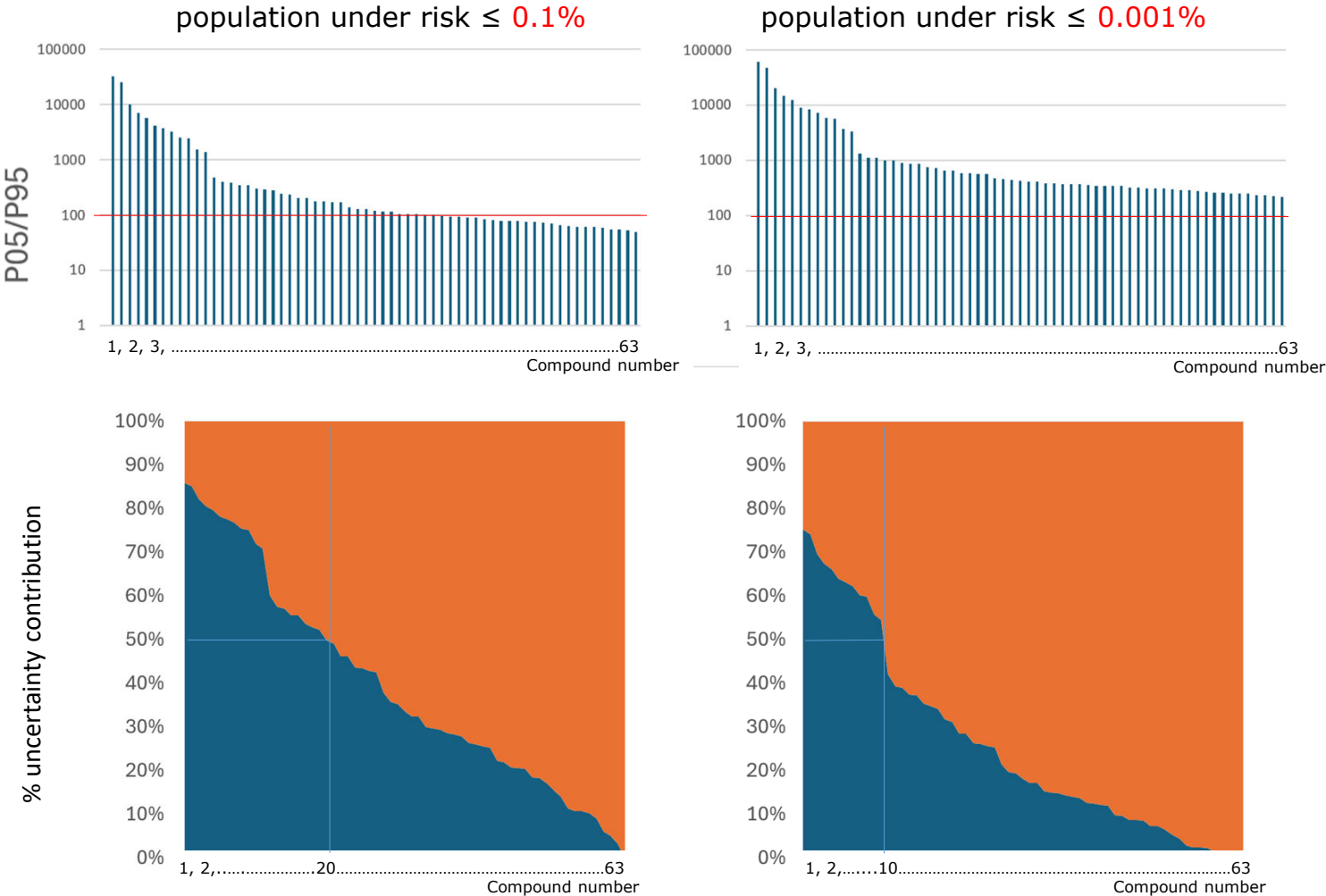
63 compounds: Integrating BMCs uncertainty from **two different BMC assessment pipelines*: tcpl & crstats** (Carstens, Doenmetz et al. 2025)

***caveat:** BMC uncertainty overestimated, since **dose-response models not visually verified**

Uncertainty for human protective concentration **increases**

% uncertainty from BMC vs. human variability modelling
is **still largely dominated by human variability, especially for lower population under risk levels**

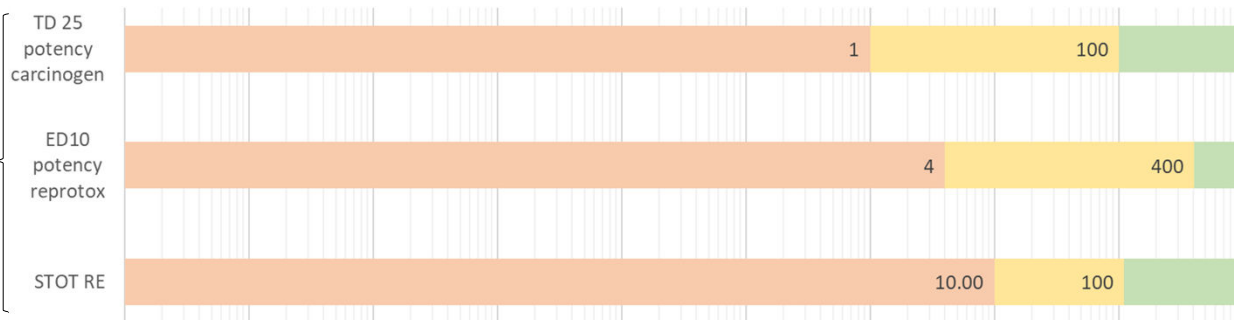
■ bmc ■ human variability



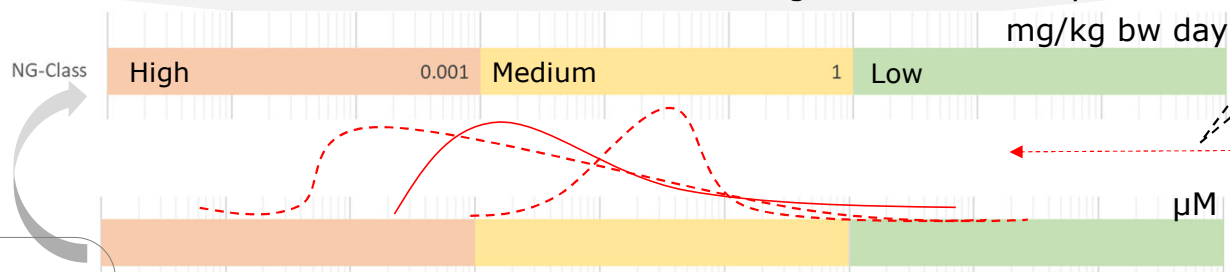
Next Generation Classification aligned with Next Generation Risk Assessment (NGRA)



GHS

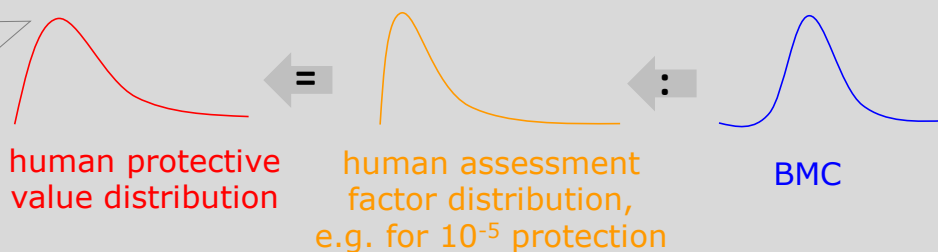


: 100 for animal -> human -> human variability
stretch medium class to 1000x considering usual uncertainty



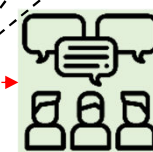
% uncertainty from bmc vs. human variability vs. PBK modelling

- match probabilistically with exposure categories



- select lowest in vitro BMC from 17 DNT IVB assays

FAIR semi-quantitative and qualitative knowledge about uncertainties from
NAMs to shift the distribution



Expert Knowledge Elicitation

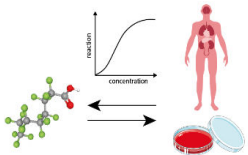
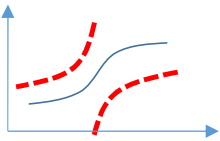


FAIR semi-quantitative and qualitative knowledge about uncertainties from
animal test data to understand if/how much specific uncertainties could theoretically be reduced to decide if DNT-IVB based result is acceptable

OECD WPHA background doc developed from
<https://doi.org/10.1016/j.reprotox.2020.08.002>



Summary



for exploiting the regulatory utility of the DNT-IVB we need

- Next Generation Classification aligned with Next Generation Risk Assessment
- probabilistic
- transparent for sources of uncertainties
- integrated with semi-quantitative expert knowledge elicitation tools

to be done:

- finalize the approach for modelling uncertainty of human variability
- integrate PBK modelling uncertainty
- test this uncertainty based decision making/reporting/communicating within CHIASMA project case studies: <https://chiasma-project.eu/>

Acknowledgement



High throughput PBK: Dr. Susana Proença & Dr Stella Fragki



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 **Federal Ministry**
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